CITY OF HOPE
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DIVISION of HEMATOLOGY & HCT and RADIATION ONCOLOGY

TITLE: **Tandem High-Dose Therapy with Melphalan and Total Marrow Irradiation (TMI) with Peripheral Blood Progenitor Cell Support and Lenalidomide Maintenance in Multiple Myeloma: A Phase I/II Trial**

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DISEASE SITE: Bone Marrow
HISTOLOGY: Myeloma
STAGE (*If applicable*)**:** I-III
MODALITY(IES): Chemotherapy and radiation therapy/Stem cell transplant
TYPE (*e.g., Pilot, Phase I*)**:** Phase I/II

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SCHEMA

PRIMING and APHERESIS

CYCLOPHOSPHAMIDE 1.5-g/m^2 and FILGRASTIM 10 µg/kg/day

CYCLE 1

DAY –2	Hydration 6 hours; MELPHALAN 100 mg/m^2 IV	2/14/06
DAY –1	MELPHALAN 100 mg/m^2 IV	

DAY 0 REINFUSION OF PERIPHERAL BLOOD PROGENITOR CELLS (PBPC)

DAY 5 START FILGRASTIM 5 µg/kg/day, IV

CYCLE 2 START TOTAL MARROW IRRADIATION (TMI) AT LEAST 6 WEEKS FROM DAY 1 and NOT BEYOND 18 WEEKS

~~DAY - 6~~	~~200 cGy /D to 200 cGy BID~~	
~~DAY - 5~~	~~200 cGy /D to 200 cGy BID~~	
DAY - 4	200 cGy /D to 200 cGy BID	03/19/08
- 3	200 cGy /D to 200 cGy BID	
- 2	200 cGy /D to 200 cGy BID	
- 1	200 cGy /D to 200 cGy BID	

DAY 0 Reinfusion of PBPC

DAY 0 START FILGRASTIM 5 µg/kg/day, IV 2/14/06

STARTING WITHIN 6-8 WEEKS OF DAY ZERO OF CYCLE 2, (except for the patients with slow recovery after cycle 2, who need more time)LENALIDOMIDE 10 MG/D WILL BE ADMINISTERED ORALLY 2/14/06

1.0 OBJECTIVES

1.1 PRIMARY OBJECTIVES

1.1.1 To assess the feasibility and toxicities of tandem cycle ablative therapy consisting first of high-dose melphalan and then escalating doses of fractionated total marrow irradiation (TMI) using helical tomotherapy in patients with advanced multiple myeloma. To establish the maximum tolerated dose of TMI using helical tomotherapy.

1.1.2 To assess response rate, progression free and over-all survival following treatment with tandem cycle ablative therapy consisting first of high-dose melphalan and then escalating doses of TMI using helical tomotherapy with Dexamethasone/Thalidomide maintenance therapy in patients with advanced multiple myeloma.

1.1.3 To assess the feasibility of adding decadron and thalidomide as maintenance following the second cycle of high-dose therapy.

1.2 SECONDARY OBJECTIVES

1.2.1 To perform cytogenetic, gene rearrangement, and fluorescence *in situ* hybridization (FISH) studies on baseline and post-treatment bone marrow and blood specimens and correlate the presence/persistence of these features with treatment outcome.

1.2.2 To bank/develop cell lines developed for future investigations of tumor biology, and for potential assessment of efficacy of novel therapeutic agents.

2.0 BACKGROUND AND RATIONALE

2.1 The incidence of multiple myeloma (MM) has been on the rise with an estimated 15,000 new cases being predicted in 2004, accounting for approximately 13% of all hematological malignancies (1). The entire spectrum of plasma cell dyscrasias affects an even greater percentage of the population. These diseases include benign gammopathy, macroglobulinemia, solitary plasmacytoma and, within the category of MM, smoldering and indolent forms as well as immunoblastic lymphoma and plasma cell leukemia (2). Adverse prognostic factors such as high plasma cell labeling index, elevated beta-2 microglobulin, low albumin at diagnosis, the presence of specific chromosomal abnormalities, plasmablastic morphology and abnormal renal function, poor performance status at diagnosis and elevated serum levels of interleukin-6 are of grave clinical significance (3-6). Chemotherapy with melphalan and prednisone, a combination of alkylating agents, or vincristine, doxorubicin and dexamethasone is effective in 50-70% of patients with newly diagnosed MM; however, less than 10% of patients will achieve complete remission (7,8). Unfortunately, the effects of chemotherapy are

usually short lasting. This lack of long-term effectiveness is due to either primary, or acquired resistance. Attempts to improve overall response and response duration have been focusing on overcoming drug resistance due to over expression of the MDR-1 gene product (9), or utilizing myeloablative therapy followed by allogeneic, or autologous bone marrow, or peripheral blood progenitor cell rescue (PBPC) (10). There has been a statistically significant but moderate trend with improved 5-year relative survival rates ranging from 24 months to 31 months, when comparing patients treated from 1974-76, 1983-85, and 1992 through 1999 (1). While recent incorporation of both older, rediscovered agents (thalidomide), and newly developed classes of drugs (bortezomib) have contributed to our ability to better control the myelomatous process both as initial and salvage therapy, the long-term impact of these and other agents under development is still unknown (11,12).

2.2 High-dose chemo-/radiotherapy in the treatment of MM.

Single agent high-dose melphalan therapy results in response rates of > 80% with complete response rates of >30% as described in earlier studies, but pancytopenia-related toxicities without the use of stem cell support are substantial. In an update, 1/3 of the patients from an early cohort treated with high-dose melphalan were reported to be alive at 9 years (13). Thousands of patients with multiple myeloma have received dose-intense bone marrow ablative therapy followed by autologous bone marrow, or peripheral stem cell rescue. Following such interventions, increased complete remission rates have been reported in selected cohorts of patients with good performance status and already limited tumor burden at the time of initiating high-dose therapy (10). Induction regimens consisting of total body radiation with cyclophosphamide or melphalan, melphalan alone, or combination chemotherapy, have resulted in similar outcome (14-17). A prospective randomized study comparing high-dose consolidation therapy and stem cell rescue following induction therapy vs. conventional chemotherapy alone, yielded higher complete response rates (22% versus 5%) and improved progression-free and overall survival following high-dose therapy; projected 5 year event-free and overall survivals were 28% and 52% versus 10% and 12%, thereby establishing the role of high-dose chemotherapy as standard, for patients with multiple myeloma (18). A second trial yielded similar results, with a median survival of 54 months versus 42 months favoring outcome for patients treated with high-dose chemotherapy (19). Comparison of early vs. late (at the time of progression) autologous transplant favors early high-dose therapy, resulting in prolonged progression-free survival and better quality of life (20). Tandem cycle high-dose chemo/radiotherapy in the setting of "total therapy" in the largest series by a single institution suggested additional benefit associated with the second transplant in a series of 231 patients, independent of the presence of unfavorable cytogenetics and elevated beta 2 microglobulin; with a median follow-up of 4.2 years among surviving patients actuarial 5-year event-free and overall survivals were 58% and 42%, respectively (4). More recently, a prospective randomized trial of tandem cycle high-dose therapy consisting of melphalan 140 mg/m^2 first, followed by melphalan 140 mg/m^2 and total body

irradiation with 8 Gy versus single cycle high-dose melphalan 140 mg/m^2 and total body irradiation with 8 Gy resulted in a 20% probability of 7-year event-free survival versus 10% (21).

Allogeneic bone marrow transplantation has resulted in a disappointing median overall survival of 13 months as described in a registry review by the European Group for Blood and Bone Marrow Transplantation, with approximately 40% early, treatment-related mortality (22). More recent data suggest diminished early mortality rates possible due to incorporation of PBPC reinfusions, in addition to the increased non-myeloablative transplants (23-24).

Early utilization of myeloablative therapy is recommended both with autologous and allogeneic bone marrow transplantation in order to consolidate complete or partial response to conventional treatment.

2.3 High-dose Chemotherapy Regimens in Multiple Myeloma

The most frequently used single high-dose regimens in an autologous stem cell transplant setting include melphalan alone, or in combination with busulfan, cyclophosphamide, or with fractionated total body irradiation. (16, 17) There are no definitive comparative studies evaluating these regimens, except for melphalan 200 mg/m^2 versus melphalan 140 mg/m^2 and FTBI 8 Gy. (14). In a comparative, randomized, prospective study patients treated with melphalan alone experienced better projected 45-month overall survival rates of ~66% versus ~ 46%, but event-free survivals were equivalent. Toxicities, especially cytopenias were substantially worse in the melphalan/FTBI-treated cohort.

2.4 Rationale for total marrow irradiation (TMI) in multiple myeloma

Rapid advances in computer and medical imaging technologies have resulted in the ability to deliver radiotherapy with greater precision and conformality. External beam radiotherapy has traditionally relied on radiologic imaging to direct therapy to appropriate anatomic regions. The integration of CT imaging into radiation treatment planning, allows for a three dimensional view of each patient's tumor relative to dose-limiting adjacent normal organs, allowing for customized beam shaping, beam orientation and dose conformality. The use of 3D conformal radiotherapy allows for further escalation of dose, which has resulted in higher tumor control, while maintaining risks and side effects at acceptable levels.

Intensity modulated radiation therapy (IMRT) has opened a new era in radiation oncology. By delivering therapy from multiple directions using multiple segmented or modulated beamlets, one can now sculpt radiation doses to fit the unique shape of each patient's tumor, optimizing radiation delivery to complex volumes and regions of the body. Some compare IMRT to "painting" radiation with a finer brush, where more precise, conformal and sophisticated dose patterns are now possible. This has also resulted in a greater degree of conformal dose avoidance of adjacent normal organs. Dose escalation is now possible with

IMRT, which was not possible with technology just a decade ago. For example, radiation doses for prostate cancer, which have been limited to approximately 7000 cGy with conventional technologies, are now >8000 cGy using IMRT. As a result, a significant improvement in tumor control and a reduction in bladder and rectal toxicities have been reported (25).

Helical tomotherapy (HT) represents the next major breakthrough in beam delivery systems. HT is a ground breaking, FDA approved radiation therapy delivery device, which is a marriage of spiral CT and IMRT technology. Specifically, a 6 MV linear accelerator is mounted on a CT ring gantry and rotates around the patient as the patient translates through the ring. The treatment fan beam is segmented using a 64-leaf collimator. Each leaf casts a 0.6 mm width shadow at 85 cm isocenter distance with the fan beam, which varies in width from 0.5 to 5 cm. The minimum voxel or beamlet size is therefore 5 x 6 mm. By rapid opening and closing of leaves as a function of gantry angle while the patient slides trough the ring, helical tomotherapy provides unprecedented ability to sculpt radiation doses to complex shaped tumor regions while simultaneously avoiding dose to normal organs (26, 27). Grigorov et al. (28) evaluating HT treatment plans for prostate cancer, demonstrated rapid drop-off of dose around the target (prostate gland) in all directions resulting in excellent sparing of rectum, bladder and femoral heads superior to prior IMRT techniques. Scrimger et al. (29) predicted that for select patients with lung cancer, tumor doses as high as 16,000 cGy will be achievable while maintaining normal lung doses (and therefore risks) at comparable levels as with conventional delivery methods, which are limited to doses of 6,000 cGy to the tumor in most patients.

In addition, an array of detectors mounted on the same rotating gantry and positioned directly opposed to the beam source, gives the HT delivery system two unique capabilities not found on any other delivery systems. First, these detectors allow for the generation of megavoltage CT (MVCT) images using the 6 MV beam. Resolution and contrast of MVCT is more than adequate to easily distinguish tissue planes and organ boundaries (26), as shown in the figure below. This allows the HT system to automatically align beam orientation to anatomic external landmarks and internal organs in 3 dimensions prior to each daily session, vastly improving the precision of radiation delivery. Second, these same arrays can be used to monitor output of the beam as it exits through the patient, providing an additional level of dose verification. In the future, it is anticipated that future software and hardware modifications will allow for this type of "adaptive radiotherapy" to occur in real time, constantly modulating beam output to account for minute-by-minute variations in tumor and organ motion.

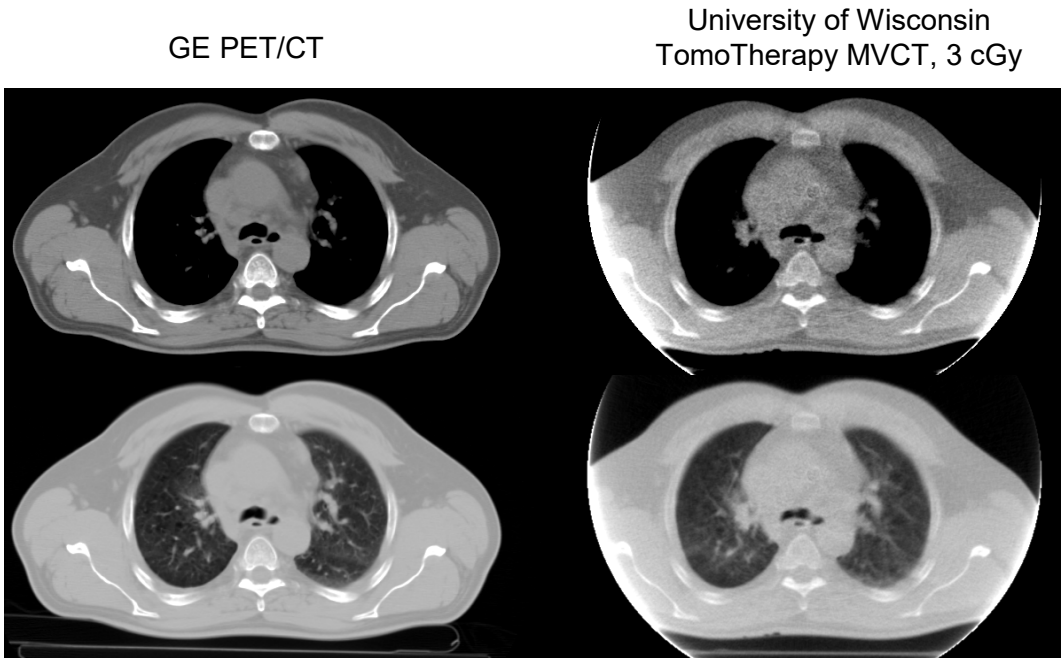
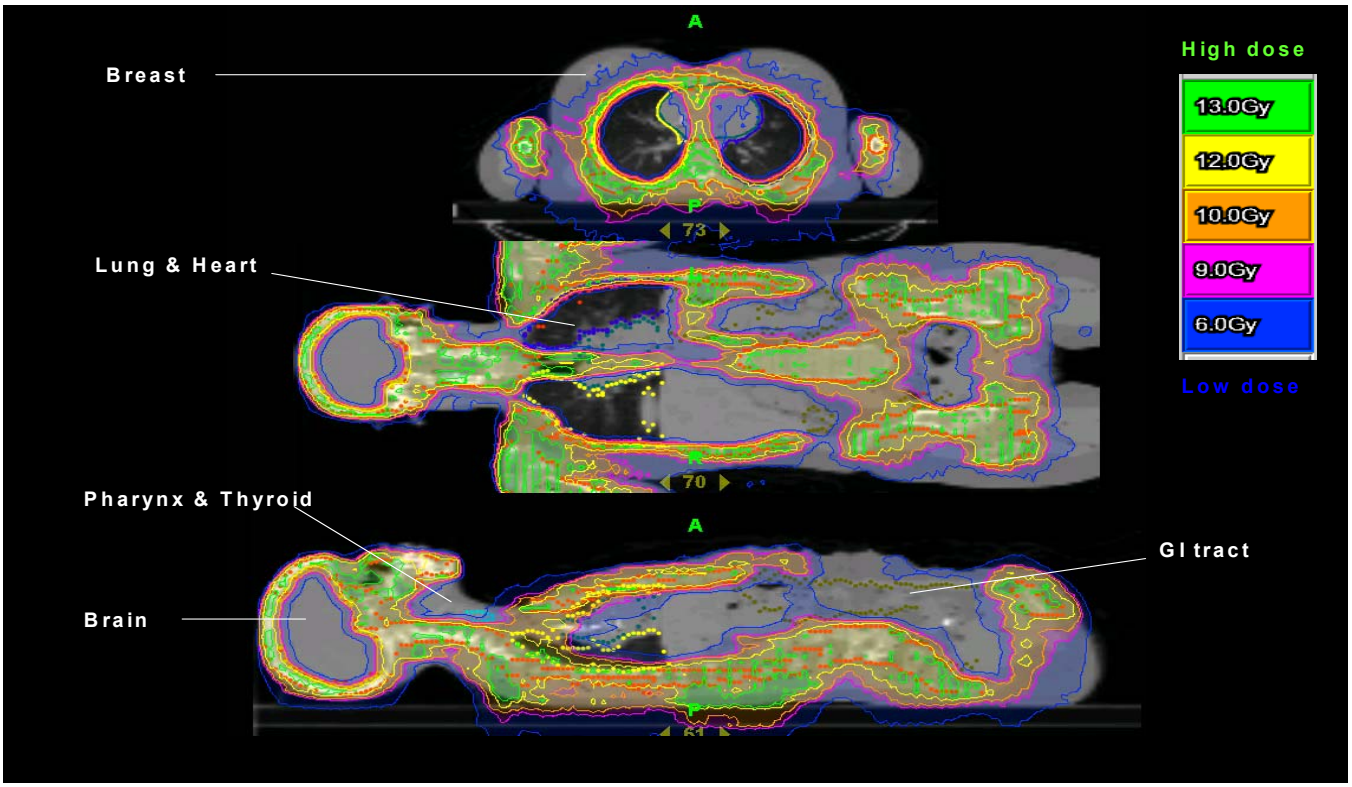
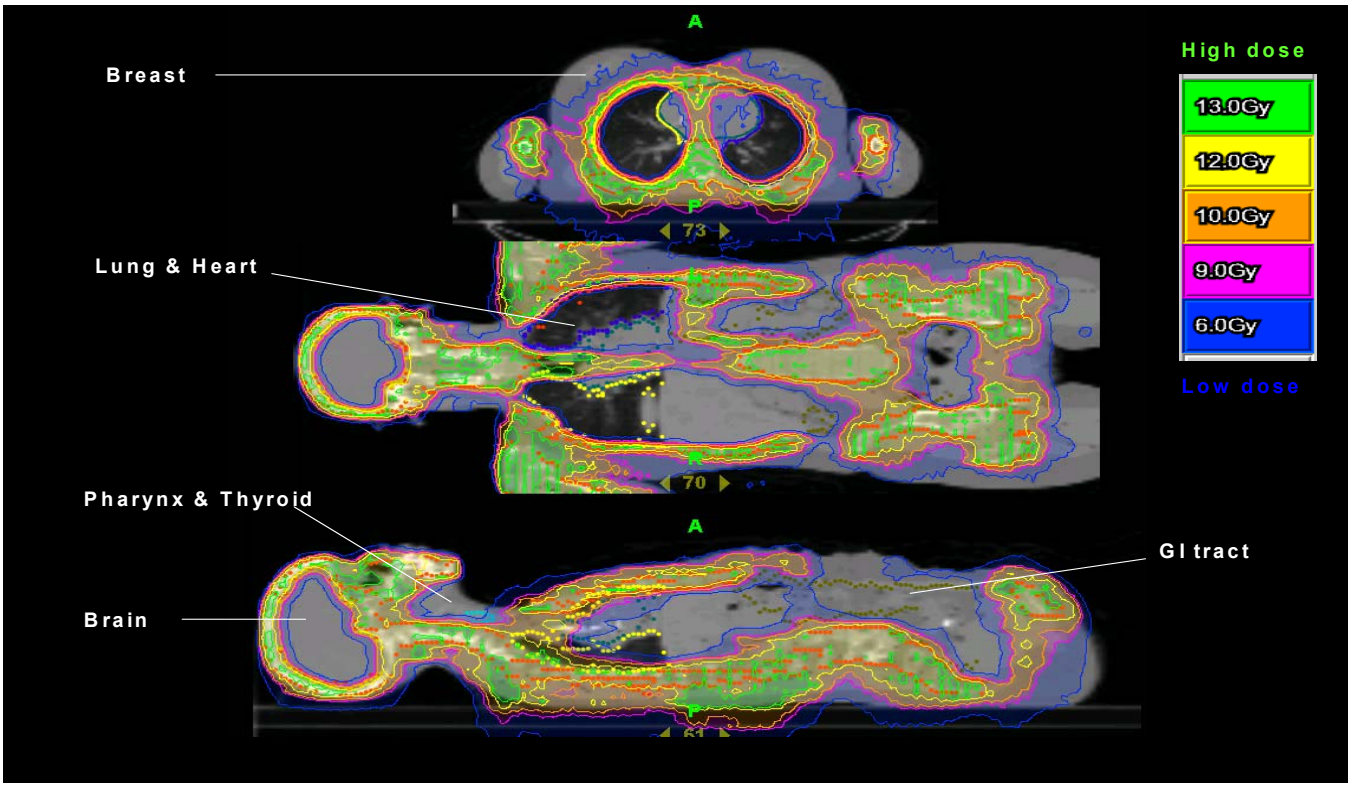


Figure 1. Top row are soft tissue windows and bottom are lung windows

The advent of HT brings for the first time to the clinic the potential to deliver highly conforming dose distributions to large complex target shapes. For example, with HT shaping the dose to the entire pleural surface, while sparing lung parenchyma is now possible for patients with mesothelioma.

At the City of Hope, TBI is often used as part of the preparatory regimen for many patients undergoing bone marrow transplants. Although TBI will effectively treat the target region which includes the marrow space, and, in some patients, extramedullary hematopoietic sites, such as spleen and lymph nodes, TBI also delivers the same dose to all other normal organs resulting in dose-limiting toxicity, such as nausea and vomiting, mucositis and pneumonitis. Working with collaborators at the University of Wisconsin and Tomotherapy, Inc. (manufacturers of HT), we have recently evaluated the feasibility of delivering conformal radiation doses to just the skeletal bone containing the marrow spaces as a possible alternative to TBI. Total marrow irradiation (TMI) using HT would dramatically reduce dose to normal tissues, reducing short-term and long-term toxicities. Using whole body CT images captured on the COH Radiation Oncology Picker CT treatment planning system, normal organs and target skeletal bone compartments were contoured. After defining appropriate target and organ dose constraints, inverse planning using the HT planning station was used to generate dose distributions and dose volume histograms. An example of a TMI dose distribution plan is shown in the accompanying figure.


A
Breast
High dose
13.0Gy
12.0Gy
10.0Gy
9.0Gy
6.0Gy
Low dose
Lung & Heart
73
70
Pharynx & Thyroid
A
GI tract
Brain
61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TBI remains a part of the preparatory regimen for many patients undergoing transplantation for hematologic malignancies. There have been a few clinical trials evaluating the feasibility of increasing TBI dose in an effort to improve outcomes. A phase III randomized trial compared 12 Gy + Cytoxan vs. 15.75 Gy TBI + Cytoxan in patients with AML. The 3-year probability of relapse was 35% for the 12 Gy group and 12% for the 15.75 Gy group (1). A similar study was carried out by the same group of investigators for CML. The four year probability of relapse was 25% for the 12 Gy group and 0% for the 15.75 Gy group (2). However in both studies survival was not improved due to increased transplant related mortality at the higher TBI dose. Appelbaum concluded that relatively small changes in TBI dose can result in significant increases in anti-leukemic effects, but also resulted in increases in toxicities, primarily of the lung, mucus membranes and liver (3). Therefore benefit was established for dose escalation, but a more targeted form of radiation therapy was needed to allow for further dose escalation without excessive toxicities (3). Multiple myeloma is also a radiosensitive malignancy with improved response rates after myeloablative therapies. However, incorporation of TBI into conditioning regimens has been challenging due to associated increased toxicities.

The tables below compare TBI as currently done at COH with TMI. Dose estimates for COH conventional TBI (with 50% lung blocks and electron boost to the chest wall) and helical tomotherapy TMI were recently generated on our treatment planning stations in the same patient (adult female). Both plans used a prescribed dose of 1200 cGy. Table 1 compares the minimum dose for TBI vs. TMI for normal organs. There is a 1.4 to 10.6-fold reduction of minimum dose to normal organs with TMI compared to TBI.

Table 1. Comparison of minimum dose to normal organs with TBI vs. TMI

Structure	TBI Minimum Dose (Gy)	TMI Minimum Dose (Gy)	TBI/TMI
Right Lung	5.5	2.9	1.9
Left Lung	5.6	2.6	2.2
Esophagus	12.3	2.9	4.2
Oral Cavity	9.5	0.9	10.6
Breast	4.5	3.2	1.4
Kidneys	12.0	3.7	3.2
Liver	10.2	2.5	4.1
Heart	5.6	2.9	1.9
Brain	10.7	1.1	9.7
Parotids	6.7	2.7	2.5
GI Tract	12.0	1.9	6.3
Thyroid	10.0	2.0	5.0
Lens	4.7	1.5	3.1

Table 2 compares the median dose (Dose 50%) for TBI vs. TMI for normal

organs. There is a 1.6 to 5.4-fold reduction in normal organ median dose with TMI compared to TBI. Data from Table 2 show that one can escalate the prescribed dose with helical tomotherapy TMI by a factor of 1.8 before reaching a median lung dose comparable to standard TBI. Since median lung dose from TBI correlates to risk of lung toxicity (4) and since 2000 cGy is only 1.67 times higher than 1200 cGy, the risks of pulmonary toxicity should not be greater than standard TBI. Mucosal surfaces of the oral cavity and esophagus are reduced by a factor of 3.2 to 5.4, which should result in reduced mucositis and esophagitis with the doses proposed compared to standard TBI. Median liver doses are reduced 3.3 fold making the likelihood of hepatotoxicity less compared to TBI. Of note, in a review of radiation tolerance of the liver by Dawson et al. (5), the risk of radiation related hepatotoxicity was zero if mean liver doses were below 31Gy. In addition, if the volume of liver irradiated was < 1/3, the risk of hepatotoxicity for doses up to 90 Gy was estimated at 5%.

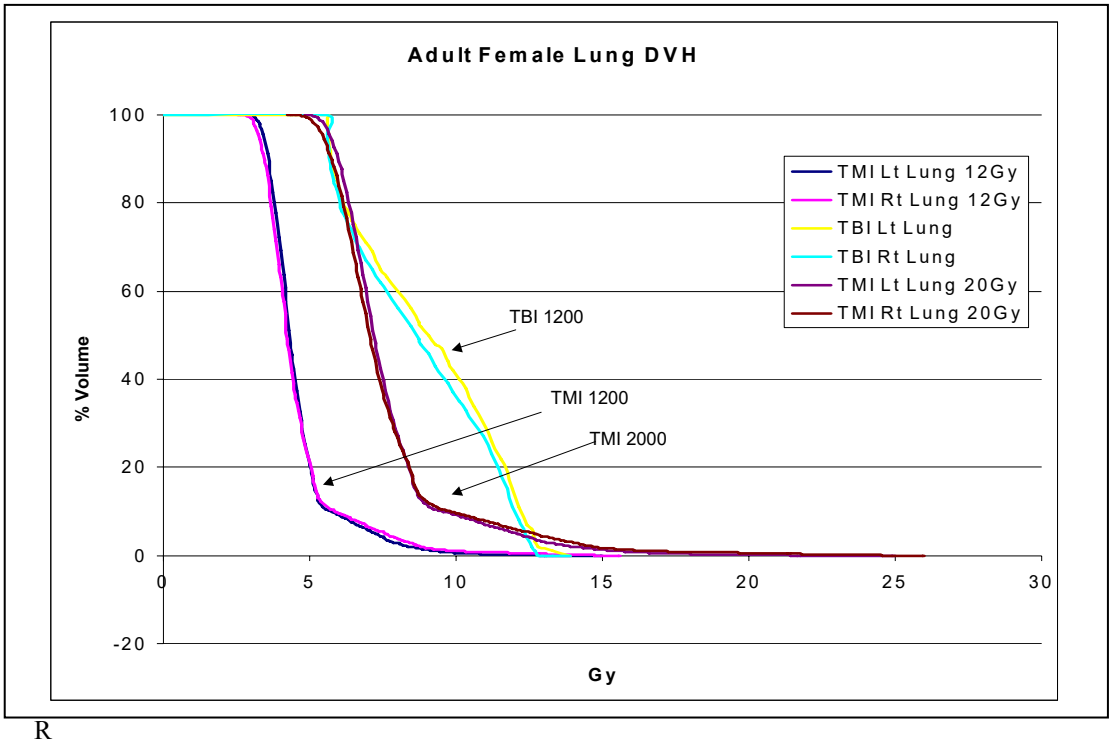
Table 2. Comparison of median dose (dose 50%) to normal organs with TBI vs. TMI

Structure	TBI (Gy)	TMI (Gy)	TBI/TMI Ratio
Right Lung	8.8	5.0	1.8
Left Lung	8.8	5.0	1.8
Esophagus	12.4	3.9	3.2
Oral Cavity	11.8	2.2	5.4
Breast	11.5	5.8	2.0
Kidneys	12.2	3.7	3.3
Liver	12.3	4.0	3.1
Heart	12.1	7.7	1.6
Brain	12	5.3	2.3
Parotids	11.8	5.5	2.1
GI Tract	12.2	5.5	2.2
Thyroid	12.1	6.5	1.9
Lens	11.3	3.7	3.1

Finally the graph below shows dose volume histograms (DVH plots) for lung for 3 scenarios: TBI to 1200 cGy (with 50% lung shielding and electron chest wall boost), TMI to 1200 cGy, and TMI to 2000 cGy. The DVH lung plots for TMI 1200 are to the left of the DVH plots for TBI 1200, indicating a substantially lower dose to the lungs for TMI. When the TMI dose is escalated to 2000, the DVH plots shift right but still remain to the left of the TBI 1200 plots, indicating that almost the entire lung volume will receive a lower dose with TMI 2000 than TBI.

The use of dose volume histograms is an established method of predicting lung toxicity for a given dose to lung, with multiple studies demonstrating minimal risks of radiation pneumonitis if 20-30% of the lung volume irradiated is kept at doses below 20-25 Gy (6). Of note, most multi-institutional clinical lung cancer protocols now use these DVH limits as part of the protocol requirements (RTOG, SWOG, etc.). As shown in the graph above, for a patient receiving 2000 cGy TMI, the V20 (20 % of lung volume) receives approximately 8 Gy, well below the 20-25 Gy limit required by these protocols.

Therefore, given all of the above, the planned highest dose level to marrow of 2000 cGy TMI is felt to be appropriately conservative and should not result in toxicities that exceed TBI, but rather will likely result in reduced toxicities at least up to 2000 cGy.



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reference List

1 Clift,R., Buckner,C.D., Appelbaum,F.R., Bearman,S., Petersen,F.B., Fisher,L.D., Anasetti,C., Beatty,P., Bensinger,W.I., Doney,K., Hill,R.S., McDonald,G.B., Martin,P., Sanders,J., Singer,J., Stewart,P., Sullivan,K.M., Witherspoon,R., Storb,R., Jansen,J.A. and Thomas,E.D. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: A randomized trial of two irradiation regimens, Blood, 76: 1867-1871, 1990.

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6 Rodrigues,G., Lock,M., Souza,D.D., Yu,E. and Van Dyk,J. Prediction of radiation pneumonitis by dose - volume histogram parameters in lung cancer - a systematic review, Radiotherapy and Oncology, 71: 127-138, 2004.

In the proposed study we plan to deliver a TMI dose level of 1000 cGy, a starting dose below the traditional fractionated total body irradiation dose of 1200 cGy, and slightly above the 800 cGy usually administered together with 140 mg/m^2 of melphalan. The dose will then be escalated in cohorts of 3-6 patients per Phase I trial design as shown in the table below. If two fractions are delivered on the same day there must be a minimum of 6 hours between fractions.

Day 1 (cGy)	**Day 2 (cGy)**	**Day 3 (cGy)**	**Day 4 (cGy)**	**Day 5 (cGy)**	**Total Dose (cGy)**
200	200	200	200	200	**1000**
200 AM 200 PM	200	200	200	200	**1200**
200 AM 200 PM	200 AM 200 PM	200	200	200	**1400**
200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	200	200	**1600**
200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	200	**1800**
200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	**2000**

Conformal avoidance of dose is planned for lung, kidneys, heart, brain, thyroid gland, oral cavity, oropharynx, lens, GI tract, breasts, parotids, liver and spleen**.**

2.5 Maintenance Therapy

In bone marrow samples of patients with active MM there is ample evidence for the presence of active angiogenesis (30); expression of certain adhesion molecules is also increased on the surface of such plasma cells in comparison to those from patients with MGUS. In at least one study, diminished vascularity following high-dose therapy and PBPC seemed to be associated with better outcome (31). Alpha

interferon, an agent with possible antiangiogenetic and other activities, has been found to exhibit antitumor activity in the therapy of multiple myeloma. Data from our institution and from Europe have demonstrated prolonged disease-free and overall survival with maintenance interferon therapy, but compliance, and feasibility of delivering set doses at regular frequency and for the planned duration is questionable (32, 33). Maintenance therapy with steroids has also been found to be effective following standard chemotherapy. (34) Thalidomide, an agent with possible antiangiogenesis potential, had been reported to induce tumor response-including short-lasting complete remissions- in heavily treated, relapsed patients with MM (35, 36). Hence, thalidomide, an agent effective in both salvage and first line therapeutic settings is a potentially promising tool in attempting further consolidation of the response/survival gains achieved following high-dose therapy and PBPC. More recently, Lenolidomide, which is approved for second line therapy of multiple myeloma, has shown great promise as a maintenance therapy.

2.6 Pamidronate or zoledronic acid in the therapy of multiple myeloma.

Bisphosphonates– presumably by interfering with osteoclast-mediated bone resorption- are useful in reducing the incidence/complications of lytic metastases. Both pamidronate and zoledronic acid had been found effective in reducing the number skeletal complications, and may also alter the natural history of MM by a direct effect on the myeloma cells. (37, 38) In a study evaluating the role of zoledronic acid to prevent osteoporosis, less frequent yearly or every 3 months, and monthly administration were found to be equally effective (39).

2.7 Chromosomal abnormalities as prognostic indicators in MM

Cytogenetic abnormalities can be detected in significant numbers of MM cases; the presence of 11q, -13 and deletion 13q have been associated with worse survival (4); frequent abnormalities observed in MM include t(4;14) (p16;q32), t(11;14) (q13;q32), t(8;14) (q24;32), t(14;18) 9 q32;q21), 13q14 (Rb loss) and others.(40) One of these translocations, t(4;14) may lead to dysregulations of two separate oncogenes providing one of many potential targets for specific interventions in the future (40, 41).

Autologous stem cell transplantation following high-dose chemo-/radiotherapy may contribute to the development of clonal hematopoietic evolution (or unmask/accelerate previously existing clonal abnormalities). Hence, we will apply a unique assay (specific only in female patients) to detect the presence of clonal hematopoiesis prior to high-dose therapy as well as to monitor for the development of such clones following treatment, in female participants.

2.8 COHNMC experience with tandem cycle high-dose therapy in MM

Between 5/94 and 3/03, we treated 104 patients with stages I-III multiple myeloma on 2 sequentially developed tandem cycle high-dose chemotherapy

trials. Treatment consisted of cycle 1 of melphalan 150 mg/m^2, and cycle 2 of oral busulfan 16 mg/kg x 4 days and cyclophosphamide 60 mg/kg x 2 days (46 patients) followed by G-CSF primed PBPC on the first trial, and the same combination but using IV busulfan 0.8 mg/kg x 4 days and cyclophosphamide (1.5 gm/m^2) and G-CSF primed PBPC support (58 patients), on the second trial. Patients with ≤ 10% bone marrow involvement in response, or with stable disease, and 2 prior treatment regimens, (first trial) and subsequently with ≤ 40% marrow involvement and inclusive of patients even with plasma cell leukemia, and up to 3 prior treatment regimens (second trial) were eligible. All patients were to receive maintenance therapy with intereferon -α 2, starting at 3 million units/m2, given subcutaneously, three-times/ week. Patients enrolled on the second trial were to receive thalidomide up to 400 mg/day in addition to interferon, if they were not in complete remission by 6 months from initiating high-dose therapy. The median age was 52-years, (range, 38-65), 2/3rd of patients were diagnosed with stage III myeloma, and 40% received prior radiation therapy. The median number of prior treatment regimens was 1 (1-3). Median time from diagnosis to high-dose therapy was 8 months (range, 2-74). Eighty nine percent of patients received both cycles at a median interval of 75 days (29-134). Among the 46 patients treated with oral busulfan there were 7 cases of venous-occlusive disease (VOD) with 3 fatalities (Treatment-related mortality [TRM]: 7%). Among 58 patients treated with IV busulfan, there were 6 cases of non-fatal VOD and one septic death (TRM: 1.7%). Fifty-five percent of the 104 patient cohort achieved ≥ 90% response (complete response rate: 39%; very good partial response: 16%). While 92 % of patients tolerated at least 1 million unit/m^2 of interferon 2-3 times/week, only 8 patients were able to tolerate concomitant administration of interferon and up to 200 mg of thalidomide beyond 3 months, with 2 patients converting into complete responders.

Three-year progression-free survival is 48.5% (95% CI, 38-59%) and overall survival is 74.4% (95%CI, 65-83%) for the entire group. Progression-free survival and overall survival are 67% and 93.9% for the first and 38% and 64.5% for the second cohort of patients. Possible explanations for the somewhat worse outcome for the second cohort are the inclusion of less responsive patients (≤ 40% vs. ≤ 10% bone marrow involvement), inclusion of patients with plasma cell leukemia, and up to 3 vs. 2 prior treatment regimens (33, 21).

2.9 Rationale for novel tandem high-dose chemotherapy and TMI followed by PBPC and lenalidomide/bisphosphonate maintenance.

Based on the feasibility and possibly better complete response / very good partial response rate and progression-free survival of tandem cycles of melphalan and busulfan/cyclophosphamide followed by alpha interferon +/- thalidomide, and based on the positive data supporting tandem therapy in a randomized, prospective trial and in view of the encouraging, survival data in this relatively "low tumor bulk" population with responding, or stable multiple myeloma we propose to treat a larger cohort of patients with exposure to ≤ 2 prior treatment regimens with tandem high-dose therapy.

Patients will be eligible with up to ≤ 10% marrow involvement provided that they are either responding to induction therapy or have stable disease.

We will continue to incorporate cyclophosphamide both as a priming agent and to provide *in vivo* purging prior to Filgrastim priming.

In view of the known therapeutic efficacy of radiation to myelomatous bone involvement, and with the availability of a likely safer method to deliver total marrow irradiation (TMI) with the potential to escalate the total dose, we propose to replace busulfan and cyclophosphamide as the conditioning regimen for cycle 2. Since the concomitant administration of conventionally delivered fractionated total body/marrow radiation has not been more effective than, and possibly compromised delivery of full dose melphalan, total marrow irradiation as a single therapeutic modality during cycle 2 will be tested in a phase I-II setting, followed by PBPC rescue.

While the recently published data comparing tandem cycle melphalan/fractionated total body irradiation followed by melphalan seemed to yield better outcome in terms of progression-free and overall survival, with 80% of patients projected to progress by 7 years after tandem therapy, further improvements are badly needed.

3/24/10

Based on recent data presented at the American Society of Hematology meetings in 2009 describing the potential benefit of Lenalidomide maintenance following an autologous stem cell transplant procedure from multiple groups but most specifically from the US Inter-group (Mc/carthy P, et.al. Phase III Inter-group study of Lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant for multiple myeloma [CALGB 100104]: Initial report of patient accrual and adverse events. Blood ASH annual meeting abstracts, Nov 2009; 114:3416:)

In addition, bisphosphonates will be allowed to continue, or will be recommended to be administered, for a period of 2 years. However, to avoid any potential adverse interactions between bisphosphonates and thalidomide, and in view of the lasting presence of bisphosphonates in the bone, pamidronate or zoledronate will be administered at a frequency of every 3 months (39, 43).

Cytogenetic abnormalities by standard and FISH analysis to assess their role as predictors of response, monitors of residual disease and predictors of survival will be assessed. Patients' myeloma cells will be banked frozen/cell lines will be developed for future investigations of tumor biology, drug testing, and for the potential to assess efficacy of novel therapeutic agents.

3.0 THERAPEUTIC AGENTS

3.1. Cyclophosphamide

3.1.1 Mechanisms of Action: This drug is biotransformed principally in the liver to active alkylating metabolites which prevent cell division by cross linking strands of DNA and it also inhibits DNA synthesis.

3.1.2 Human Toxicity: Toxicity from cyclophosphamide includes bone marrow suppression which usually occurs ten to twelve days after administration, nausea and vomiting, reversible alopecia, hemorrhagic cystitis which can frequently be prevented with increased hydration and co-administration of MESNA, and sterility and decreased gonadal function. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration, and jaundice.

3.1.3 Pharmaceutical Data: Formulation; Cyclophosphamide is supplied in 100 mg, 200 mg, and 500 mg vials as a white powder. The drug can re reconstituted in either normal saline or D5W.

3.1.4 Administration: The drug should be dissolved in about 500 cc of D5W and it is infused IV over 2 hours. An added dose of IV fluids may help prevent bladder toxicity. Cyclophosphamide 1.5 gm/m^2 (based on actual body weight) will be administered for mobilization, prior to apheresis. There will be no correction for extremely obese patients.

8/8/07
7/17/08

3.1.4 Supplier: This drug is commercially available for purchase by the third party.

3.2 Melphalan (L-phenylalanine mustard, L-PAM, Alkeran)

3.2.1 Mode of Action: In common with other nitrogen mustards, melphalan reacts with DNA to produce either DNA-DNA or DNA-proteins cross-linked products probably by binding at the N-7 position of guanine.

3.2.2 Supply, Reconstitution and Administration: Melphalan is commercially available by Burroughs Wellcome Company in sterile vials containing 50 mg lyophilized drug as the hydrochloride salt. It is formulated with 20 mg povidone per 50 mg vial. Sterile diluent is supplied which contains per 10 ml: sodium citrate 0.20 g, propylene glycol 6 ml, ethanol (95%) 0.526 ml, sterile water q.s. 10 ml. Reconstituted vials (undiluted solutions) are stable for 90 minutes. Melphalan diluted in NS to 0.1-0.45mg/ml is stable for only 60 minutes. Melphalan is unstable when diluted with NS to 2mg/ml. The rate of infusion should be 30 minutes or less.

3.2.3 Toxicity: The dose-limiting toxicity of melphalan is myelosuppression. Other toxicities after IV melphalan include mucositis, nausea, vomiting, and diarrhea. Alopecia is generally seen only with high doses associated with bone marrow transplant settings. Rarely reported reactions include pulmonary fibrosis, skin rash, vasculitis, and allergic reactions. With high dose chemotherapy, gastrointestinal toxicity becomes dose limiting. At such high doses, elevated transaminases, syndrome of inappropriate

antidiuretic hormone secretion, depression, interstitial pneumonitis, and hepatic veno-occlusive disease have been reported. Acute nonlymphocytic leukemia and myeloproliferative syndromes may occur as secondary cancers from any alkylating agent such as melphalan. Amenorrhea, permanent in many cases, have been noted when melphalan was used in premenopausal women undergoing adjuvant therapy for breast cancer. Azoospermia would be expected, but is not well documented in the literature.

3.3 Filgrastim (r-metHuG-CSF)

3.3.1 Description

Filgrastim is a human granulocyte colony-stimulating factor (G-CSF), produced by recombinant DNA technology. NEUPOGEN® is the Amgen Inc. trademark for Filgrastim, recombinant methionyl human granulocyte colony stimulating factor (r-metHuG-CSF).

Approximately 6,400 patients in U.S. and international based trials have participated in clinical trials of Filgrastim to date, and the worldwide commercial populations receiving Filgrastim totaled approximately 190,000. The drug has been found to be well tolerated at dosages up to 60 µg/kg/day given IV or SC, with no toxic effects attributable to Filgrastim. A maximum tolerated dose has not yet been determined.

3.3.2 Contraindications

NEUPOGEN® is contraindicated in patients with known hypersensitivity to E. coli-derived proteins, Filgrastim, or any component of the product.

3.3.3 Adverse Reactions

The only consistently observed clinical toxicity described with Neupogen® is medullary bone pain. Other clinical toxicities that have been described include skin rash, and cutaneous vasculitis. Since commercial introduction of Neupogen®, there have been rare reports of allergic-type reactions. Biochemical abnormalities that may occur include increases in alkaline phosphatase, uric acid, and lactate deydrogenase.

3.3.4 Dilution and Storage

If required, NEUPOGEN® may be diluted in 5% dextrose. NEUPOGEN® diluted to concentrations between 5 and 15 mcg/mL should be protected from adsorption to plastic materials by addition of Albumin (Human) to a final concentration of 2 mg/mL. Do not dilute with saline at any time; product may precipitate.

NEUPOGEN® should be stored in the refrigerator at 2-8 degrees Centigrade (36-46 degrees Fahrenheit). Do not freeze. Avoid shaking. Prior to injection, NEUPOGEN® may be allowed to reach room temperature for a maximum of 24 hours. Any vial left at room temperature for greater than 24 hours should be discarded.

3.3.5 Supplier

Commercial NEUPOGEN® is available in 1 mL and 1.6 mL vials at a concentration of 300 mcg/mL. Discard unused portions. Use only one dose per vial; do not reenter the vial. Do not save unused drug for later administration.

3.4 Lenalidomide

Common toxicities described for lenalidomide include:

- Neurologic: Somnolence, dizziness, headache, confusion, tremor, loss of co-ordination, asthenia, paresthesia, numbness, and leukoencephalopathy (radiographic findings). 3/24/10
- Hematologic: anemia, neutropenia, leucopenia, lymphoenia and thrombocytopenia; thromboembolic events (deep vein thrombosis and pulmonary embolism).
- Gastrointestinal: Constipation, dehydration, dry mouth, diarrhea, dyspepsia, nausea, vomiting and stomatitis.
- Constitutional: Weakness, insomnia, rigors, chills, sweating, weight loss and fever.
- Reproductive: teratogenicity and miscarriage.
- Musculoskeletal: arthralgia, back/neck pain, joint pain, muscle cramp and weakness.
- Cardiac: hypotension.
- Dermatologic: rash, dry skin, itching.
- Endocrine: hypothyroidism.
- Infection.
- Pulmonary: cough, dyspnea.
- Metabolic: hypokalemia, liver damage.
- Renal: increased creatinine, renal failure.

3.5 Pregnancy reporting:

Pregnancies occurring while the subject is on lenalidomide or within four weeks after the subject's last dose of lenalidomide are considered expedited reportable

events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

The Investigator will follow the subject until completion of the pregnancy, and must report the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures report the event within 24 hours of the Investigator's knowledge of the event).

Any suspected fetal exposure to lenalidomide must be reported within 24 hours of being made aware of the event. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to lenalidomide should also be reported.

In the case of a live "normal" birth, the outcome should be reported as soon as the information is available.

Other instructions related to lenalidomide:
Only one cycle of therapy may be dispensed to the patient each month. During maintenance a max of a 28-day supply may be dispensed. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should <u>not</u> be made up. Patients taking more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately. See Appendices D (Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods) and E (Education and Counseling Guidance Document).

3.6 Total Marrow Irradiation (TMI)

3.6.1 Administration: Ionizing radiation is an established and effective method

in treating multiple myeloma. Multiple myeloma is in general a radiosensitive disease. Total marrow irradiation will be delivered using a Helical Tomotherapy HiArt System (Tomotherapy, Inc). The administration schedule and dose escalation scheme are described below.

3.6.2. Acute toxicities: Toxicities from TMI may include bone marrow suppression, alopecia, fatigue, and skin erythema. Other acute toxicities, which occur with traditional total body irradiation and may also occur with TMI (but anticipated to be of lower frequency and/or less severity) include mucositis, esophagitis, enteritis, cystitis, proctitis, pneumonitis, nausea and vomiting and sterility.

3.6.3. Potential Late Toxicities: Due to conformal avoidance of dose to normal organs, late toxicities from TMI are anticipated to be less frequent and/or severe compared with total body irradiation. Potential late toxicities may include sterility, endocrinopathies (i.e. hypothyroidism), cataract formation, pneumonitis, veno-occlusive disease, and second malignancy induction.

3.7. Pamidronate

3.7.1. Mechanism of Action: Pamidronate is an inhibitor of bone resorption and, in addition may interfere with the release, deposition of metastatic tumor deposits.

3.7.2. Toxicity: Fatigue, fever, diarrhea, nausea, arthralgias, and rarely hypocalcemia, phlebitis at the site of injection have been observed.

3.7.3. Pharmaceutical Data: Pamidronate is supplied in 30, 60, and 90 mg vials as a freeze-dried powder. Reconstitution can be done in 10 mL of sterile water, than the appropriate volume of pamidronate will be missed with normal (0.9%) saline to a total volume of 250 mL. Pamidronate will be infused over 2 hours. If the reconstituted solution is not used immediately, it can be stored at temperatures between 36-46 °F and can be used for up to 24 hours.

3.7.4. Pamidronate is commercially available.

3.8. Zoledronic Acid

3.8.1. Mechanism of Action: Zoledronic acid is an inhibitor of bone resorption and, in addition may interfere with the release, deposition of metastatic tumor deposits.

3.8.2. Toxicity: Fatigue, fever, diarrhea, nausea, arthralgias, and rarely hypocalcaemia, phlebitis at the site of injection have been observed.

3.8.3. Pharmaceutical Data: Zoledronic acid is supplied in 5 mL vials which contains 4.264 mg zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis, 220 mg of mannitol, USP, water for injection and 24 mg of sodium citrate, USP. Zoledronic acid will be infused over 15 or more minutes, in 100 mL normal saline.

3.8.4. Zoledronic acid is stored at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

3.8.5. Zoledronic acid is commercially available.

4.0 STAGING CRITERIA

4.1 Criteria for Diagnosis of Multiple Myeloma (44)

4.1.1 Major Criteria

Plasmacytomas on tissue biopsy.

Bone marrow plasmacytosis with > 30% plasma cells.

Monoclonal globulin spike on serum electrophoresis exceeding 3.5 gm% for G peaks or 2.0 gms for A peaks. ≥ 1.0 gm/24 hours of kappa or lambda light chain excretion on urine electrophoresis in the absence of amyloidosis.

4.1.2 Minor Criteria

Bone marrow plasmacytosis 10% - 30%.

4.1.3 Monoclonal globulin spike present, but less than the levels defined above.

4.1.4 Lytic bone lesions.

4.1.5 Normal lgM less than 50 mg%, lgA less than 100%, or lgG less than 600 mg%.

4.1.6 Diagnosis will be confirmed when any of the following features are documented in symptomatic patients with clearly progressive disease. The diagnosis of myeloma requires a minimum of 1 MAJOR + 1 MINOR CRITERION or 3 MINOR CRITERIA which must include a+b, i.e.:

4.1.6.1 l+b, l+c, l+d (l+a not sufficient)

4.1.6.2 ll+b, ll+c, ll+d

4.1.6.3 lll+a, lll+c, lll+d

4.1.6.4 a+b+c, a+b+d

4.1.7 The presence of certain nonspecific disease features will support the diagnosis, particularly if of recent onset.

4.1.7.1 Anemia

4.1.7.2 Hypercalcemia

4.1.7.3 Azotemia

4.1.7.4 Demineralization and compression fractures

4.1.7.5 Hypoalbuminemia

4.1.8 Great care must be taken to distinguish between active myeloma as defined above and MGUS or indolent/smoldering myeloma (see Section 4.2).

4.2 Criteria for Monoclonal Gammopathy of Undetermined Significance (MGUS), Indolent Myeloma and Smoldering Myeloma (Stage I or IIA)

4.2.1 MGUS

4.2.1.1 Monoclonal gammopathy
4.2.1.2 M-Component level

4.2.1.2.1 IgG $\leq$ 3.5 gm%

4.2.1.2.2 IgA $\leq$ 2.0 gm%

4.2.1.2.3 BJ $\leq$ 1.0 gm/24 hours

4.2.1.3 Bone marrow plasma cells < 10%

4.2.1.4 No bone lesions

4.2.1.5 No symptoms

4.2.2 Indolent Myeloma Criteria as for myeloma (see Section 4.2) except (all of the following):

4.2.2.1 No or only limited bone lesions ($\leq$ 3 lytic lesions); no compression fractures.

4.2.2.2 M-component levels

4.2.2.2.1 IgG < 7 gm%

4.2.2.2.2 IgA < 5 gm%

4.2.2.3 No symptoms or associated disease features, i.e.:

4.2.2.4 Performance status > 50%

4.2.2.4.1 Hemoglobin > 10 gm%

4.2.2.4.2 Serum calcium normal

4.2.2.4.3 Serum creatinine < 2.0 mg%

4.2.2.4.4 No infections

4.2.3 Smoldering Myeloma Criteria as for indolent myeloma except:

4.2.3.1 NO bone lesions

4.2.3.2 Bone marrow plasma cells ≤ 30%

4.3 Assessment of Tumor Mass

4.3.1 High Tumor Mass (Stage III) - One of the following abnormalities must be present:

4.3.1.1 Hemoglobin < 8.5 gm%, hematocrit < 25 vol.%, or

4.3.1.2 Serum calcium > 12 mg%, or

4.3.1.3 Very high serum or urine myeloma protein production rates:

4.3.1.3.1 IgG peak > 7 gm%

4.3.1.3.2 IgA peak > 5 gm%

4.3.1.3.3 Bence Jones protein > 12 gm/day (24 hours), or

4.3.1.3.4 > 3 lytic bone lesions on bone survey (bone scan not acceptable)

4.3.2 Low Tumor Mass (Stage I) ALL of the following must be present:

4.3.2.1 Hemoglobin > 10.5 gm% or hematocrit > 32 vol.%

4.3.2.2 Serum calcium normal

4.3.2.3 Low serum myeloma protein production rates:

4.3.2.3.1 IgG peak < 5 mg%

4.3.2.3.2 IgA peak < 3 gm%

4.3.2.3.3 Bence Jones protein < 4 gm/day (24 hours)

4.3.2.3.4 Bone lesions scaled 0 (none) or 1 (osteoporosis)

4.3.3 Intermediate Tumor Mass (Stage II)

All other patients who do not qualify specifically for high or low tumor mass categories are considered to have intermediate tumor mass.

4.4 Assessment of Renal Status

4.4.1 A = Good Renal Function (creatinine $\leq$ 2.0 mg%)

4.4.2 B = Poor Renal Function (creatinine > 2.0 mg%)

4.5 Assessment of Myeloma Cell Mass

		STAGE III High	STAGE I Low	STAGE II Intermediate
Cell Mass Category # of myeloma cells Requirements		> 1.2 x $10^{12}/m^2$ One of: A,B,C,D	< 0.6 x $10^{12}/m^2$ All of: A,B,C,D	0.6-1.2 x $10^2/m^2$ Neither High or Low
Hemoglobin (gm%) (pretransfusion)	A	< 8.5	> 10.5	$\geq$ 8.5
Serum calcium (mg%)	B	> 12	Normal	$\leq$ 12
M-Component	C	IgG > 7 gm% IgA > 5 gm% BJ > 12 gm/day	< 5 < 3 < 4	$\leq$ 7 $\leq$ 5 $\leq$ 12
Bone lesions (on skeletal survey only; bone scan not acceptable)	D	Scaled 3 (> 3 lytic lesions)	scaled 0 or 1 (no lesions or osteoporosis only)	Scaled 0, 1, or 2

NOTE: The staging of patients with IgD or IgE monoclonal spikes is based upon other (non M-component) criteria.

5.0 PATIENT ELIGIBILITY

5.1 Patients with multiple myeloma (stages I-III) will be eligible if they are either in response, or have stable disease. 2/7/05

5.2 Patients with smoldering myeloma are eligible if there is evidence of progressive disease requiring therapy ($\geq$ 25% increase in M protein levels or Bence Jones excretion; Hgb $\leq$ 10.5 g/dl; frequent infections; hypercalcemia; rise in serum creatinine above normal on two separate occasion)

5.3 Patients with non-quantifiable monoclonal proteins are eligible provided they meet other criteria for multiple myeloma, or smoldering myeloma, and they have evaluable or measurable disease by other (radiographic) means.

5.4 Unlimited prior chemotherapy regimens allowed. 2/7/05

5.5 KPS $\geq$ 70%

5.6 Patients with Waldenstrom's macroglobulinemia are not eligible.

5.7 Less than 18 months since diagnosis. 2/7/05

5.8 Patients must be $\leq$ 70 years old at the time of enrollment. 2/7/05

5.9 No contraindication to the collection of a minimum of 4 x 10^6 CD34+ cells/kg by apheresis.

5.10 All patients must have signed a voluntary, informed consent in accordance with institutional and federal guidelines.

5.11 Adequate hepatic function as demonstrated by bilirubin, $\leq$ 1.5 mg/dl, and SGOT and SGPT < 2.5 x upper limits of normal.

5.12 Adequate renal function as demonstrated by: creatinine of measured or calculated creatinine clearance of $\geq$ 50 cc/min.

5.13 Absolute neutrophil count of > 1000/µl, platelet count of > 100,000/µl.

5.14 Cardiac ejection fraction $\geq$ 50% by MUGA scan and/or by echocardiogram.

5.15 Adequate pulmonary function as demonstrated by FEV1 > 60% and DLCO > 50% of predicted lower limit.

5.16 Hepatitis B antigen, Hepatitis C RNA and HIV antibody tests negative.

5.17 No other medical, or psychosocial problems, which in the opinion of the primary physician or principal investigator would place the patient at unacceptably high risk from this treatment regimen.

5.18 Females of reproductive age not using adequate birth control measures/ or who are pregnant are not eligible.

5.19 History of other malignancies within the last 3 years, as long as patients have remained in complete remission for at least 2 years, except for non-melanoma skin cancer and in situ carcinoma of the cervix.

5.20 Patients should have finished their prior chemotherapy at least 14 days prior to cyclophosphamide priming, and should have received their last dose of thalidomide, dexamethasone, or bisphosphonate ≥10 days prior to cyclophosphamide priming. 7/18/05 10/20/05

5.21 Pre-treatment tests must have been performed within 6 weeks prior to initiation of cyclophosphamide. A CBC, platelet count and comprehensive chemistry panel should be performed within 1 week prior to initiating cyclophosphamide priming. 2/14/06

5.22 Known hypersensitivity to Filgrastim or to E. coli derived proteins is an exclusion.

5.23 Inability to lie supine in a full body cast for approximately 30 minutes, the anticipated duration of each treatment session, is an exclusion.

5.24 Previous radiation therapy to more than 20% of bone marrow containing areas, or to any area exceeding 2000 cGy, is an exclusion.

5.25 Patients must be fully aware of the teratogenic potential of thalidomide and agree to fully comply with the mandated guidelines regarding contraception as stated in the informed consent and the patient warning document attached to the consent form. Women of childbearing potential must have a negative pregnancy test performed within 24 hours prior to beginning thalidomide, except for woman who have been postmenopausal for at least 2 years, or underwent hysterectomy. Use of effective means of contraceptive should be started at least 2 weeks prior to initiating thalidomide.

6.0 TREATMENT PLAN

6.1 Pre-treatment Evaluation

6.1.1 History and physical examination.

6.1.2 Radiographic evaluation: MRI of the entire spine and pelvis and skeletal survey will be performed.

6.1.3 Chest X-ray.

6.1.4 Pulmonary function tests

6.1.5 MUGA scan or echocardiogram.

6.1.6 CBC, differential count, platelet count, PT, PTT, SMA 18, Mg.

6.1.7 Urine analysis.

6.1.8 24-urine collection for total protein, protein electrophoresis, immune electrophoresis, and creatinine clearance.

6.1.9 Hepatitis panel, HIV antibody, HSV and CMV antibody.

6.1.10 Unilateral bone marrow biopsy and aspirate for morphology, cytogenetics/FISH. Aspirate for HUMARA (females only).

6.1.11 Peripheral blood for FISH (including clonal hematopoiesis markers), gene rearrangement, and for lymphocyte subset analysis.

6.1.12 Serum protein electrophoresis, quantitative serum immunoglobulins, serum immunofixation electrophoresis

6.1.13 Beta-2 Microglobulin level.

6.1.14 Urine pregnancy test.

6.1.15 HLA, ABO and Rh typing.

6.1.16 Double lumen Hickman catheter will be placed ($\geq$ 12 French catheter).

6.2 Patient Registration

After all pre-treatment evaluations have been performed patients can be entered on study. Eligibility requirements must be reviewed by a member of the department of Biostatistics and the principal investigator. Patients may be screened for eligibility by calling the Department of Biostatistics at extension 62468.

6.3 Harvesting and Cryopreservation of Stem Cells

Cyclophosphamide 1.5 gm/m^2 (based on actual body weight) will be administered with 500 cc D5/W over 2 hours. Filgrastim 10 µg/kg (based on actual body weight) daily, sq or iv will be administered starting 24 hours after cyclophosphamide and continue through the completion of apheresis (total daily Filgrastim dose equals 10 µg/kg/day).

Beginning day 10, provided that the peripheral blood white cell count is > 1000/µL and rising**,** apheresis will commence and continue until a minimum of 4 x 10^6 CD34+ cells/kg are collected. For patients with good CD34+ cell yields

during apheresis (once the minimum CD34+ requirements are secured), a target of $\geq 10 \times 10^6$ will be set and no more than 10 apheresis are recommended.

Filgrastim will continue to be given daily; Filgrastim dose will be held if the total white cell count is $\geq 80{,}000/\mu l$. If the yield from the first 3 days of apheresis is $< 1 \times 10^6$/kg, the dose of Filgrastim will be increased to 10 µg/kg, bid.

The collections will last 4 hours, or until a volume of 12 liters has been processed. Peripheral stem cells will be processed and cryopreserved following standard methods at the City of Hope National Medical Center.

Patient who have already undergone mobilization and blood stem cell collection prior to signing this consent form, their physician will make a judgment to decide whether the quantity and quality of those previously collected blood stem cells is sufficient enough to proceed with the proposed treatment or alternatively, may have to undergo additional stem cell mobilization and leukopheresis. 3/19/08

6.4 High-Dose Chemotherapy

Cycle 1: Melphalan

DAY –2

Admission, history and physical, SMA 18, Mg, CBC, differential , VRF evaluation, and PLT count, urine analysis. Review of required laboratory, screening and radiographic data, signing of consent form. 7/18/05

Prophylactic IV, or p.o. fluconazole at 400 mg daily will be given to patients with AGC < 1000/µl. 8/8/07

Intravenous hydration with normal saline at 200 cc/hr and KCL 15 MeQ/1 will be started. After 6 hours of hydration melphalan 100 mg/m^2 will be infused in # 30min. IV hydration will continue with normal saline at a rate of 200 cc/hr and KCL 15 MeQ/l for a total of at least 24 hours.

Appropriate intravenous antiemetics will be given.

When calculating chemotherapeutic dose, ideal body weight will be used.

DAY –1

Melphalan 100 mg/m^2 will be infused in # 30min. IV hydration will continue with normal saline at a rate of 200 cc/hr and KCL 15 MeQ/l for a total of at least 24 hours.

DAY 0

Half of the previously collected CD34+ cells will be reinfused.
DAY +5

Filgrastim 5 µg/kg daily, IV, or SQ will be started. Continue with Filgrastim until AGC > 1000/µl for 3 consecutive days

Prophylactic IV, or p.o. fluconazole at 400 mg daily will be given to patients with AGC < 1000/µl. 7/18/05 8/8/07

Patients will be supported through iv hydration and red cell and platelet transfusions as needed. CBC, PLT and SMA7, SMA 12, and Mg and weekly chest x-ray as well as the necessary fever workup will be done. Patients can be followed as outpatients unless they develop neutropenic fever, uncontrollable diarrhea or other problems requiring inpatient care. All blood products will be filtered and radiated.

Cycle 2:

Total marrow radiation will start a minimum of 6 weeks and a maximum 18 weeks from day 0 of cycle number 1. 2/7/05

DAY -6 7/18/05

Admission to either outpatient, or inpatient unit, history and physical, SMA18, Mg, CBC, differential and PLT count, urine analysis, and VRE evaluation. Review of required laboratory, screening and radiographic data, check for signing of consent form. 7/18/05

~~DAY -5~~	~~200 cGy/D to 200 cGy BID~~
DAY -4	200 cGy/D to 200 cGy BID 03-19-08
DAY -3	200 cGy/D to 200 cGy BID 7/18/05
DAY -2	200 cGy/D to 200 cGy BID
DAY -1	200 cGy/D to 200 cGy BID

TMI doses to previously irradiated regions will be limited to a total dose of no more than 1600 cGy.

Prophylactic IV, or p.o. fluconazole at 400 mg daily will be given to patients with AGC < 1000/µl. 7/18/05 8/8/07

DAY 0

Filgrastim

Half of the previously collected CD34+ cells will be reinfused and 5 µg/kg daily, IV, or SQ will be started. Continue with hydration as needed. Continue with Filgrastim until AGC > 1000/µl for 3 consecutive days.

Patients will be supported through iv hydration and TPN, red cell and platelet transfusions as needed. Daily CBC, PLT and SMA7, every Monday, Wednesday, Friday SMA 18, and Mg and weekly chest x-ray, biweekly PT, PTT as well as the necessary fever workup will be done. Patients can be followed in the outpatient unit unless they develop neutropenic fever, uncontrollable diarrhea or other problems requiring inpatient care. All blood products will be filtered and radiated according to standards at the COH.

Maintenance Therapy

Starting no sooner than 30 days from day 0 of the second cycle (TMI), Lenalidomide 10 mg/d will be initiated daily for 3 months, and should the patient tolerate this dosing, the dose will be escalated to 15 mg/d for a total duration of 3 years unless the patient cannot tolerate this medication or his or her disease progression. (See section 6.5.2 for dose modifications.) 2/14/0

Aredia 90 mg iv every 12 weeks, or zoledronic acid 4 mg IV every 12weeks will be administered and will be continued for 36 months.

6.5 Dose Adjustments

6.5.1 Melphalan

There will be no dose adjustments for melphalan

Pre-cycle 2 requirements should be met prior to initiating the second cycle.

6.5.2 Lenalidomide

Dose Modifications – In the instance of more than one observed toxicity, the greatest dose reduction should be applied

Hematologic Dose Modification Months 1-3

- **If on 2 capsules per day,** the ANC is < 500/µL or the platelet count is <30,000/µL, then the study drug may be held for up to 8 weeks. Study drug may be re-instituted at 1 capsule per day if ANC is ≥ 500/µL or the platelet count is under ≥ 30,000/µL. If, however, after an 8 week treatment

delay, the ANC remains < 500/μL or the platelet count < 30,000/μL, the patient will be removed from protocol therapy.

- **If on 1 capsule per day**, the ANC is < 500/μL or the platelet count is < 30,000/μL, then the study drug may be held for up to 8 weeks. If ANC ≥ 500/μL or the platelet count is ≥ 30,000/μL, then study drug may be re-instituted at 1 capsule per day for 21 of 28 days. If, however, after an 8 week treatment delay, the ANC remains < 500/μL or the platelet count < 30,000/μL, the patient will be removed from protocol therapy.
- **If on 1 capsule per day** for 21 of 28 days, the ANC is < 500/μL or the platelet count is < 30,000/μL, then the patient will be removed from protocol therapy.

Hematologic Dose Modification beyond Month 3

- **If on 3 capsules per day**, the ANC is < 500/μL, then the study drug may e held for up to 8 weeks. Study drug may be re-instituted at 2 capsules per day if ANC is ≥ 500/μL or platelet count is ≥ 30,000/μL. If, however, after an 8 week treatment delay, the ANC remains < 500/μL or platelet count < 30,000/μL, the patient will be removed from protocol therapy.
- **If on 2 capsules per day,** the ANC is < 500/μL or the platelet count is < 30,000/μL, then the study drug may be held for up to 8 weeks. If ANC is ≥ 500/μL or the platelet count is ≥ 30,000, then study drug may be re-instituted at 1 capsule per day. If, however, after an 8 week treatment delay, the ANC remains < 500/μL or the platelet count < 30,000/μL, the patient will be removed from protocol therapy.
- **If on 1 capsule per day**, the ANC is < 500/μLor the platelet count is < 30,000/μL, then the study drug may be held for up to 8 weeks. If ANC ≥ 500/μL or the platelet count is ≥ 30,000/μL, then study drug may be re-instituted at 1 capsule per day for 21 of 28 days. If, however, after an 8 week treatment delay, the ANC remains < 500/μL or the platelet count < 30,000/μL, the patient will be removed from protocol therapy.
- **If on 1 capsule per day** for 21 of 28 days, the ANC is < 500/μL or the platelet cunt is < 30,000/μL, then the patient will be removed from protocol therapy.

Dose Escalation beyond Month 3

If a dose reduction has occurred and ANC ≥ 1000/μL and platelet count is ≥ 75.000/μL, the study drug dose may be re-escalated by one level (i.e., one capsule every day to two capsules every day, etc.). Hematologic parameters must remain at these threshold values for one month before another dose escalation may occur. Maximum study drug dose will be 3 capsules per day.

If for any reason, a patient is not able to be dose escalated, dose escalation should be attempted by the time of the next re-staging. If at next restaging,

the patient has not recurred or progressed, and the patient is not able to be dose escalated, patient may continue on treatment at current dose level.
If for any reason the drug is held for a non-grade 3 hematologic toxicity, the drug will be held until the toxicity resolves and the drug started at one dose level lower. The drug should be re-escalated to the original dose within 4 weeks. The drug should be escalated as per the criteria listed above.

Non-Hematologic Toxicity Dose Modifications

Neurologic Toxicity

- **If on 3 capsules per day**, a patient experiences ≥ grade 3 neurologic toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 2 capsules per day. If, however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.
- **If on 2 capsules per day**, a patient experiences ≥ grade 3 neurologic toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 1 capsule per day. If, however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.
- **If on 1 capsule per day**, a patient experiences ≥ grade 3 neurologic toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 1 capsule per day for 21 of 28 days. If, however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.
- **If on 1 capsule per day** for 21 of 28 days, a patient experiences ≥ grade 3 neurologic toxicity, then the patient will be removed from protocol therapy.

Cardiac Toxicity

- **If on 3 capsules per day,** a patient experiences ≥ grade 2 cardiac toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 2 capsules per day. If, however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.
- **If on 2 capsules per day,** a patient experiences > grade 2 cardiac toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 1 capsule per day. If, however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.

- **If on one capsule per day,** a patient experiences > grade 2 cardiac toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 1 capsule per day for 21 of 28 days. If, however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.
- **If on one capsule per day for 21 of 28 days,** a patient experiences ≥ grade 1 cardiac toxicity, then the patient will be removed from protocol therapy.

Other Non-Hematologic Toxicity

- For other grade 3 non-hematologic toxicity, hold CC-5013 until toxicity resolves to ≤ grade 2, then the study drug should be resumed at the next lower close level.
- For patients who develop grade ≤ non-hematologic toxicity, an attempt will be made to maintain the patient at that dose level. If the patient cannot tolerate this dose level, the treating physician should decrease the dose to the next lower dose level.
- For other grade 4 non-hematologic toxicity, discontinue study drug and contact the Study Chair or Co-Chair.

In the event of any grade 1 or 2 toxicity that the patient finds intolerable, the study drug may be held until the toxicity resolves and the study drug resumed at the next lower dose level. Alternatively, the study drug may be continued at the next lower dose level without cessation of study drug. However, study drug should be held for the occurrence of a resh consistent with evolving Stevens-Johnson syndrome or toxic epidermal necrolysis (bullous, blistering that is purpuric in nature) until appropriate evaluation is made. Study drug may be held for up to 8 weeks. Contact the Study Chair or Co-Chair for consultation.

Venous Thrombosis

Patients who develop signs of symptoms suggestive of thrombosis should be evaluated and treated as clinically indicated. CC-5013 should be held for patients with venous thrombosis CC-5013 may resume when patient is adequately anticoagulated. Patients with recurrent thrombosis despite adequate anticoagulation should ge removed from protocol therapy.

Renal Toxicity

- For creatinine clearance (CrCI) < 30 mL/min skip Lenalidomide and reassess in four weeks. If CrCI remains < 30 Ml/min after four weeks, then discontinue Lenalidomide.
- For CRCI < 60 mL/min but ≥ 30 mL/min:
    - **If on 3 capsules per day,** decrease Lenalidomide to 1 capsule alternating with 2 capsules daily (1 capsule on day, followed by 2

capsules the next day…etc.). Reassess after four weeks and attempt to re-escalate Lenalidomide.

- **If on 2 capsules per day,** decrease Lenalidomide to 1 capsule per day. Reassess after four weeks and attempt to re-escalate Lenalidomide.
- **If on 1 capsule per day,** decrease Lenalidomide to 1 capsule per day for 21 of 28 days. Reassess after four weeks and attempt to re-escalate Lenalidomide.

6.5.4 Pamidronate or zoledronic acid

There will be no dose adjustments. Pamidronate or zoledronate can be premedicated with a non-steroidal anti-inflammatory agent, or with acetaminophen, if fever or constitutional symptoms occur following administration.

7.0 EVALUATION AND TOXICITIES

Physical evaluation, laboratory and radiographic evaluation will be performed as outlined below. When evaluating toxicity CTCAE version 3 will be used.

7.1. Patients will be examined and graded by the treating physician for subjective and objective evidence of toxicities according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE), which can be found at: <http://ctep.cancer.gov/reporting/ctc.html> daily during both the first and second treatment cycle through recovery, monthly for the first year and then yearly for the first three years.

7.2 Dose Limiting Toxicity (DLT):

Dose Limiting Toxicity (DLT) will be based on toxicities observed following the second cycle: TMI followed by PBPC

Toxicity grading will be based on the NCI CTCAE version 3.0 which can be found at http://ctep.cancer.gov/reporting/ctc.html.

To be fully treated and fully followed for toxicity, a patient must receive both cycles of the tandem transplant (cycle 1: melphalan, followed by cycle 2: TMI) at the planned doses and be observed for at least 4 weeks after the start TMI, or have experienced DLT following the second cycle. All patients who are not fully treated and fully followed for toxicity will be replaced before dose escalation is permitted.

Toxicity will be graded according to the NCI common toxicity criteria (CTCAE v3.0). Dose limiting toxicity (DLT) in a given patient is defined as:

7.2.1 Any Grade 3, non-hematologic unexpected toxicity (not reversible to 2/14/06

grade 2 or less within one week from the onset).

7.2.2 Grade 4 thrombocytopenia, if it lasts beyond 28 days

7.2.3 Grade 4 neutropenia associated with fever or infection and lasting beyond three weeks, or grade 4 neutropenia lasting for more than 28 days.

7.2.4 The following will **not** be considered DLT:

7.2.4.1 ≥ Grade 3 nausea or ≥ Grade 3 vomiting that occurs following non-compliance with protocol prescribed antiemetic therapy

7.2.4.2 ≥ Grade 3 diarrhea that occurs following non-compliance with protocol prescribed therapy

7.1.5.3 any Grade 3 fatigue

7.3 Dose Escalation Rules:

A Phase I Tracking log will be completed and kept by the Clinical Research Associate (CRA) and the Statistician from the Department of Biostatistics.

Rules for dose escalation and expansion in cohorts of patients are based on DLT occurring following each patient's second transplant in the tandem. Patients who drop out prior to the second cycle will be considered inevaluable. Three patients will be treated at each new dose level. If 0/3 patients experience DLT attributable to the study treatment, 3 patients will be treated at the next dose level. If DLT attributable to the treatment (i.e. definitely, probably, or possibly attributed) is experienced in exactly 1/3 of patients, 3 more patients (for a total of 6) will be treated at that dose level. If no additional DLT, attributable to the treatment, is observed at the expanded dose level (i.e. 1/6 with DLT), the dose will be escalated. Escalation will terminate as soon as two or more patients experience any DLT attributable to the study treatment, at a given dose level or a treatment related death is observed following the 2^{nd} cycle. The Phase I trial will be closed when 6 patients have been treated at the next lower dose level, and at most 1/6 patients experience DLT. If more than 1/6 patients experience DLT, the next lower dose will be expanded.

Once the MTD has been determined, additional accrual at the MTD will commence, beginning the phase II portion of the study (the initial 6 patients treated at the MTD during the dose escalation will be counted in the phase II portion).

8.0 STUDY PARAMETERS

	Within 6 Wks Pre-Cytoxan	Pre-Cycle 1	Cycle 1	Pre-Cycle 2	Cycle 2	30 days**	Q 6 mos#	Q yr+	
History and Physical	X	X		X	X	X	X#**	X	2/7/05
CBC, DIFF, PLT/SMA7	X^	X	Daily	X	Daily	X	X#**	X	2/7/05
SMA 18, MG^{++}	X^	X	M,W,F	X	M,W,F	X	X#**	X	2/7/05
PT, PTT	X	X		X	QO Week			X	
Urinalysis, Creat Clearance	X			X					
Chest X-ray	X		Q Week	X	Q Week				
MRI of axial skeleton or PET scan as clinically indicated by bone x-rays	X						X **	X	
SPEP, IEP, Beta-2 Microglobulin	X			X		X‡	X#**	X	2/7/05
24 hr urine for PEP, IEP, total protein, creatinine clearance	X			X		X‡	X#**	X	2/7/05
MUGA Scan/ or echo	X			X				X **	
VRE Evaluation (by Swab or Stool		X			X				7/18/05
EKG	X			X				X **	
PFT	X								
AB, RH, HLA Typing	X								
BM, ASP, BX, morphology, cytogenetics, FISH, clonal hematopoiesis, (two cyto tubes and three green tops) vascular density establishing cell lines-	X			X		X‡	X#**	X	2/7/05 7/18/05 2/14/06 8/8/07
Blood for Cytogenetics,FISH and clonal hematopoiesis (Humara- two green tops)	X						X#**	X	2/7/05 2/14/06

	Within 6 Wks Pre-Cytoxan	Pre-Cycle 1	Cycle 1	Pre-Cycle 2	Cycle 2	30 days**	Q 6 mos#	Q yr+
PBPC product for cytogenetics, FISH clonal hematopoiesis two cytogenetic tubes.		X						
Urine Pregnancy Test (For female patients)	X							
HIV, Hepatitis Panel to include A,B,C; Herpes and CMV Titer	X							

2/7/05 2/14/06 7/18/05

#Counting from day 0 of cycle 2 only during the first year.
* (pre-Lenalidomide) and 4 months from day 0 of cycle 1;
**During the first year if the MRI/PET scans are positive pre-study initiation and/or as clinically indicated;
‡ At 30 days from day 0 of cycle 2
2/7/05 ^ within a week prior to cyclophosphamide priming

9.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

The following definitions will be used for this study. Response can be defined as a 50% or better reduction in serum myeloma protein production and further categorized as completed and partial.

9.1 Response Gradations:

9.1.1 Complete response: Defined as the absence of bone marrow or blood findings of multiple myeloma on at least 2 measurements at a minimum of a 6 week interval. Thus all evidence of serum and urinary M-components must disappear on electrophoresis as well as by immunofixation studies. The follow-up bone marrow may not contain more than 5% plasma cells on aspiration or core biopsy and no evidence of increasing anemia. Skeletal X-rays must either show recalcification or no change in osteolytic lesions. Resolution of soft tissue plasmocytomas.

9.1.2 Partial Response: Sustained decrease of the monoclonal serum protein by $\geq$ 50% reduction) on at least two measurements of at least 6 week interval. A response is clear-cut for patients who achieve a 75% or greater reduction in the serum myeloma protein concentration without evidence of increasing anemia. Responding patients must also have a sustained decrease in 24-hour urine M-component to less of the initial prestudy value, and to less than 0.2 gm/day on at least two measurements at three-week intervals. For a response to be confirmed, a marked reduction in both serum myeloma protein and in Bence-Jones protein excretion must be present. Bone marrow plasma cells should be reduced by at least 50% from the pretreatment level, and soft tissue plasmocytomas should be reduced by $\geq$ 50%.

Very Good Partial Response: Defined as reduction of bone marrow or blood findings of multiple myeloma on at least 2 measurements at a minimum of a 6 week interval By ≥ 90%

9.1.3 In all complete, and responding patients, the size and number of lytic skeletal lesions must not increase, and the serum calcium must remain normal. Any of the following ancillary data will support the conclusion that an objective response has occurred, but are not required to confirm response: 1) recalcification of lytic skull or pelvis lesions (occurs in about 20% of responding patients with lytic lesions); 2) significant increase in depressed normal immunoglobulins, as in lgM increments exceeding 20 mg%, lgA exceeding 40 mg%, and lgG exceeding 400 mg% (occurs in about 15% of responding patients); 3) fall in the level of the serum beta-2 microglobulin to the normal range (less than 1.0 mg/dl).

9.2 Minor response: Patients with 25 - 49% tumor mass regression without new symptoms or signs of myeloma with declines in the serum myeloma protein production of 25% to 49% , or 50-89% reduction in 24 hour urinary light chain excretion, which still exceeds 200 mg/24 hours, and maintained for a minimum of 6 weeks.

9.3 Stable disease: Is defined as a lack of progression (change of ≤ 25% myeloma protein) for a minimum duration of 3 months.

9.4 Progression: Any of the following: patients with a > 25% increase in myeloma protein production and confirmed at least once on repeated examination within 2-4 weeks, or other signs of disease such as hypercalcemia > 11.5 mg/dL, or new bone/plasmocytoma lesions. >25% increase in bone marrow biopsy of plasma cells, with a minimum of 10% involvement.

9.5 Relapse: This is defined by the unequivocal objective evidence and constitutes the earliest of any of the following: 1) an increase by more than 100% from the lowest level of the serum myeloma protein production; 2) an increase above the response level of the myeloma peak (i.e., relapse to more than 25% of the baseline myeloma protein production); 3) reappearance of the myeloma peaks that had disappeared with the treatment; 4) definite increase in the size and number of lytic bone lesions recognized on radiographs; 5) Newly developed soft tissue plasmocytoma; 6) >25% increase in bone marrow biopsy of plasma cells, with a minimum of 10% involvement. Compression fractures per se do not constitute a relapse.

9.6 Performance Status: Karnofsky Performance status will be recorded.

10.0 REPORTING DATA

All primary data will be maintained by the Department of Biostatistics, City of Hope National Medical Center. This includes on study flow sheets, consent forms and off-study forms.

11.0 STATISTICAL CONSIDERATIONS

11.1 STUDY DESIGN FOR THE PHASE I PART OF STUDY AND RULES FOR DOSE ESCALATION

Rules for dose escalation, dose expansion, and termination of escalation are given below.

For each patient, the enrollment, course initiation, dose, and adverse event data must be submitted on case report forms within two weeks of the end of the first course, as these data will form the basis for dose escalation decisions. No additional patients may be enrolled at an escalated dose until all patients from the current dose level have been fully followed, and their data collection forms have been received and the escalation has been approved by the PI and study coordinator.

11.2 Dose Limiting Toxicity (DLT) will be based on toxicities observed following the second cycle: TMI followed by PBPC

Toxicity grading will be based on the NCI CTCAE version 3.0.

To be fully treated and fully followed for toxicity, a patient must receive both cycles of the tandem transplant (cycle 1:melphalan, followed by cycle 2:TMI) at the planned doses and be observed for at least 4 weeks after the start TMI, or have experienced DLT following the second cycle. All patients who are not fully treated and fully followed for toxicity will be replaced before dose escalation is permitted.

Toxicity will be graded according to the NCI common toxicity criteria (CTCAE v3.0). Dose limiting toxicity (DLT) in a given patient is defined as:

11.2.1 Any Grade 3, non-hematologic unexpected toxicity (not reversible to grade 2 or less within one week from the onset). 7/12/06

11.2.2 Any Grade 4 non-hematologic toxicity

11.2.3 Grade 4 thrombocytopenia, if it lasts beyond 28 days

11.2.4 Grade 4 neutropenia associated with fever or infection and lasting beyond three weeks, or grade 4 neutropenia lasting for more than 28 days.

11.2.5 The following will **not** be considered DLT:

11.2.5.1 ≥ Grade 3 nausea or ≥ Grade 3 vomiting that occurs following non-compliance with protocol prescribed antiemetic therapy

11.2.5.2 ≥ Grade 3 diarrhea that occurs following non-compliance with protocol prescribed therapy

11.2.5.3 any Grade 3 fatigue

11.3 Maximum Tolerated Dose (MTD)

The maximum tolerated dose (MTD) is defined as the highest dose tested in which there is no treatment related mortality and none or only one patient experienced DLT attributable to the study drug(s), when at least six patients were fully treated at that dose and fully followed for toxicity. The MTD is one dose level below the lowest dose tested in which 2 or more patients experienced DLT attributable to the treatment or there was a treatment related death. At least 6 patients will be treated at the MTD.

11.4 Dose Escalation Schedule

The dose of melphalan is fixed. The dose of the helical radiation will follow the dose escalation according to the schedule given below.

Level	Day 1 (cGy)	Day 2 (cGy)	Day 3 (cGy)	Day 4 (cGy)	Day 5 (cGy)	Total Dose (cGy)
1	200	200	200	200	200	**1000**
2	200 AM 200 PM	200	200	200	200	**1200**
3	200 AM 200 PM	200 AM 200 PM	200	200	200	**1400**
4	200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	200	200	**1600**
5	200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	200	**1800**
6	200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	200 AM 200 PM	**2000**

If at any time during the dose escalation part of this study, a treatment related mortality is observed, that dose level will be closed and the dose below will either be declared the MTD or further patients will be accrued at that lower dose level if less than 6 evaluable patients have been accrued to that level.

11.5 Numbers of Patients and Rules for Dose Escalation

Rules for dose escalation and expansion in cohorts of patients are based on DLT

occurring following each patient's second transplant in the tandem. Patients who drop out prior to the second cycle will be considered inevaluable. Three patients will be treated at each new dose level. If 0/3 patients experience DLT attributable to the study treatment, 3 patients will be treated at the next dose level. If DLT attributable to the treatment (i.e. definitely, probably, or possibly attributed) is experienced in exactly 1/3 of patients, 3 more patients (for a total of 6) will be treated at that dose level. If no additional DLT, attributable to the treatment, is observed at the expanded dose level (i.e. 1/6 with DLT), the dose will be escalated. Escalation will terminate as soon as two or more patients experience any DLT attributable to the study treatment, at a given dose level or a treatment related death is observed following the 2nd cycle. The Phase I trial will be closed when 6 patients have been treated at the next lower dose level, and at most 1/6 patients experience DLT. If more than 1/6 patients experience DLT, the next lower dose will be expanded.

Once the MTD has been determined, additional accrual at the MTD will commence, beginning the phase II portion of the study (the initial 6 patients treated at the MTD during the dose escalation will be counted in the phase II portion).

11.6 This is a Phase I/II study of tandem high-dose therapy consisting of melphalan (cycle 1) and then TMI (cycle 2) for patients with multiple myeloma. During the dose escalation, the melphalan dose will be held constant, and the radiation dose will be escalated to find the maximum tolerated dose, which will also be deemed the recommended dose.

11.7 This study is expected to accrue a minimum of 31 evaluable patients, with an expected accrual of 53-75 patients. The study should be completed by early 2013 the latest with a projected minimum yearly accrual of 6 patients per year.

11.8 Analysis of Clinical Endpoints of Phase I portion: The design of the Phase I portion of the trial is described above, together with the definition DLT, and MTD.

The toxicities observed at each dose level will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI Common Toxicity Criteria (version 3) and nadir or maximum values for the laboratory measures), time of onset (i.e. course number), duration, and reversibility or outcome. Tables will be created to summarize these toxicities and side effects by dose and by course. Baseline information (e.g. the extent of prior therapy) and demographic information will be presented, as well, to describe the patients treated in this study. All responses will be reported. Survival and time to failure will be summarized both by pooling across dose levels and by dose level, although the primary outcome of the phase II portion will include only the patients accrued at the MTD.

11.9 Study design and sample-size for Phase II portion of study:

11.9.1 Sample-size for Phase II portion: For the purpose of this analysis the rate response is defined as sum of a near CR (Very Good Partial Response) or a CR as described in the response criteria. To estimate the response rate a two stage minimax design suggested by Simon will be used [ref 2]. It is assumed that a true response rate less than 50% would not warrant further study of this regimen. It is also assumed that a response rate of 68% would be considered promising for further studies. In the first stage, 28 evaluable patients will be entered. If less than 14 responses are observed, the accrual will stop with the conclusion that the regimen is not promising for further study. If 15 or more responses are observed in the first 28 patients, an additional 22 patients will be accrued during the second stage of the phase II accrual. 30 or more responses out of 50 patients will be considered as evidence warranting further study of the regimen providing other factors, such as toxicity and survival, also appear favorable. If less than 30 responses out of 50 patients are observed, further study of the regimen would not be warranted. The probability of falsely declaring an agent with a 50% response probability as warranting further study is 0.1 (alpha) and the probability of correctly declaring an agent with a 68% response probability as warranting further study is 90% (power). As evaluation of response takes several months, it is likely that accrual will exceed the interim stopping point prior to being able to evaluate the first 28 patients. If that is the case, curtailed sampling will be employed two months after the first 28 patients have been treated to estimate the probability of passing the required threshold. If the probability of failing to meet the required threshold exceeds 50% under the promising response rate assumption, accrual will cease until additional follow-up is obtained on the 28 patients (up to 6 months may be required for a confirmation of a response). With 50 patients the true probability of response can be estimated with a maximum standard error equal to 7%.

11.9.2 Accrual to the Phase II portion: Based on the current referral patterns to the City of Hope, it was expected that approximately 20 patients per year will be eligible for this study. With a goal of 50 patients treated at the MTD. The protocol will need to remain open through 2013. As the majority of relapses are expected to occur within 3 years, and it will take approximately 1 year to find the MTD, this study will continue to allow for sufficient follow-up for the secondary goal of analyzing disease progression and survival.

11.9.3 Early Stopping Rules:

Number of Patients Accrued at MTD	Number of treatment-related deaths Permitted
20	<2
30	<3
40	<3

11.9.4 Specifically, if there are 2 treatment related deaths in the first 20 patients, the study will be stopped. If there are 3 treatment related deaths in the first 40 patients, the study will be stopped. Due to the follow-up time, if there are two treatment related deaths in the first 20 patients, but the treatment related deaths occur when there are a total of 30 patients accrued, no further accrual will occur, until six months of follow-up are obtained on the 30 patients. If there are no further treatment related deaths, accrual will recommence. Additional safe guards/stopping rules include: Grade 4 thrombocytopenia lasting beyond 28 days, Grade 4 neutropenia associated with fever or infection and lasting beyond 3 weeks, or grade 4 neutropenia lasting beyond 28 days without fever in more than 2 of 20 patients, or more than 3 of 30 patients, or more than 4 of 40 patients during the second phase of the study.

11.9.5 This stopping rule provides a 41% probability of stopping at 20 patients if the true TRM rate is 7%, and provides a greater than 50% chance of stopping prior to completion of accrual. If the true TRM rate is 1.5%, there is less than a 4% chance of stopping at 20 patients, and less than a 10% chance of stopping prior to the completion of accrual.

11.9.6 Survival Analysis: If our accrual goal is met with no premature termination due to significant toxicity or lack of response, a secondary goal of assessing progression-free survival (PFS) and overall survival (OS) will be carried out. Survival estimates will be made using the product-limit method of Kaplan and Meier, with 95% confidence limits calculated using the logit transformation. These estimates will be contrasted with the historical rates at the City of Hope of 48.5% PFS and 74.4% OS at three years, although formal hypothesis testing will not be conducted.

12.0 GENDER AND ETHNICITY STATEMENT

The City of Hope has a plan in place to increase minority recruitment to our studies in compliance with the National Institute of Health policy for recruitment of women and minorities.

The table below shows the distribution by sex and race of the patients accrued to therapeutic clinical studies at City of Hope for the past five years with the same primary site of disease targeted for this protocol (breast). Our goal is to maintain our high accrual of women while continuing to increase the accrual of minority subjects.

Accrual Goal by Sex and Ethnicity								
		By Sex		By Ethnicity				
Site	Accrual Goal	Female	Male	White	Hispanic	Black	Asian/ Other	Unknown
Multiple Myeloma	367	172 (47%)	195 (53%)	213 (58%)	66 (18%)	70 (19%)	14 (4%)	4 (1%)

13.0 ETHICAL AND REGULATORY CONSIDERATIONS

This study is to be approved by the Institutional Review Board of the City of Hope. All patients will have signed an informed consent for participation in research activities, and will have been given a copy of the Experimental Subject's Bill of Rights.

When results of this study are reported in medical journals or at meetings, identification of those taking part will be withheld. Medical records of patients will be maintained in strictest confidence, according to current legal requirements. However, they will be made available for review, as required by the Food and Drug Administration (FDA) or to other authorized users such as the National Cancer Institute (NCI) under the guidelines established by the Federal Privacy Act.

14.0 DATA AND SAFETY MONITORING 2/14/06

14.1 Definition of Risk Level

This is a Risk Level 3 study, as defined in the "Guidance, Policy and Procedures for Data and Safety Monitoring for In-House Trials at City of Hope", http://www.infosci.coh.org/gcrc/doc/dsmp.doc because it is a Phase I/II clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of the knowledge that may result.

14.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of stopping rules for safety.

Reporting of data to the DSMB during the Phase I portion will occur at each decision to escalate a dose, and a Phase I tracking log will be submitted in addition to the toxicity summaries to the DSMB. During the Phase II portion, reporting of data will occur at intervals separated by no more than six months, 10 patients or a treatment related death. This report (the PMT report) will include a summary of accrual, adverse events and treatment related mortality.

Type of Adverse Event	When Reported
• ***UNEXPECTED* & SERIOUS ADVERSE EVENTS ≥ GRADE 3** that are **possibly, probably or definitely related** to the study procedures	Within **5 business days** (The report will be forwarded to the **IRB concurrent** with the DSMB review. The report and the DSMB review will also be forwarded to the CPRMC when the DSMB review is complete.)
• ***UNEXPECTED* & SERIOUS ADVERSE EVENTS ≥ GRADE 4** that are **unrelated or unlikely related** to the study procedures	Within **10 business days** (The report and the DSMB review will be forwarded to the IRB and the CPRMC when the DSMB review is complete.)
• ***EXPECTED* & SERIOUS ADVERSE EVENTS ≥ GRADE 4** **Cancer** Therapeutic **Trials without dose escalation:** thrombocytopenia and non-hematologic events ≥ Grade 4 **Cancer Therapeutic Trials with dose escalation**: neutropenia, thrombocytopenia and non-hematologic events ≥ Grade 4 **Non-Cancer Studies:** All events ≥ Grade 4	Within **10 business days** (The report and the DSMB review will be forwarded to the IRB and the CPRMC when the DSMB review is complete.)

14.3 Adverse Events

14.3.1. Reporting: Adverse events must be reported to the COH DSMB, IRB, and GCRC (if GCRC supported) according to definitions and guidelines at http://www.infosci.coh.org/gcrc/doc/dsmp.doc and http://resadmin.coh.org/doc/irb3810.doc, which are defined below. SAEs will be monitored by the PMT. Less than serious adverse events will be reported only at the time of protocol continuation reports. In the event that an SAE is categorized as an "unacceptable toxicity" or "treatment related mortality", the tables in section 11 will be checked to verify that no toxicity based stopping condition has been met.

14.3.2. Adverse Event - An adverse event (AE) is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention. All AEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be recorded on the City of Hope National Medical Center Adverse Events (COH AER) form (http://resadmin.coh.org/doc/irb3820.doc).

14.3.3 Serious Adverse Event- A serious adverse event (SAE) is defined as *any expected or unexpected adverse event* (AE, generally equivalent to CTCAE grades 3, 4 or 5) that is *related or unrelated* to the intervention that results in any of the following outcomes:

- Death
- A life-threatening event
- In-patient hospitalization (not required as part of the treatment) or prolongation of existing hospitalization

- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Causes cancer
- Is an overdose

Certain medical events that may not result in death, be life-threatening, or require hospitalization, may also be considered a serious adverse event when appropriate medical or surgical intervention is necessary to prevent one of the outcomes listed above.

14.3.4 Unexpected Adverse Event – Any event in which the severity or specificity is not consistent with the risk information described in the protocol, and the event is not anticipated from the subject's disease history or status.

14.3.5. Expected Adverse Event - Any event in which the severity or specificity is consistent with the risk information described in the protocol or is anticipated based on the subject's medical history.

14.3.6. Attribution - For reporting purposes, attribution is the assessment of the likelihood that an AE is caused by the research agent or protocol intervention. The attribution is assigned by the Principal Investigator after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. This is recorded using the Adverse Event Report (COH AER) form (http://resadmin.coh.org/doc/irb3820.doc) in one of 5 categories scored as the following: 5=related, 4=probably related, 3=possibly related, 2=unlikely related and 1=unrelated. The attribution is subject to change as follow-up information becomes available, and it can be changed by the DSMB or by the IRB in the process of review.

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