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Protocol Title

Phase II Trial of High Dose Interleukin-2 Followed by Intermittent Low Dose Temozolomide in Patients with Metastatic Malignant Melanoma

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1.0 BACKGROUND INFORMAITON AND RATIONALE FOR STUDY

1.1 Introduction

Metastatic malignant melanoma remains a disease with a very poor prognosis and median survival duration of less than one year. Durable remissions with conventional therapy are rare and therefore clinical trials remain a primary treatment modality for metastatic disease. There are 2 currently FDA-approved therapies for metastatic melanoma. Chemotherapy with single agent parenteral dacarbazine or its oral pro-drug, temozolomide, are capable of producing responses in 6.5 to 20% of patients. These responses are usually minor to partial at best and are not durable (1). Combination with other chemotherapeutic drugs has not been successful (2). The immune system also seems to play a role in malignant melanoma. High dose Interferon therapy is the current standard therapy for the adjuvant treatment of stage IIB, IIC and III melanoma after surgical resection in which it has shown to result in modest improvements in DFS and OS (3). In metastatic disease, various immunologic approaches have been utilized as well. High dose IL-2 can produce a response rate of about 10-15% in patients with metastatic melanoma. About 5-10% of responses are complete and some of these complete responses are durable so that the lucky few patients who have a durable complete response are for all intents and purposes cured (4). Attempts to combine chemotherapy with immunotherapy, so called biochemotherapy, although improving response rates, has not impacted survival as summarized in recent meta-analysis (5).

A phase II trial of temozolomide followed by high dose IL-2 was conducted by UPMC (6). This study concluded that although it was safe to combine these agents and the combination had lower toxicity than previous biochemotherapy regimens, the overall response rates and durability of responses did not exceed those of single agent high dose IL-2. In this study, the patients received temozolomide at 75 mg/m^2 for 3 weeks continuously followed by high dose IL-2 off the temozolomide. This was repeated again and then response was determined. Responding and non-progressing patients received repeated courses up to 4 maximum. A course consisted of 2 cycles of high dose IL-2 as noted above with temozolomide for 21 days prior to each cycle. The overall response rate for the trial was 16.1%. CR rate was 9.7% and PR rate was 6.5%. Two of the 3 CR patients had durable responses. As noted, in this trial the temozolomide was given before the IL-2. We have reasons to suspect that the sequence of the tow drugs as therapy would be crucial for response and indeed that is what led to the design of the current trial described below.

1.2 Rationale for Sequence-Specific Combination of High Dose IL-2 and Temozolomide in Metastatic Melanoma

As noted, we have recently observed that many patients who had received high dose IL-2 and failed to respond to it but who then go immediately to temozolomide seemed to enjoy extremely good responses which seem better quality and longer duration than typically observed for temozolomide alone. To date, we have observed 5 sequentially treated patients with metastatic melanoma who had failed high dose IL-2 but who then went on to receive immediate temozolomide given at 75 mg/m^2 per day for 21/28 days (7). Two of these patients had CRs, and 3 had very strong PRs. One CR has been durable to date which is a marked anomaly for single agent temozolomide. For comparison, in a recent phase II of extended low dose temozolomide alone given in the same manner as to the post-IL-2 patients noted above, the response rate was 12.5% and all of these were partial responses only. The median time to progression was 3.3 months (8). The responses that we observed were at a much higher rate of response as well as much better quality than expected for temozolomide alone as noted above. The responses were

also better than those observed when temozolomide was given first and then followed by high dose IL-2 in the UPMC study. We concluded that perhaps the major benefit we observed was a result of the prior high dose IL-2 therapy modulated by the temozolomide and that the sequence of treatment was clearly crucial for this response. We have not observed this effect in 2 patients who received dacarbazine post IL-2. These 2 patients had rapid progressive disease and died.

A possible explanation for this observation entails the T-reg population of lymphocytes (CD4+ CD25+) which act as natural brakes on the immune response and are the main contributors to immunologic tolerance and poor responses to immunotherapy against tumors. They comprise about 2-3% of CD4+ human T-cells. Patients with melanoma typically have high levels of T-reg cells and overactive T-reg cell function (9). These cells act to down- regulate any effective anti-melanoma immune response. Of interest, patients with melanoma who respond to high dose IL-2 have low levels of T-reg cells and their activity. It has been recently demonstrated in animals that low dose continuous temozolomide but not standard dose temozolomide can downregulate T-regs and their function (10). The low dose temozolomide that was given to our patients after they had completed and failed high dose IL-2 is completely compatible to the dosing that was used in this animal study. Based on our clinical experience of an unusually high rate of response in general and CR in particular in patients with melanoma receiving temozolomide post IL-2, we postulate that the temozolomide is acting to inhibit T-reg induction of tolerance resulting in better and somewhat more durable responses. The apparent sequence specific responsiveness noted is satisfactorily explained by this model. We hypothesize that incorporating low dose temozolomide after each cycle of high dose IL-2 for the up-front treatment of melanoma will improve response rate and allow more patients to go to additional course of IL-2 leading to increased CR rate, hopefully many of which will prove to be durable leading effectively to cure of the metastatic disease.

Both high dose IL-2 and temozolomide are FDA approved for use in metastatic malignant melanoma. They have been combined safely before as noted but without significant benefit when combined at least when the temozolomide is followed by the IL-2 (6). We feel that the combination needs to be sequence specific with the IL-2 given first to work. This is based on our ongoing clinical observations and the known effect of temozolomide on T-reg T-cells (7, 10). If a means to improve response, response durability and cure can be achieved with conventional available treatment merely through alterations in the sequence of delivery, this would prove to be a major and relatively cheap innovation in melanoma treatment. We therefore propose a prospective phase II trial to test this hypothesis directly together with appropriate correlative science immunoassays to see if the mechanism of response appears related to the depletion of the T-reg cells.

1.3 Study Synopsis

We propose a simple phase II trial of High Dose IL-2 followed by low dose temozolomide. The study would be a preliminary phase II efficacy trial and will be conducted using a modified Simon 2 stage design in up to 40 patients total. The historic overall response rate of high dose IL-2 in melanoma is about 5-10% with CR rate about 2.5 to 5%. The response to temozolomide alone is about 13% with CR rate of about 0%. We would hypothesize that the new combination therapy would increase response rate and CR rate by at least 2 fold compared to IL-2 alone based on our retrospective experience (7). Patients with metastatic melanoma who are considered good candidates i.e. ECOG <2, Creat<2.0 Bilirubin< 2.0 for a trial of high dose IL-2 would be offered participation. Patients with a history or clinical evidence of brain metastasis must have completed radiation therapy or surgical treatment of brain lesions and have no evidence of CNS

progression for at least eight weeks at the time of enrollment. Patients must not require corticosteroids for treatment of cerebral edema for brain metastases. Patients must be evaluated with a head MRI within 4 weeks prior to enrollment. Patients may have had prior dacarbazine or temozolomide since the mechanism of action of the temozolomide to be used in the context of this study is related more to effects on immune cells than to its known anti-melanoma effects. Patients would receive baseline staging imaging and laboratory assessment including study-specific immunologic correlative science testing. Patients would receive HD IL-2 according to standard procedure as in-patients on the PSHCI inpatient clinical unit. Patients would receive Cycle 1 of aldesleukin at 600,000 International Units/kg every 8 hours as tolerated up to a maximum of 14 doses. On or about day 10 after discharge from Cycle 1, they would be re-admitted for Cycle 2 of treatment. Then, 28 days after discharge from Cycle 2, they would receive temozolomide at 75 mg/m^2 daily for 21 days. Two cycles of HD IL-2 therapy as performed above plus 21 days of temozolomide would constitute one course of therapy. After this they would be scanned to assess response with CT/PET or CT(CAP). Responding patients (CR, PR, SD, Minor Response) would be given a 2nd course of treatment as above. Patients with a CR would receive one additional course of treatment and would then be observed. Patients with SD after 2nd course of treatment would go off study. Patients with a PR or Minor Response would continue treatment up to a maximum of 4 courses (8 cycles). If they develop Progressive Disease at any time during this treatment then they would go off study. If they develop a CR then they would have one additional course of treatment provided this course does not make more than 4 total courses. If they have PR or Minor Response after Course 2 then they would receive up to 2 additional courses.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives:

1) To determine the clinical response (complete response, partial response, minor response, stable disease or disease progression) to high dose IL-2 followed by low dose temozolomide.
2) To determine the duration of response, and safety and toxicity of high dose IL-2 followed by low dose temozolomide.

2.2 Secondary Objectives:

1) To determine the quantitative effects of high dose IL-2 followed by low dose temozolomide on lymphocyte subsets, particularly the T-reg cells.
2) To determine the quantitative effects of high dose IL-2 followed by low dose temozolomide on cytokine production and anti-melanoma specific T-cell immune cells.
3) To determine the effects of high dose IL-2 followed by low dose temozolomide on autoimmune laboratory markers and clinical manifestations of autoimmunity.

3.0 STUDY DESIGN

This would be a non-randomized, open label, phase II, modified 2-stage preliminary efficacy study in patients with metastatic melanoma who are considered good candidates, i.e. ECOG <2, Creat <2.0, Bilirubin < 2.0 for a trial of high dose IL-2 treatment. Standard doses and delivery of both the high dose IL-2 and the temozolomide would be utilized. The total accrual goal for the trial would be up to 40 patients given in 2 stages. If no responses are noted in the first 12 patients accrued then the study will be terminated. If there is any response in the first 12 patients (CR, PR

or MR) then accrual of an additional 25 patients will ensue. Three additional patients would be allowed to accrue to cover any early drop-outs (receipt of less than 2 complete cycles of treatment). Eligible patients would have baseline imaging with CT or CT/PET. A head MRI to rule out asymptomatic occult brain metastases will be performed on all patients as well. Patients with known brain metastases will have baseline MRI done as well and would then have follow-up MRIs performed after each course. An echocardiogram to check cardiac function and PFTs with DLCO will be performed in all patients to assure that they have adequate cardiopulmonary reserve to sustain HD IL-2 as is standard. Patients would have baseline laboratory testing done pre-treatment and at every cycle initiation. An autoimmune panel will be preformed pre-treatment and after every cycle of treatment. Correlative science immunoassays will be performed pre-treatment and after every cycle of treatment. Response as per radiologic imaging assessment and physical assessment of accessible and measurable skin metastases if applicable will be performed after every course of treatment (2 cycles HD IL-2 and 21 days of temozolomide.). Response will be determined after course 1 of treatment as a complete response (CR), partial response (PR), minor response (MR), stable disease (SD) or progressive disease (PD) according to standard definitions of response. Patients with CR will receive another complete course of treatment and will then go off study except for follow-up. Patients with progressive disease (PD) will go off study after course 1. Patients with stable disease (SD) after course one will repeat one additional course maximum. Patients with PR or MR will continue with additional courses as determined by response up to a maximum of 4 courses total (8 cycles). Responses and their durability will be compared to known rates of response and their durability using HD IL-2 alone. For a population of 40, using standard HD IL-2, the expected response rate 10% would be in 4 of the 40 and the CR rate 5% in about 2 of the 40. We would hypothesize that we can at least double these at a minimum using the methods described in this protocol.

3.1 Inclusion Criteria

At time of registration, patients must have following inclusion criteria:

1) Metastatic malignant melanoma, pathologically confirmed
2) Age $\geq$ 18 years and ability to provide informed consent
3) ECOG Performance Status of 0 or 1
4) Patients should be considered good candidates, i.e. ECOG <2, Creat< 2 Bilirubin<2 for conventional high dose IL-2
5) No chemotherapy, hormonal therapy, immunotherapy or radiation therapy within 1 month of entry
6) Patients with a history or clinical evidence of brain metastasis must have completed radiation therapy or surgical treatment of brain lesions and have no evidence of CNS progression for at least eight weeks at the time of enrollment. Patients must not require corticosteroids for treatment of cerebral edema for brain metastases. Patients must be evaluated with a head MRI within 4 weeks prior to enrollment.
7) Patients may have had prior high dose IL-2 or temozolomide but not together or with high dose IL-2 followed by temozolomide
8) Patients may have had prior high dose interferon as adjuvant treatment for high risk Melanoma
9) Serum Cr < 2mg/dL
10) Bilirubin < 2mg/dL (except for Gilbert's Syndrome)

3.2 Exclusion Criteria

At time of registration, patient must lack the following exclusion criteria:

1) Inability to provide informed consent
2) Hypersensitivity to temozolomide or HD IL-2
3) Active gastrointestinal disorders or cardiac disorders i.e. cardiac failure, MI within 6 months as determined by the investigator
4) EF < 50% by echo or corrected DLCO < 50% on diffusion capacity testing PFTs
5) PLT < 100K, ANC < 1000
6) Chronic use of steroids other than for simple adrenal replacement

4.0 TREATMENTS

The study drugs will be IL-2 aldesleukin (Proleukin), and temozolomide (Temodar). IL-2 will be given IV according to standard procedures using the Pittsburgh clinical guidelines for management. This is the current standard operating procedure on the PSCI inpatient clinical unit. The physicians, nursing and ancillary staff of this unit are very experienced in the delivery of high dose IL-2 and the management of the expected transient toxicities. There are several dosing regimens for temozolomide. Temozolomide is an oral chemotherapy agent and is dosed according to BSA. We will choose the chronic low dose regimen of temozolomide at 75 mg/m^2 daily as noted previously (8). This regimen is widely used for management of metastatic melanoma and is a standard regimen in the PSHCI melanoma clinic. It is extremely well tolerated.

4.1 High Dose IL-2: Dosage, Administration, Toxicity and its Management

Aldesleukin is currently an FDA approved drug for the treatment of metastatic melanoma and metastatic renal cell carcinoma. Only high dose regimens can reproducibly result in highly durable, complete responses and this is the current standard regimen at PSHCI

4.1.1 Aldesleukin Dosage, Administration and Dose Modifications

The dose of IL-2 is 600,000 International Units/kg given intravenously every 8 hours as tolerated by the Pittsburgh clinical guidelines for management up to a maximum of 14 doses. Patients rarely get to 14 doses. Patients are supported symptomatically and with fluid boluses. Vasopressors are not used. No dose modifications are utilized. Doses are held per the clinical guidelines.

4.1.2 Aldesleukin Drug Information

Aldesleukin is a recombinant produced natural human cytokine. It is manufactured by Novartis. It is given in very large doses. The mechanism of action is unclear but it results in expansion of T-cell populations and results in production of other cytokines including tumor necrosis factor. The administration is associated with characteristic severe but reversible toxicities for which care in a specialized unit is ideal and as is the case at PSHCI. Administration of HD IL-2 mimics acute bacterial sepsis with inflammatory constitutional symptoms and signs including rigors, high fever, lassitude, anorexia, somnolence, hypotension and capillary leak. The toxicities are

transient and resolve usually completely within 24 hours of stopping the drug. They are managed supportively with fluids, antiemetics, antipyretics and analgesics. Mortality due to high dose IL-2 in the current era is < 2%. We have not had a fatality due to this treatment at PSHCI. Dosing and withholding dosing is carefully regulated by a treatment algorithm developed at the UPMC.

4.1.3 Aldesleukin Potential Toxicities and their Management

> 10% rigors, fevers, diaphoresis, lassitude, somulence, nausea, vomiting, anorexia, edema, water weight gain

1 to 10% transient bone marrow suppression, cholestasis, prerenal azotemia

< 1% delirium

4.2 Temozolomide: Dosage, Administration, Toxicity and its Management

Temozolomide is currently an FDA approved drug for the treatment of metastatic melanoma and primary brain tumors. It has also been used off label for brain metastases and low grade neuroendocrine tumors. It is manufactured by Schering-Plough.

4.2.1 Temozolomide Dosage, Administration and Dose Modifications

The dose of temozolomide is based on the BSA for the patient. Patients would receive temozolomide at 75 mg/m^2 at bedtime daily for 21 days beginning 28 days after discharge from Cycle 2 of high dose IL-2. Ondansetron 8mg po will be administered 30 minutes prior to and every morning after each dose of temozolomide. The medication is oral and is available in various doses to accommodate wide range of BSA. Typically, this low dose of temozolomide does not result in cytopenias requiring dose reduction. If, however, PLT are < 100 K or ANC is < 500, then the Temozolomide would be given with a 25% dose reduction for remaining cycles.

4.2.2 Temozolomide Drug Information

Temozolomide is a synthetic atypical alkylator. It can cross the blood brain barrier and has excellent bioavailability. Patients would be given Zofran and Compazine as antiemetic support.

4.2.3 Temozolomide Potential Toxicities and their Management

> 10% nausea, vomiting

1 to 10% fatigue

< 1% bone marrow suppression particularly platelets, immunosuppression, PCP pneumonia, secondary leukemia

5.0 TRIAL PROCEDURES

5.1 Screening and Consent

Patients with metastatic melanoma seen in the PSHCI clinic who are considered good candidates for high dose IL-2 therapy will be asked to participate in this trial and their eligibility will be reviewed using the inclusion and exclusion criteria noted. After explanation of the nature and logistical aspects of the study, patients will be asked to review the consent document carefully. If they have any questions regarding any aspect of the study, these will be answered to the satisfaction of the patient. The patient will sign the consent document to verify that they are fully interested in participation in the study as defined by the consent form. An eligibility checklist will be completed and signed by study personnel after consent has been executed (Appendix I Eligibility Checklist). The demographics and clinical plan data will be recorded on forms (Baseline Interval Form) (Recist 1.1 Measurement Form)

5.2 Baseline Evaluation

Patients will have an initial history and physical examination by the investigator. Patients will have baselines labs: CBC with differential, CMP, LDH, autoimmune panel and correlative science labs drawn, and will also have a baseline imaging with CT/PET or CT (CAP). A brain MRI will be obtained to evaluate for brain metastases. Patients will have a 2D and M-mode echocardiogram performed to assess ejection fraction and will have pulmonary function testing with carbon monoxide diffusion capacity testing (DLCO) to test for adequate cardiopulmonary reserve. These studies should be within 4 weeks of starting study treatment. See Appendix III Active Treatment Flow Chart/Time and Events Schedule which lists testing over time.

5.3 Therapy

After baseline studies have been completed, the patients would be admitted to the PSHCI inpatient clinical unit for Course 1 Cycle 1 of HD IL-2 treatment. Treatment will proceed according to the standard treatment algorithm utilized by the PSHCI inpatient clinical unit. Patients will be given as many doses of IL-2 up to a maximum of 14 at 8 hr intervals as allowed by the algorithm at 600,000 International Units/kg. Patients will receive standard supportive measures including fluid boluses, antiemetics and antipyretics as indicated. The patients will be discharged when the acute toxicities of the IL-2 have subsided. They will be reassessed on or about Day 10 after discharge from Cycle 1 and will be re-admitted for Cycle 2. After Cycle 2 of HD IL-2, they would begin temzolomide at 75 mg/m^2 on the 28th day after discharge and they would take it daily at bedtime for 21 days. Approximately 14 days after the final dose of temozolomide, patients will be assessed for response via imaging. The response determined after restaging post course 1 would determine the next step. Patients with progressive disease would go off study. Patients with a CR would receive one additional course of treatment and would then be observed. Patients with SD would receive one additional course of treatment. Patients with a PR or minor response would continue treatment up to a maximum of 4 courses (8 cycles HD IL-2 and 4 cycles of temozolomide). If they develop progressive disease at any time during this treatment then they would go off study. If they develop a CR then they would have one additional course of treatment provided this course does not make more than 4 total courses. If they have PR or minor response after course 2 then they would receive up to 2 additional courses.

5.5 Removal of Patients from Therapy

Patients can remove themselves from the study at any time for any reason. Patients will be removed from the study by an investigator for undue toxicity as determined by an investigator. Patients will also be removed if they demonstrate disease progression or stable disease as defined above.

5.6 Post-Study Follow-Up

After patients are off the study either for the reasons noted above or for completion of study therapy, then they will be followed for time to progression, progression free and overall survival by review of patient records. Follow up will be according to clinical practice this is generally every 6 months or less.

6.0 ASSESSMENTS

6.1 Clinical Assessments

The logistics of the study are summarized in the table, 15.1.8. Patients will be evaluated in the clinic by an investigator before each treatment cycle. Before each cycle of therapy, patients will have routine and correlative science labs performed along with a history and physical examination. These data will be recorded on a form (15.1.4 Clinical Evaluation). An adverse event form will also be completed at each of these evaluations by the study nurse-coordinator (see below). Patients will have staging performed with CT/PET or CT (CAP) after every complete course of treatment (2 complete cycles of HD IL-2 plus 4 weeks of rest plus 3 weeks of oral temozolomide plus 2 weeks of rest prior to reimaging = 1 complete course = approximately 12 weeks). Patients with measurable skin and/or subcutaneous lesions would have 2-dimensional measurements performed using a ruler after each complete course of therapy. They will also have an autoimmune panel drawn after each complete cycle. The autoimmune panel will include an ESR, CRP, ANA, RF, and TSH. Patients with known brain metastases will have repeat MRI of the head after each course. Patients with or without known brain metastases can get repeat MRI at any time should they develop neurologic symptoms as determined by the investigator. Response will be by modified RECIST criteria 1.1 and will employ the following definitions of response:

CR – complete response - no evidence of disease, 100% reduction in the volume of disease
PR – partial response - $\geq$50% but < 100% reduction in volume of disease

MR – minor response - $\geq$ 25% but < 50% reduction in volume of disease
SD – stable disease - < 25% increase in volume of disease to < 25% reduction in volume of disease
PD – progressive disease - $\geq$ 25% increase in volume of disease

The final response will be the best response observed during the course of treatment while on study

6.2 Toxicity Assessments

Patients will have standard toxicity assessments performed before each cycle. These data will be recorded on a form. Safety outcomes will be based on observed or reported adverse events (AEs).

Other safety data will include other AEs or SAEs, as defined below, including abnormal results of objective tests that resulted in change in study drug dosage or discontinuation or clinically significant changes in physical examination findings unrelated to disease progression. Deaths will be reported immediately as SAEs, and autopsies requested.

6.2.1 Data Safety Monitoring Board

The Penn State Hershey Cancer Institute Data and Safety Monitoring Board (PSHCI DSMB) will serve as the independent board for data and safety review. The principal investigator (PI) will continuously monitor study progress for safety and will hold monthly meetings with the Disease Center Personnel to review overall conduct and progress of this study. During these meetings, accrual and all adverse events/safety issues will be discussed. The PI will provide the PSHCI DSMC annual safety and monitoring reports including the number of subjects enrolled, SAE assessments, information on any protocol deviations and breaches of confidentiality. Summary of all adverse events will be reported to the IRB annually; unexpected adverse events will be reported as they arise as well as any significant literature reporting developments that may affect the safety of participants in this study. Serious and unexpected adverse events will also be reported to PSHCI DMSB simultaneously with the IRB reporting. The PI will beresponsible for ensuring the proper conduct of the study with regard to protocol adherence and the validity of the data recorded on case report forms. Reports from the PSHCI DSMB will be sent to the IRB at least annually.

6.2.2 Correlative Science Testing

Patients would have 50 ml of blood drawn for correlative science studies at baseline, 24-72 hours after the last dose of IL-2 for each cycle, the day patient starts temozolomide (-2/+0 days), and at the end of each complete course of treatment. The tests are described in more detail in Appendix III Studies would include FLOW cytometry for quantification of T-cell subsets including T-reg cells, ELIspot for cytokine production (IL-2, TNF, IL-6, IL-12) and FLOW-based tetramer analysis for reactivity against common melanoma antigens such as MART and S100. Correlative science studies will be completed by Todd Schell's lab (extension 5577).

7.0 ADVERSE EVENT REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs. They will be submitted to the PSCI DSMB and the HMC IRB for evaluation by those bodies.

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 for grading of all adverse events.

Definition of an AE

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal assessments (e.g., ECGs, X-rays, and vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Abnormal laboratory findings < Grade 3 (per CTCAE version 4) will only be recorded if

deemed clinically significant by the investigator. Clinically significant abnormal laboratory findings or other abnormal assessments present at baseline which significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.
The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

Time Period, and Frequency of Detecting AEs and SAEs

From the time a subject consents to participate in the study until he or she has completed the study (including any follow-up period), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a study concomitant medication, will be reported promptly to DSMB and the IRB

Prompt Reporting of SAEs

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

In addition, SAEs, whether regarded as study drug-related or not, will be reported promptly to DSMB and the IRB once the investigator determines that the event meets the protocol definition of an SAE.

Timeframes for Submitting SAE Reports to the DSMB and the IRB

Once the investigator becomes aware that an SAE has occurred in a study patient, she/he will report the information to the DSMB and IRN within 24 hours. Facsimile transmission of the SAE report is the preferred method to transmit this information. The SAE report will be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded within 24 hours of knowledge of the event. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the DSMB and IRB of the event. The report will be updated and sent to the DSMB and the IRB when additional information is received. The investigator will provide an assessment of causality at the time of the initial report.

8.0 DATA ANALYSIS AND STATISTICAL METHOD

8.1 Sample Size Determination

The study will employ a Simon 2-stage optimal design with the following specifications: $p_0 = 0.05$, $p_1 = 0.20$, $\alpha = 0.10$, $\beta = 0.10$, where p_0 is the ineffective response rate, p_1 is the effective response rate, α is the false positive rate, and β is the false negative rate. With these specifications, a 2-stage Simon optimal design, which minimizes the expected sample size given an ineffective response rate, will enroll a total of 37 patients with 12 during stage 1 and 25 during stage 2. If there is no response among the first 12 patients, then the drug is considered ineffective and the enrollment will be stopped. Otherwise, the study will proceed to stage 2. The drug will be considered effective if there are at least 4 responses by the completion of the trial.

The design will assure good statistical power with respect to differentiating response rates of 5% and 20% (12). Three additional patients will be enrolled to allow for dropouts to a total of 40.

8.2 Efficacy Determination

Efficacy analysis will be performed on the intention-to-treat set, which comprises of all patients enrolled in the trial. Patients must have completed at least one complete course (2 cycles) to be considered for response assessment. Patients receiving less than one course will be considered drop-outs from the study in terms of response. Patients who do complete at least one course of treatment will be classified as responders or non-responders. The overall response rate, which is the proportion of the responses among patients in the intention-to-treat set who have completed at least one complete course, will be obtained. In addition, a 95% confidence interval for the overall response rate will be constructed. Responses will be recorded after each course of therapy and will be tabulated as complete response, partial response, minor response, stable disease or progressive disease. Only PR and CR will be included in the numerator of the analysis for overall response but all responses will be recorded. The time to progression (TTP) in months for each patient will be recorded to ascertain the durability of the responses. Waterfall plots for a continuous assessment of response will also be generated. Correlative science results will be studied by non-parametric methods for differences in a given individual over time and between individuals.

9.0 QUALITY CONTROL AND QUALITY ASSURANCE

The investigator is obligated to conduct this study in accordance with federal regulation 21 CFR 312.60-69 as specified on the signed form FDA 1572, applicable state laws, and the International Conference on Harmonization: Good Clinical Practice (GCP): Consolidation Guideline. Data will be collected in accordance with applicable regulations, GCP, and Penn State Milton S Hershey Medical Center procedures.

Data generated by the methods described in the protocol will be recorded on forms maintained in the patient research folders. It will be liable for audit by the IRB, FDA or other approved licensing agencies.

10.0 DATA HANDLING AND RECORD KEEPING

Records will be maintained by the Clinical Trials Office personnel who will retrieve the data from source clinical documents and place these data on the study forms. They will be locked and only available to study personnel. The data within the study forms will be entered into a data base (Oncore System) which will also only be available to study personnel.

11.0 REFERENCES

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APPENDICES – STUDY FORMS

I. Eligibility Checklist
II. Off-Study Form
III Active Treatment Flow Chart/ Time and Events Schedule-x
-IV Study Schema Algorithm
-V Correlative Science Immunoassays

Eligibility Criteria

Inclusion criteria - *Subjects must fulfill all inclusion criteria to be included in the study.*

	YES	NO
1. Provision of written informed consent.	☐	☐
2. Metastatic malignant melanoma, pathologically	☐	☐
3. Age $\geq$ 18 years and ability to provide informed consent	☐	☐
4. Patients should be considered ECOG <2, Creat <2, Bili <2 for conventional high dose IL-2	☐	☐
5. No chemotherapy, hormonal therapy, immunotherapy or radiation therapy within 1 month of entry	☐	☐
6. Patients with a history or clinical evidence of brain metastasis must have completed radiation therapy or surgical treatment of brain lesions and have no evidence of CNS progression for at least eight weeks at the time of enrollment. Patients must not require corticosteroids for treatment of cerebral edema for brain metastases. Patients must be evaluated with a head MRI within 4 weeks prior to enrollment.	☐	☐
7. Patients may have had prior high dose IL-2 or temozolomide but not together or with high dose IL-2 followed by temozolomide	☐	☐
8. Patients may have had prior high dose interferon as adjuvant treatment for high risk melanoma	☐	☐
9. Serum Cr < 2mg/dL	☐	☐
10. Bilirubin < 2mg/dL (except for Gilbert's Syndrome)	☐	☐

Exclusion criteria- *The following criteria are considered to be exclusionary for Subjects to be considered for inclusion in the study:*

	YES	NO
1. Inability to provide informed consent.	☐	☐
2. Hypersensitivity to temozolomide or HD IL-2	☐	☐

3. Acute gastrointestinal disorders, or cardiac disorders i.e. cardiac failure, MI within 6 months as determined by the investigator ☐ ☐

4. EF < 50% by echo or corrected DLCO < 50% on diffusion capacity testing PFTs ☐ ☐

5. PLT < 100K, ANC < 1000 ☐ ☐

6. Chronic use of steroids other than for simple adrenal replacement ☐ ☐

Off Study Form

Dear _____:

It has been unfortunate that you wish to stop your participation in the Phase II Trial of High Dose Interleukin-2 followed by intermittent low dose Temozolomide in patients with Metastatic Malignant Melanoma. In order to complete our records, as requested by the trial, I would appreciate you indicating your interest below.

If you have any questions or wish to schedule a meeting, please call me at 531-7417. Thank you for your participation in the Phase II Trial of High Dose Interleukin-2 followed by intermittent low dose Temozolomide in patients with Metastatic Malignant Melanoma.

Sincerely,

Michele St. Pierre, RN
Clinical Trials Coordinator

Check what contact you would like:

☐ I, _____, wish to continue my treatment in the Phase II Trial of High Dose Interleukin-2 followed by intermittent low dose Temozolomide in patients with Metastatic Malignant Melanoma.

☐ I, _____, do not wish to continue my treatment in the Phase II Trial of High Dose Interleukin-2 followed by intermittent low dose Temozolomide in patients with Metastatic Malignant Melanoma but wish to continue with **Direct** follow-up.

☐ I, _____, do not wish to continue my treatment in the Phase II Trial of High Dose Interleukin-2 followed by intermittent low dose Temozolomide in patients with Metastatic Malignant Melanoma but agree to continue with **Indirect** follow-up contact. HMC may contact my Physicians office for medical records.

☐ I, _____, do not wish to continue my participation in the Phase II Trial of High Dose Interleukin-2 followed by intermittent low dose Temozolomide in patients with Metastatic Malignant

Melanoma and do not wish to continue with follow-up visits. Permanent refusal of future contact and No direct or Indirect follow-up allowed.

Signature	Date	Printed Name
Witnessed Signature	Date	Printed Name

ACTIVE TREATMENT FLOW CHART/TIME AND EVENTS SCHEDULE

TREATMENT:

Procedure	Baseline[1]	Pre-IL-2 Cycle 1	Post-IL-2 Cycle 1	Pre-IL-2 Cycle 2	Post-IL-2 Cycle 2	Temozolomide Day 1 (-2/+0 days)	Post Course[6]
Informed consent	X						
Inclusion/exclusion criteria	X						
H&P	X	X		X			X
PET/CT scan or CT(CAP)	X						X
MRI of head[2]	X						X
Echo/PFT	X						
Autoimmune panel[3]	X		X[8]		X[8]	X[7]	X
Immunoassays[4]	X		X[8]		X[8]	X	X
Routine Labs[5]	X	X		X		X	X

[1] – Baseline within 28 days of starting treatment
[2] – Patients with or without known brain metastases can get an MRI at any time, should they develop neurological Symptoms as determined by the investigator
[3] – Will include ESR, CRP, ANA, RF and TSH
[4] – Will include flow cytometry, Elispot, flow- based tetramer analysis (To be procesed by Todd Schell's lab x5577)
[5] CBC, diff, platelets, CMP, LDH,
[6] This scheme will be repeated up to 4 courses
[7] – CRP only
[8] - Post-cycle labs will be drawn 24-72 hours after completion of the last dose of IL-2 for each cycle. These may be obtained while the patient is admitted, as long as it falls within the 24-72 hour timeframe and has been arranged with the study coordinator.

One Course is comprised of 2 cycles of high dose IL-2 followed by 4 weeks off, then 3 weeks of continuous low dose oral temozolomide, with another 2 weeks off prior to reimaging (approximately 12 weeks in duration from start to finish)

Study Schema Algorithm: Phase II Trial of High Dose Interleukin-2 followed by intermittent low dose Temozolomide in patients with Metastatic Malignant Melanoma