The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Phase III Trial of High Dose Interferon Alpha-2b versus Cisplatin, Vinblastine, DTIC Plus IL-2 and Interferon in Patients with High Risk Melanoma (SWOG S0008): An Intergroup Study of CALGB, COG, ECOG and SWOG

Flaherty, et al

DOI: 10.1200/JCO.2013.53.1590

SOUTHWEST ONCOLOGY GROUP

PHASE III TRIAL OF HIGH DOSE INTERFERON ALPHA-2b VERSUS CISPLATIN, VINBLASTINE, DTIC PLUS IL-2 AND INTERFERON IN PATIENTS WITH HIGH RISK MELANOMA

PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS AND PATHOLOGISTS; ECOG AND COG - **U.S. INSTITUTIONS ONLY**

STUDY COORDINATORS:

PRINCIPAL INVESTIGATOR

Lawrence E. Flaherty, M.D. (Medical Oncology)
Wayne State University
Karmanos Cancer Institute
Division of Medical Oncology
4100 John R
Detroit, MI 48201
Phone: 313/576-8715
Fax: 313/576-8726
E-mail: flaherty@karmanos.org

John A. Thompson, M.D. (Medical Oncology)
Seattle Cancer Care Alliance
825 Eastlake Avenue
Mailstop G3-200
Seattle, WA 98109-1023
Phone: 206/288-2044
Fax: 206/288-6210
E-mail: jat@u.washington.edu

AGENTS:

Cisplatin (CDDP) (Platinol®) (NSC-119875)
Dimethyl Triazeno Imidazole Carboximide (DTIC), (Dacarbazine), (NSC-45388)
Filgrastim (r-metHuG-CSF) (NSC-614629) (BB-IND-2704)
Interferon Alpha-2b (Intron-A) (NSC-377523)
Recombinant Interleukin-2 (Chiron-Cetus) (IL-2) (NSC-373364)
Vinblastine sulfate (Velban) (NSC-49842)

P.Y. Liu, Ph.D. (Biostatistics)
James Moon, M.S.
Southwest Oncology Group Statistical Center
at Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
Fax: 206/667-4408
E-mail: pyl@fhcrc.org
E-mail: jmoon@fhcrc.org mb

(Version Date 08/31/07)

STUDY COORDINATORS (contd.):

John T. Vetto, M.D. (Surgery)
OHSU, Surgical Oncology
3181 SW Sam Jackson Park Road
L223A
Portland, OR 97201-3098
Phone: 503/494-5501
Fax: 503/494-8884
E-mail: vettoj@ohsu.edu

Ralph J. Tuthill, M.D. (Pathology)
Department of Anatomic Pathology L-25
Cleveland Clinic Foundation
One Clinic C2enter
9500 Euclid Avenue
Cleveland, OH 44195-0001
Phone: 216/444-2245
Fax: 216/445-6967
E-mail: tuthillr@ccf.org

Vernon K. Sondak, M.D. (Surgery)
University of Michigan Medical Center
Division of Surgical Oncology
1500 E. Medical Center Drive
3306 Cancer/Geriatrics Center Box 0932
Ann Arbor, MI 48109-0932
Phone: 734/936-7938
Fax: 734/647-9647
E-mail: vsondak@umich.edu

Jeffrey A. Sosman, M.D. (Molecular Coorrelates)
Vanderbilt University School of Medicine
Division of Hem/Onc
777 Preston Research Building
2220 Pierce Ave
Nashville, TN 37232-7602
Phone: 615/322-4967
Fax: 615/343-7602
E-mail: jeff.sosman@mcmail.vanderbilt.edu

ECOG STUDY COORDINATOR:

Michael Atkins, M.D. (Medical Oncology)
Division of Hematology/Oncology
Beth Israel-Deaconess Medical Center
330 Brookline Avenue
Kirstein Hall 1, Room 158
Boston, MA 02115

John M. Kirkwood, M.D. (Medical Oncology)
Professor and Chief
Division of Medical Oncology
University of Pittsburgh Medical Center
200 Lothrop Street
Pittsburgh, PA 15213-2592

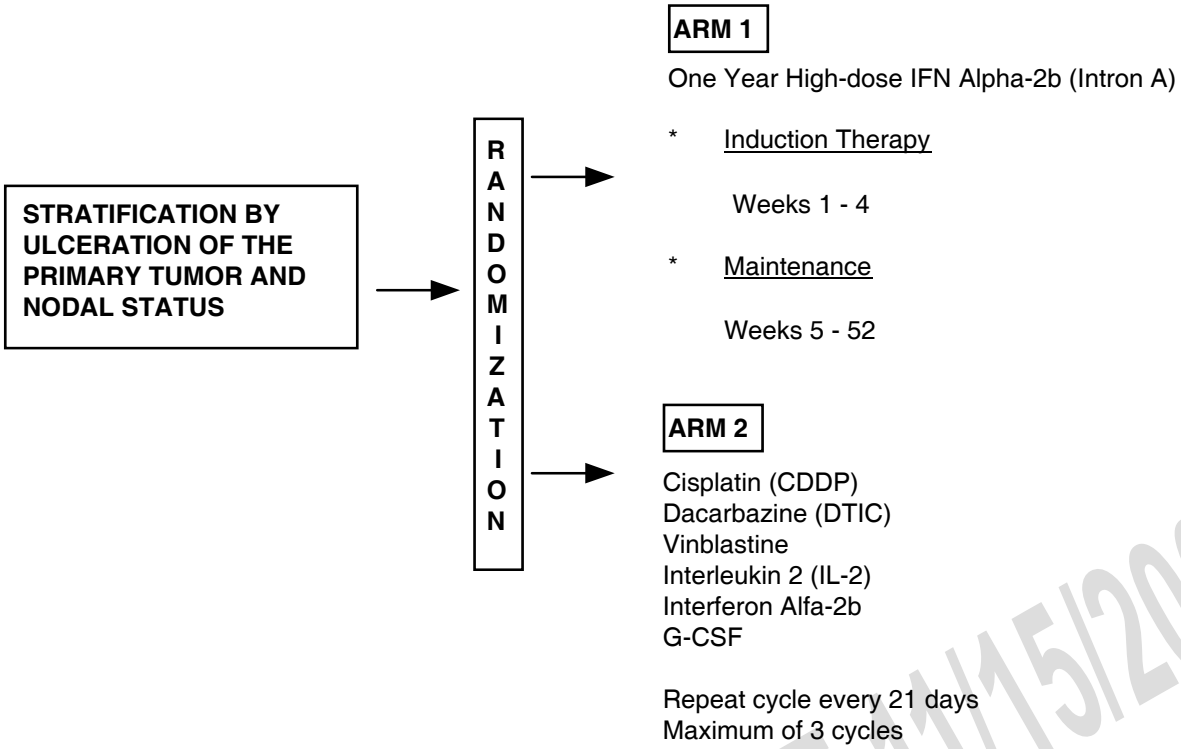
COG STUDY COORDINATOR:

Alberto Pappo, M.D.
Hospital for Sick Children
Discipline: Pediatrics
Division of Hematology/Oncology
555 University Avenue, 9411 A
Toronto, ON M5G 1X8

COG logistical information is found in Appendix 19.7.

Please refer all questions regarding chemotherapy treatment or dose modifications to Dr. Flaherty at 313/576-8715 or Dr. Thompson at 206/288-2044. For pathology related questions, contact Dr. Tuthill at 216/444-2245. Please refer any questions regarding surgery to Dr. Vetto at 503/494-5501 or Dr. Sondak at 734/936-7938.

SCHEMA



All patients are followed until death or 10 years.

1.0 OBJECTIVES

1.1 To compare overall survival and disease-free survival between patients with high risk melanoma who receive high dose interferon alpha-2b versus cisplatin, vinblastine, DTIC plus IL-2 and interferon.

1.2 To evaluate the toxicities of these two regimens in this patient population.

1.3 To investigate the predictive value for disease outcome (OS and DFS) and explore the relationship with patient clinical characteristics (# of involved lymph nodes, ulcerated primary, extracapsular extension) of minimal residual disease (MRD) by RT-PCR in the peripheral blood at baseline.

1.4 To investigate the effects of treatment (high dose IFN vs. biochemotherapy) on the status of MRD in peripheral blood at 12 and 52 weeks.

1.5 To explore the relationship between MRD status at 12 weeks and 52 weeks, with subsequent overall survival.

2.0 BACKGROUND

Malignant melanoma has been well recognized to affect a young patient population. The median age of diagnosis of patients with lymph node involvement in the recent Intergroup trials E1684 and E1690 was in the late 40's. *(1, 2)* Adjuvant high-dose interferon (IFN) given for a one year period of time has benefited this important group of patients. In both trials of high-dose IFN, there was a statistically significant relapse-free survival advantage, when compared with observation alone. In E1684, there was also a statistically significant overall survival advantage associated with treatment, and was the basis of a successful application to the FDA in patients with high-risk Stage IIB and Stage III melanoma. This overall survival advantage has not been reproduced in the E1690 trial to date. These results indicate some benefit associated with the use of high-dose interferon. High-dose interferon is likely to remain the treatment of choice for patients at high risk who wish to receive treatment. Clearly, however, additional strategies are warranted for this young, high-risk population, which still experiences a 50% likelihood of metastasis and death at 5 years.

High-dose IFN has been combined with both dacarbazine (DTIC) and tamoxifen in patients with metastatic melanoma in a recent Eastern Cooperative Oncology Group (ECOG) trial E3690. The addition of high-dose IFN to DTIC did not provide significant improvement in either response rate, time to treatment failure or overall survival, but was associated with greater toxicity. *(3)* Dacarbazine and cisplatin have also been combined with high-dose IFN in a Southwest Oncology Group study **SWOG-9350** for patients with metastatic melanoma. Only one response (4%) was seen among the 25 patients treated. A moderate incidence of Grade 3 and 4 toxicities made this a difficult treatment regimen. *(4)* Overall, it appears unlikely that additional chemotherapies can be added to high-dose IFN with the expectation of improved response rates and without additional toxicities.

Interleukin-2 (IL-2) has demonstrated single-agent activity in patients with metastatic melanoma including a durable complete response rate of 6%. *(5)* The single-agent activity of IL-2 in metastatic melanoma prompted many investigators to combine IL-2 with available single and multi-agent chemotherapy regimens beginning in the late 1980's. To date, well over 1,000 patients have been treated with IL-2 combined with chemotherapy. The majority of treatment regimens have been Phase II trials where IL-2 was administered on an inpatient basis. *(6 - 17)* Two recent large reviews have summarized experience with IL-2 both alone and in combination. Keilholz et al in a recent review compared the results of IL-2 alone, IL-2 plus IFNα, IL-2 plus chemotherapy, and Il-2 plus IFNα and chemotherapy. *(18)* The IL-2 was given by continuous infusion in all of the 631 patients. Interleukin-2 with IFN and chemotherapy was associated with the highest response rates (44.8%, p=.001) and the longest median survival duration (11.4 months). The 5-year survival of patients treated with IL-2, IFN and chemotherapy, was 12%. Allen et al, in a meta-

analysis, compared chemotherapy (DTIC or cisplatin based regimens) with IL-2 alone, IL-2 plus IFNα and IL-2 combined with IFNα and chemotherapy. *(19)* One-hundred fifty-four studies involving over 7,000 patients were analyzed. The highest response rates (47%) were found when IL-2 was combined with IFN, cisplatin, and dacarbazine. Response duration for IL-2, IFN and chemotherapy (10.0 months), were statistically superior ($p<0.05$) to either IL-2 alone or chemotherapy alone (8 and 7 months, respectively).

The best way to combine or sequence chemotherapy with biologic therapies has been an area of some interest. Legha, et al., in several Phase II trials, has evaluated various schedules of cisplatin, vinblastine, DTIC (CVD), chemotherapy combined with IL-2 and interferon. *(9)* Sequential therapy with alternating cycles of biotherapy and chemotherapy have been evaluated. Trials have evaluated both biotherapy and chemotherapy first. A large experience with concurrent administration of chemotherapy and biotherapy has also been reported. *(20)* The greatest benefit has generally been associated with regimens in which the chemotherapy has been given either first or concurrently. The concurrent biochemotherapy regimen of Legha, et al., has been reported in 53 assessable patients with metastatic melanoma and demonstrated 11 complete and 22 partial remissions for an overall response rate of 64%. *(20)* The median response duration was 6 months and the number of durable complete remissions beyond 2 years was 9%. The high response rates and overall benefit associated with this regimen was of interest to the cooperative groups and its administration over a brief 5-day hospitalization appeared practical. Of concern, however, was the incidence of neutropenic fever and bacteremia (64% and 51%, respectively). In addition, two-thirds of patients required transfusion with pack cells and almost 50% required platelet transfusions. A modification of this regimen was piloted by Atkins, et al., and reported in 1997. *(21)* Modifications included prophylactic antibiotics, the replacement of central lines with each treatment cycle, the reduction of the velban dose to 4.8 mg/m^2, the addition of G-CSF on Days 7 - 16 of each cycle, and the aggressive use of antiemetics. In addition, strict conservative dose modifications criteria were incorporated, and patients were treated for a maximum of 4 cycles. Forty evaluable patients have been reported with this regimen demonstrating a response rate of 48% with 20% of patients achieving a complete remission. Of particular note is that over half of these patients had received prior high-dose interferon as adjuvant therapy. Unfortunately, in this series of patients, 6 responding patients relapsed first in the central nervous system. The ability to administer effective system therapy at an earlier time point in the adjuvant setting has the potential to prevent secondary seeding to the central nervous system. Biochemotherapy approaches also have the advantage of being delivered over a shorter treatment period than high dose Interferon (9 weeks versus 52 weeks) which may improve patient acceptance for receiving adjuvant therapy, particularly if it is more effective. Eligible patients for this treatment trial will be high-risk patients with nodal, satellite, and in-transit involvement and those with recurrent nodal disease. This group is estimated to have a 60% or greater risk of metastasis and death within 5 years of diagnosis and therefore would be most likely to benefit from this type of treatment.

A Phase III trial in metastatic melanoma is presently underway, Intergroup **E3695**, which is comparing chemotherapy alone with biochemotherapy. A logical question is whether biochemotherapy should be evaluated in the adjuvant setting before there is data that it is superior to chemotherapy alone in metastatic disease. There is adequate precedent for this in both melanoma and other areas of the cancer field. In colon and rectal cancer, 5-FU combinations have demonstrated response rates in the 20% range in metastatic disease with rare long-term survival. However, in the adjuvant setting several of these combinations have been associated with up to a 33% reduction in relapse rate and an overall survival improvement. High-dose interferon has demonstrated only modest activity in the metastatic melanoma setting with response rates in the 15% range. In two large adjuvant trials in patients with high-risk melanoma, however, it has demonstrated consistent relapse-free survival advantage and in one trial, an overall survival advantage. Thus, the degree of efficacy in the metastatic disease setting may not be the most effective guide for considering therapies in the adjuvant setting. It does make sense, however, to consider promising treatment combinations which have demonstrated their effectiveness in the metastatic setting in well designed prospective randomized adjuvant Phase III trials in patients at high risk for metastasis.

Use of IL-2 in Children

A Phase I study of IL-2 conducted in children established a maximum tolerated dose (MTD) of 3 x 10^6 U/m^2/day x 5 by continuous infusion. *(22)* This pediatric study used Roche IL-2. The conversion from Roche Units to International Units is 1:3; thus the pediatric MTD would be 9 x 10^6 IU/m^2/day x 5 days. A Phase II study in children was then conducted using the 3 x 10^6 U/m^2/day dose x 4 days weekly x 3. *(23)* This MTD is also the same MTD established in adults, 3 x 10^6 U/m^2/day x 7 days. *(24)*

Given that the MTD in children and adults are the same and that the dose used in the **S0008** trial is the same as the pediatric MTD, an IND is not necessary for this study.

The use of various body fluids to diagnose and monitor human cancer which is below the level detectable by standard imaging approaches has been long sought by a number of cancer researchers. The development of the polymerase chain reaction (PCR) and the use of reverse transcriptase to transcribe RNA into DNA, made it feasible to detect small numbers of RNA transcripts in samples which contained over 10^6 or 10^7 cells. The use of RT-PCR and approaches based on this technique rapidly led to the development of assays for minimal numbers of tumor cells based on their patterns of gene expression. *(25 - 30)* Some of these were tumor specific such as a fusion or hybrid mRNA, or a unique gene rearrangement in ALL or other lymphoid derived tumors. *(25 - 28)* In solid tumors, the efforts have been targeting tissue restricted or even epithelial derived transcript which would not be expected to be normally found in the blood. *(29, 30)* Unexpectedly, a number of cancer patients have expressed transcripts of tumor-associated genes in their blood suggesting hematogenous dissemination. *(29 - 31)* Melanoma represents an ideal disease to evaluate this approach due in part to the large number of genes which are lineage restricted (gp100, MART-1, Tyrosinase,) and/or embryonic/testis (MAGE-3). The lineage-restricted genes being tested in this study are pigmented cells-melanocyte lineage. A number of studies have examined the presence of RNA transcripts in either the blood or the lymph nodes of patients with different stages of melanoma. *(31 - 40)* These retrospective analyses have yielded provocative results and even suggested that patients with histologically negative sentinel lymph nodes which are RT-PCR + for melanoma expressed genes are much more likely to develop progressive disease. *(39, 40)* The findings in the peripheral blood can be summarized as follows: *(32 - 38)*

1. RT-PCR+ in blood correlated with clinical stage and tumor bulk

2. RT-PCR+ in blood defined a patient subset more likely to relapse -2-3 fold in small trials; and has been associated with shortened DFI

3. RT-PCR+ in blood correlated with AJCC staging and prediction of relapse

4. Approximately 35 - 55% of patients have +RT- PCR in blood from Stage III patients based on several small retrospective studies

5. The more marker genes which were positive by RT-PCR then the better the correlation and accuracy with stage and outcome (predictive value)

Inclusion of Women and Minorities

The following table shows the distribution of gender and race in two previous Southwest Oncology Group coordinated or participated adjuvant melanoma trials.

	N (eligible)	Male	Female	White	Black	Other
	586	343	243	576	1	9
SWOG-9111 (E1690)	589	378	211	583	4	2

The reason for the high proportion of white patients is that melanoma occurs most frequently in whites. Its occurrence is much less frequent in other races. This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Based on the patient distributions of **SWOG-9035** and **SWOG-9111**, the projected accrual by race and gender for this study are as follows:

N (eligible)	Male	Female	White	Black	Other
410	252	158	404	2	4

Previous reports have suggested gender differences in the incidence and outcome of melanoma in favor of female patients. However little data exist regarding potential gender and treatment interactions. The current study will explore this interaction but is not adequately powered to answer the question due to the large sample size requirement and study length constraints.

3.0 DRUG INFORMATION

3.1 Cisplatin (CDDP) (Platinol®) (NSC-119875)

a. DESCRIPTION

Cis-diamminedichloroplatinum (Platinol® or cisplatin) is a heavy metal complex and is water soluble. It is a white lyophilized powder with a molecular weight of 300.1.

Mechanism of Action: It acts as a bifunctional alkylating agent.

b. TOXICOLOGY

Human Toxicology: Human toxicity includes anorexia, nausea, vomiting, renal toxicity (with an elevation of BUN, creatinine, serum uric acid and impairment of endogenous creatinine clearance, as well as renal tubular damage), ototoxicity (with hearing loss which initially is in the high-frequency range, as well as tinnitus), peripheral neuropathy and hyperuricemia. Much more severe and prolonged toxicity has been observed in patients with abnormal or obstructed urinary excretory tracts. Raynaud's phenomena and digital ischemia has been described. Anaphylactic-like reactions including facial edema, bronchoconstriction, tachycardia and hypotension may occur within minutes of administration. Myelosuppression, often with delayed erythrosuppression, is expected. In the high-dose treatment regimen with osmotic diuresis, the nadir of white cells and platelets occurred regularly at about two weeks with recovery generally at about three weeks after the initiation of therapy. Rare complications are alopecia, seizures, loss of taste and allergic reactions. Tetany may occur due to hypomagnesemia and/or hypocalcemia. Other electrolyte disturbances may occur. At high doses patients have experienced optic neuritis, papilledema,

cerebral blindness, blurred vision, and altered color perception. Patients have also experienced cardiac abnormalities, elevated SGOT and rash. Subsequent courses should not be given until serum creatinine returns to normal if elevated. Audiometric analyses should be monitored and courses withheld until auditory acuity is within normal limits. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

Pregnancy and Lactation: Cisplatin can cause fetal harm when administered to a pregnant woman. In mice, cisplatin is teratogenic and embryotoxic. No information is available on the excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

c. PHARMACOLOGY

Kinetics: After a single IV dose, increased concentration is found in the liver, kidneys and small and large intestines. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding which exceeds 90% of the radioactivity in the second phase. Urinary excretion is incomplete with only 27 to 43% of the radioactivity excreted in the first five days. The initial fractions of radioactivity are largely unchanged drugs. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents. Cisplatin penetrates into CNS poorly.

Formulation: Cisplatin is available as 10 mg and 50 mg vials of dry powder which are reconstituted with 10 ml and 50 ml of Sterile Water for Injection USP, respectively. Cisplatin is also available as an aqueous solution, 1 mg/ml, in 50 or 100 ml vials.

Storage and Stability: The intact vials may be stored at room temperature (15 - 25°C) for the lot life indicated on the package. Do not refrigerate. Once reconstituted, the solution should be kept at room temperature to avoid precipitation. The reconstituted solution is stable for 20 hours at room temperature, although, due to a lack of preservatives, the solution should be used within eight hours of reconstitution. The solution may be further diluted in a chloride-containing vehicle such as D5NS, NS, or D5-1/2NS (precipitate occurs in D5W).

Administration: In this protocol, cisplatin will be given immediately after preparation as an intravenous infusion over a 30 - 60 minute period. **Needles or intravenous sets containing aluminum parts that may come in contact with cisplatinum (Platinol) should not be used for preparation or administration, as a black precipitate is formed within 30 minutes.**

Supplier: Cisplatin is commercially available, and should therefore be purchased by a third party. This drug will not be supplied by the NCI.

3.2 Dimethyl Triazeno Imidazole Carboximide (DTIC), (Dacarbazine), (NSC-45388)

a. DESCRIPTION

The chemical structure of DTIC is 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide. Three hypotheses have been offered as the mechanism(s) of action of DTIC: inhibition of DNA synthesis by acting as a purine analog, action as an alkylating agent, and/or interaction with SH groups.

b. TOXICOLOGY

Human Toxicology: Myelosuppression is the dose-limiting toxicity. The predominant side effect observed in humans has been anorexia, nausea and vomiting. This occurs with maximal intensity on the first day of a five-day course, and in many patients, it is less with each subsequent day. Myelosuppression consisting of thrombocytopenia and leukopenia occurs in approximately one-quarter of patients after a five-day course of 250 mg/M^2. The time course for this myelosuppression is generally maximal approximately three weeks after administration with the period of recovery variable. Other side effects reported included infrequent flu-like syndrome associated with fever and myalgia, phlebitis, tissue necrosis, hepatic toxicity, anaphylaxis, photosensitivity, alopecia, and facial flushing. Rarely, DTIC has caused diarrhea.

c. PHARMACOLOGY

Kinetics: After IV administration, plasma disappearance is biphasic with the initial half-life of 19 minutes and terminal half-life of 5 hours. In patients with renal and hepatic dysfunction half-life is lengthened to 55 minutes and 7.2 hours. 40% of unchanged DTIC is excreted in the urine in 6 hours. The drug is not apparently bound to plasma proteins.

Formulation: 100 and 200 mg ampules containing a white powder.

Storage and Stability: The drug must be stored in a refrigerator 2° to 8°C (36° - 46°F) at a temperature of 4°C or less and protected from the light while stored. Once reconstitution occurs, the drug should be utilized within an 8-hour period.

Administration: Dacarbazine 100 mg/vial and 200 mg/vial are reconstituted with 9.9 ml and 19.7 ml, respectively, of Sterile Water for Injection, USP. The resulting solution contains 10 mg/ml of dacarbazine. The reconstituted drug may be given as a rapid intravenous injection (although this may be quite painful) or more preferable as an infusion in 150 - 200 cc of diluent over a 15 - 30 minute period. This latter form of administration is rarely associated with any pain along the infusion site.

Supplier: DTIC is commercially available, and therefore should be purchased by the third party. This drug will not be provided by the NCI.

3.3 Filgrastim (r-metHuG-CSF) (NSC-614629) (BB-IND-2704)

a. DESCRIPTION

Filgrastim, Neupogen®, recombinant-methionyl human granulocyte-colony stimulating factor, granulocyte-colony stimulating factor, r-methHuG-CSF, is a protein produced by E. coli into which has been inserted the human granulocyte colony-stimulating factor gene. Filgrastim differs from the natural protein in that the N-terminal amino acid is a methionine and it is not o-glycosylated. G-CSF functions as a hematopoietic growth hormone; it increases the proliferation,

differentiation, maturation and release of precursor cells into mature blood cells of the neutrophil lineage. G-CSF has demonstrated in vitro effects on mature neutrophils, including an increased expression of chemotactic receptors, enhanced phagocytosis and intracellular killing of certain organisms, as well as enhanced killing of target cells that are bound by antibodies.

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 69 µg/kg/day given IV or SC, with no toxic effects attributable to filgrastim. A maximum tolerated dose has not yet been determined.

Classification: Colony stimulating factor; cytokine.

b. TOXICOLOGY

The most frequently reported adverse effect was medullary bone pain, occurring in 20 - 25% of patients in Phase II and III trials. When bone pain was reported it often preceded a rise in the circulating neutrophil count; it occurred more frequently in patients treated with 20 - 100 µg/kg/day of intravenously administered filgrastim and less often in lower subcutaneous doses. The pain was generally mild to moderate in severity, and usually controlled with non-narcotic analgesics such as acetaminophen. Other side effects include transient but reversible increases of alkaline phosphatase, lactate dehydrogenase and uric acid levels. These occurred in 27 - 58% of patients, without clinical sequelae observed. Elevations of leukocyte alkaline phosphatase levels have also been noted but the significance is not yet known. Less frequently reported adverse events related to filgrastim administration include subclinical splenomegaly, exacerbation of pre-existing skin rashes, alopecia, and thrombocytopenia, and cutaneous vasculitis. Ischemic or infarcted colon, sometimes with involvement of other parts of the gastrointestinal tract, has been seen in patients receiving paclitaxel and G-CSF therapy. Patients reporting abdominal discomfort should be monitored closely. The specific etiologic role of paclitaxel, other chemotherapeutic agents or G-CSF is not entirely defined. It is conceivable that the high doses of chemotherapy used in these studies induced sufficiently severe neutropenia that these patients were at risk for this complication based on the myelotoxicity alone. If this is the case, then the use of G-CSF may actually assist in preventing this occurrence in other patients receiving high-dose paclitaxel chemotherapy. A review of the Amgen database of over 10,000 patients treated on company-sponsored trials reveal that the occurrence of only one case of typhlitis, two instances of intestinal ischemia, and six occurrences of intestinal perforation. However, it is remotely possible that the G-CSF may have contributed in some unforeseen way to these events.

Rarely, allergic-type reactions have occurred. Since the commercial introduction of filgrastim there have been reports (< 1 in 4,000 patients) of symptoms suggestive of an allergic-type reaction, but in which an immune component has not been demonstrated. These have generally been characterized by systemic symptoms involving at least two body systems, most often skin (rash, urticaria, edema), respiratory (wheezing, dypsnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first thirty minutes after administration and appeared to occur more frequently in those patients who received filgrastim intravenously. Rapid resolution of symptoms occurred in most cases after administration of standard supportive care, and symptoms recurred in more than half the patients when rechallenged.

Precautions: filgrastim should be used with caution in patients with pre-existing cardiac conditions such as hypertension, angina pectoris and cardiac dysrhythmias. Until further data become available, precaution should be exercised if filgrastim is administered to those patients with myeloid malignancies.

Pregnancy and Lactation: No clinical trials have been performed in pregnant or lactating women. Therefore, administration of filgrastim, (r-metHuG-CSF) during pregnancy or lactation is not recommended until further data are available.

Contraindications: filgrastim is contraindicated in those patients with known hypersensitivity to E. coli-derived proteins.

c. PHARMACOLOGY

Formulation: Recombinant G-CSF, filgrastim, NEUPOGEN®, is supplied as a clear, colorless preservative-free liquid for parenteral administration. Single use vials contain filgrastim 300 µg/ml in a preservative-free solution with 0.59 mg/ml acetate, 50 mg/ml sorbitol, 0.004% Tween® 80, 0.035 mg/ml sodium, and water for injection, USP, pH 4.0 to make 1 ml filgrastim Neupogen® is commercially available in 2 vial sizes: 300 µcg/1 ml and 480 µg/1.6 ml.

Dilution: If required, filgrastim may be diluted in 5% dextrose. Filgrastim diluted to concentrations between 5 and 15 µg/ml should be protected from adsorption to plastic materials by addition of albumin (Human) to a final concentration of 2 mg/ml. When diluted in 5% dextrose or 5% dextrose plus albumin (Human), filgrastim is compatible with glass bottles, PVC and polyolefin IV bags, and polypropylene syringes. Dilution of filgrastim to a final concentration of less than 5 µg/ml is not recommended at any time. Do not dilute with saline at any time; product may precipitate.

Mode of Action: Hematopoietic regulator with effects on both immature bone marrow progenitors and mature myeloid cells; it acts by supporting growth of human bone-marrow-derived, colony-forming units and enhancing neutrophil-mediated, antibody-dependent cellular toxicity.

Storage and Stability: Filgrastim should be refrigerated and not allowed to freeze. It is stable for 24 hours at room temperature if the solution remains clear. At a concentration of 5 mcg/ml or greater in D5W, filgrastim is stable for 7 days at room or refrigerator temperatures. At dilutions from 5 to 14 mcg/ml, albumin in a final concentration if 2 mcg/ml should be added to protect against adsorption. Addition of albumin is unnecessary when the drug is diluted to a concentration greater than or equal to 15 mcg/ml in D5W. Concentrations of less than 5 mcg/ml should not be used. Dilutions in D5W are stable in glass bottles, polyvinyl chloride, polyolefin or polypropylene bags and IV sets, and Travenol Infusors.

Dose Specifics: This study utilizes a dose of 5 µg/kg subcutaneously on Days 7 - 16 continuing until the AGC exceeds 10,000/µl on two successive determinations.

Preparation: Draw appropriate dose into syringe for subcutaneous injection.

Incompatibilities: Normal saline.

Side Effects

Musculoskeletal: In clinical trials medullary bone pain was the only consistently observed adverse event attributed to Filgrastim and was reported in approximately 24% of patients across all indications. The bone pain was generally mild to moderate in severity and controllable in most patients with non-narcotic analgesia; infrequently, bone pain was severe enough to require narcotic analgesia.

Cardiovascular**:** Rarely fluid retention; transient hypotension; pericardial effusion.

Dermatologic: Local inflammation at the injection site; rarely cutaneous vasculitis.

Other: Transient, mild to moderate elevations of uric acid, LDH, alkaline phosphatase and leukocyte alkaline phosphatase when given with cytotoxic drugs.

Nursing Guidelines

Filgrastim should be kept in the refrigerator until needed and the vials should not be shaken.

The drug should be administered at the same time each day. Vials of filgrastim are single-dose and the remaining drug should be discarded.

Refer to protocol for information regarding requirements for documentation of doses administered, temperatures, side effects, etc.

Acetaminophen is the recommended analgesic for mild bone pain.

Duration of therapy will be determined by the return of blood counts (WBC/ANC) to specific values.

Administration: Filgrastim is administered as a single daily injection by SC bolus injection, by short IV infusion (15 - 30 minutes), or by continuous SC or continuous IV infusion.

Supplier: G-CSF (Filgrastim) is commercially available. However, for the purposes of this study, G-CSF will be supplied by the drug manufacturer, Amgen, Inc., to those patients whose third party coverage does not cover the cost of the drug. Please see Appendix 19.5 for instructions.

3.4 Interferon Alpha-2b (Intron-A) (NSC-377523)

a. DESCRIPTION

Interferon alpha-2b recombinant is a water soluble protein with a molecular weight of 19,271 daltons produced by recombinant DNA techniques.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound, interferon initiates a complex sequence of intracellular events resulting in inhibition of viral replication, suppression of cell proliferation, augmentation of the phagocytic activity of macrophages, and augmentation of the specific cytotoxicity of lymphocytes for target cells.

b. TOXICOLOGY

Human Toxicity: The major toxicity of alpha interferon is a "flu-like" syndrome which occurs in a dose-dependent fashion and consists of fatigue, fever, chills, myalgias, and headache. These symptoms tend to diminish with continuing therapy. Other side effects include anemia, thrombocytopenia, leukopenia, anorexia, nausea, vomiting, diarrhea, dyspepsia, dysphagia, abdominal pain, dizziness, rash, dryness or inflammation of the oropharynx, dry skin or pruritis, weight loss, diaphoresis, paresthesias, partial alopecia, reactivation of herpes labialis, transient impotence, arthralgias, increases in bilirubin, LFTs and alkaline phosphatase. Renal/bladder toxicities include microscopic hematuria, pyuria, azotemia, proteinuria, acute renal failure, glycosuria and albuminuria. Rarely, CNS effects are seen to include numbness, confusion, paresthesia, inability to concentrate, depression, dry mouth, encephalopathy, seizure, coma, psychomotor retardation, syncope, hemianopsia, taste change, aphasia, neuropathy, tremors, somnolence, hallucinations, memory dysfunction, personality disorder, anxiety, eye pain, and agitation. Rare adverse cardiac events have included hypertension, hypotension, chest pain, arrhythmias, palpitations and myocardial infarction. Pulmonary toxicities include orthopnea, dyspnea, coughing, and pulmonary edema/ARDS. Some patients have experienced hyperglycemia, increased clotting times and cyanosis.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of Intron-A: nephrotic syndrome, renal failure, renal insufficiency, pancreatitis, and psychosis including hallucinations. Additionally, the following adverse reactions have been identified during postapproval use of Intron-A alone or in combination with Rebetol: aplastic anemia and pure red cell aplasia. Sarcoidosis or exacerbation of sarcoidosis has been reported. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

c. PHARMACOLOGY

Kinetics: Elimination half-life after SQ or IM administration was approximately 2 - 3 hours, with levels below detection limits by 16 hours. With IV administration, serum concentrations peaked by the end of infusion and were undetectable 4 hours after infusion. Serum-neutralizing antibodies have been detected but are low in occurrence. The clinical significance of this is unknown.

Formulation: Powder for Injection - The 3, 5, 18, 25 and 50 million IU packages are to be used for intramuscular or subcutaneous injection and are supplied with an accompanying diluent. The 10 million IU package is for intramuscular, subcutaneous or intralesional injection. Solution for Injection - The 10 and 25 million IU packages are for use by intramuscular or subcutaneous injection, and not for intralesional use. The alpha interferon should be reconstituted with Sterile Water for Injection, USP. Data on file at Schering indicates that the admixture of alpha interferon in 0.9% Sodium Chloride is stable up to 24 hours when all of the following conditions are met:

1. Storage is between 2 and 25°C (36 and 77°F).
2. Concentration of alpha interferon is 1 x 10^5 IU/ml or greater.
3. Parenteral container is made of glass or the following plastic parenteral containers: Lifecare® minibag from Abbott or Viaflex® minibag from Travenol (USA version only).

Since interferons adhere to glass and plastic, special care must be taken when working with low concentrations since the potential exists to lose a greater percentage of activity.

Alpha interferon is not compatible with the Travenol Infusor. It is incompatible with 5% Dextrose Injection, USP.

Storage: Lyophilized powder, accompanying diluent, reconstituted solution and injectable solution - Vials must be stored in a secured refrigerator at 2 - 8°C (36 - 46°F). DO NOT FREEZE OR SHAKE.

Preparation: For intravenous injection, it is recommended that interferon alfa-2b be administered as a 100,000 unit/ml solution to minimize adsorption of the drug to glass and plastic containers. The appropriate dose (after reconstitution of the interferon powder) should be added to 100 ml of 0.9% sodium chloride; the final concentration should not be higher than 10 MU/100 ml. The interferon alfa-2b should be used immediately after it is added to the 100 mls of 0.9% sodium chloride.

Administration: Interferon alfa-2b is administered by subcutaneous or intramuscular injection. Intravenous doses should be diluted in sodium chloride 0.9% 100 ml and given over 20 - 30 minutes.

Supplier: Interferon alpha-2b is commercially available, and should therefore be purchased by a third party. This drug will not be supplied by the NCI.

3.5 Recombinant Human Interleukin-2 (Novartis) (IL-2, Aldesleukin, Proleukin®) (NSC-373364)

a. DESCRIPTION

IL-2 was identified in 1976 by Morgan and Ruscetti. Initially described as a factor in a lymphocyte supernatant which caused proliferation of activated T-cells, IL-2 has been characterized as a protein with a molecular weight of approximately 15,000 daltons. Messenger RNA from the human cell line Jurkat was used to create cDNA which has been inserted into an E.coli expression vector. The resulting rIL-2 contains two amino acid changes from the native sequence, the result of site-specific mutagenesis, and is not glycosylated. In vitro and in vivo biological activity of the native and recombinant IL-2 have been essentially identical.

b. TOXICOLOGY

Toxicities experienced with IL-2 include the following: anemia, leukopenia, thrombocytopenia, eosinophilia, nausea and vomiting, diarrhea, mucositis, bowel perforation, glossitis, hyperbilirubinemia, elevated liver function tests, oliguria, anuria, elevation of serum creatinine and renal failure. Pulmonary toxicities include dyspnea, pulmonary edema requiring intubation, and ARDS. Arrhythmias, angina, myocardial infarction, vascular capillary leak syndrome, myocarditis, atrial flutter, and hypotension have occurred. Neurologic toxicities include disorientation, confusion, forgetfulness, inappropriate behavior, hallucinations, paranoia, paresthesia, psychosis, nightmares, obtundation, somnolence, coma, combative behavior, headache, grand mal seizures, encephalopathy, blurring vision, vision changes and focal neurologic deficit. Erythema, desquamating rash, pruritus, bronchospasm, anaphylaxis, hyperuricemia, hypoglycemia, hypocalcemia, acidosis, hyponatremia, and coagulopathies have also occurred. The following side effects have also been reported: fever (rarely to hyperthermia), malaise, chills, alopecia, arthralgia,

myalgia, myositis, acrocyanosis, dry mouth, nasal congestion, autoimmune phenomena (hypothyroidism and pemphigus), thrombophlebitis, possible predisposition to infection, and death on study.

c. PHARMACOLOGY

Kinetics: In humans, IL-2 distributes quickly in the extravascular fluid space. This results in an initial distribution phase of approximately five minutes after IV bolus injection. The beta phase of its serum disappearance is approximately 60 - 100 minutes, and excretion appears to be predominantly due to renal filtration and catabolism. IL-2 absorption and excretion in rabbits following IM or SC administration is prolonged, with a serum half-life of several hours. This has also been confirmed in humans. Evaluation of human in vivo immunological functional

changes in these trials is preliminary. Patients have been observed to have enhanced mitogen-stimulated PBL proliferation, increased NK activity, increased delayed cutaneous hypersensitivity and induction of LAK activity.

How Supplied: Supplied by Novartis Pharmaceuticals Corporation as single-use vials containing 22 million IU (~ 1.3 mg) IL-2 as a sterile, white to off-white lyophylized cake plus 50 mg mannitol and 0.18 mg sodium dodecyl sulfate, buffered with approximately 0.17 mg monobasic and 0.89 mg dibasic sodium phosphate to a pH of 7.5 (range 7.2 to 7.8).

Preparation: Each 5 cc vial has a labeled strength of 1.3 mg (22 Million IU). The IL-2 should be reconstituted with 1.2 ml of Sterile Water, providing a solution of 18 million IU/ml or 1.1 mg/ml, for injection, USP. Diluent should be directed against the side of the vial to avoid excess foaming. Swirl contents gently until completely dissolved. Do not shake. Since vial contains no preservative, reconstituted solution should be used within 8 hours.

Storage: Intact vials are stored in the refrigerator (2 - 8°C) with protection from light. Each vial bears an expiration date.

Dilution/Stability and Administration: Prepare according to the manufacturer's recommendations in the approved labeling.

Supplier: Human Recombinant IL-2 manufactured by Novartis Pharmaceuticals Corporation will be supplied by the NCI. The Clinical Drug Request Form (NIH-986) should reference NSC-373364 when rIL-2 is ordered.

Drug Ordering and Drug Accountability: NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 and a CV. If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Drug may be requested by completing a Clinical Drug Request (NIH-986) and mailing it to the Drug Management and Authorization Section, PMB, DCTD, NCI, 9000 Rockville Pike, EPN Room 707, Bethesda, MD 20892-7422 or faxing it to 301/480-4612. For questions call 301/496-5725.

Drug Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all drugs received from DCTD using the NCI Drug Accountability Record (DAR) Form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

3.6 Vinblastine sulfate (Velban) (NSC-49842)

a. DESCRIPTION

Chemistry: Vinblastine is the salt of an alkaloid derived from Vinca Rosea Linn., a common flowering herb known as the periwinkle. It has the empirical formula of $C_{46}H_{58}O_9H_4H_2SO_4$.

Mechanism of Action: Tissue culture studies suggest an interference with metabolic pathways of amino acids leading from glutamic acid to the citric acid cycle and to urea. A number of studies in vitro and in vivo have demonstrated its stathmokinetic effect and various atypical mitotic figures. Other studies indicate an effect on cell energy production required for mitosis and the interference with nucleic acid synthesis. Reversal of antitumor effect by glutamic acid and tryptophan has been observed.

b. TOXICOLOGY

Human Toxicology: Leukopenia is the usual dose-limiting side effect, with the nadir falling four to seven days post-injection. Thrombocytopenia and anemia may occur. Gastrointestinal toxicities include nausea, vomiting, diarrhea or constipation, abdominal pain, ileus, peptic ulcer, rectal bleeding and anorexia. Fever and phlebitis have also been seen when the drug is given as an infusion. Extravasation may lead to tissue necrosis. Ten percent of the patients will experience peripheral neuropathy. Alopecia can also occur. Vinblastine can also cause paresthesia, loss of deep tendon reflexes, depression, headache, dizziness and convulsions. Other toxicities include bronchospasm, dyspnea, chills, stomatitis, pharyngitis, jaw pain, bone pain, pain in organs containing tumor tissue, malaise, and weakness. When vinblastine is administered in combination with bleomycin and cisplatin, cardiac toxicities have occurred. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: After rapid IV administration, a triphasic serum decay pattern followed. The respective half-lives were 3-7 minutes, 1.6 hours, and 24.8 hours. Toxicity of the drug is increased with hepatic excretory insufficiency suggesting that the biliary system is the major route of excretion.

Formulation: 10 mg/vial, saline diluent.

Storage and Stability: Vials should be stored in a refrigerator (2° to 8°C or 36° to 46°F) to assure extended stability. Refrigerate unreconstituted drug. Reconstituted drug is stable for 30 days, if refrigerated. Solvents that raise or lower pH of the resulting solution from between 3.5 - 5.0 should not be used.

Administration: The daily dose of vinblastine will be given by intravenous injection.

Supplier: Vinblastine sulfate is commercially available, and should therefore be purchased by a third party. This drug will not be supplied by the NCI.

4.0 STAGING CRITERIA

Classification for Cutaneous Melanoma - AJCC 6th Edition, 2002

N classification

N1	one lymph node	a: micrometastasis[a] b: macrometastasis[b]
N2	2 - 3 lymph nodes positive	a: micrometastasis[a] b: macrometastasis[b] c: in-transit met(s)/satellite(s) without metastatic nodes
N3	4 or > metastatic lymph nodes; matted lymph nodes; or combinations of in-transit met(s)/ satellite(s) **and** metastatic lymph node(s)	

[a] Micrometastases are diagnosed after elective or sentinal lymphadenectomy.

[b] Macrometastases are defined as clinically detectable lymph node metastases confirmed by therapeutic lymphadenectomy or when any lymph node metastasis exhibits gross extracapsular extension.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each patient, this section must be photocopied, completed and submitted to the Data Operations Center in Seattle (see Section 14.0).

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ 5.1 Only patients with melanoma of cutaneous origin or of unknown primary are eligible for this study. (Patients with distant metastases are not eligible. Patients with melanoma of ocular, mucosal or other non-cutaneous origin are not eligible.) All patients must fulfill one of the following criteria:

FOR PATIENTS WITH NEWLY DIAGNOSED MELANOMA OR A PREVIOUSLY DIAGNOSED PRIMARY NOW WITH SUBSEQUENT, CLINICAL, REGIONAL NODAL DISEASE AND/OR SATELLITE/IN-TRANSIT DISEASE:

_____ a. ulcerated* primary melanoma with 1 or more involved lymph nodes (micro/occult or macro/clinically overt)

OR

_____ b. non-ulcerated or unknown primary with:

1. One macro/clinically overt lymph node metastasis including a single matted nodal mass;

   (Patients with non-ulcerated or unknown primary tumor and a single, micrometastatic lymph node are NOT eligible.)

OR

2. Two or more lymph node metastases (micro/occult or macro/clinically overt) and/or matted nodes;

OR

_____ c. any satellite/in-transit metastasis with or without lymph node involvement.

OR

FOR PATIENTS WITH RECURRENT DISEASE:

_____ d. Patients are eligible if there is recurrent disease in the regional nodal basin of a previous complete lymphadenectomy.

*Ulceration is defined as the absence of an intact epidermis overlying a portion of the primary melanoma based on pathologic microscopic observation of the histologic sections.

_____ 5.2 Patients are eligible for this trial either at initial presentation of their melanoma or at the time of the first detected nodal, satellite/in-transit, or recurrent disease in prior lymphadenectomy basin. Nodal, satellite/in-transit metastasis or recurrent disease in a prior complete lymphadenectomy basin must have been confirmed histologically by H & E stained slides.

_____ 5.3 Patients with multiple regional nodal basin involvement are permitted as long as they are the appropriate anatomic drainage basins for the primary site. Gross or microscopic extracapsular nodal extension is permitted.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ 5.4 Patients at initial presentation of melanoma must undergo an adequate wide excision of the primary lesion, if present, meeting the criteria outlined in Appendix 19.1 (Surgical Requirements).

Patients with previously diagnosed melanoma must have had all current disease resected with pathologically negative margins and must have no evidence of disease at the primary site or undergo re-resection of the primary site.

A full lymphadenectomy meeting the criteria outlined in Appendix 19.1 is required for all patients including those with positive sentinel nodes and those with positive satellite/in-transit metastasis. Patients with recurrent disease who have had a prior complete lymphadenectomy fulfill this requirement. All disease must have been resected with negative pathological margins and no clinical, radiologic, laboratory, or pathological evidence of any incompletely resected melanoma.

Patients must be registered within 56 days of either lymphadenectomy OR surgery to remove recurrent disease (if complete lymphadenectomy has previously been performed).

Lymphadenectomy or surgery to remove recurrent disease (circle one)

Date performed _____

_____ 5.5 Patients must not have had prior radiotherapy, chemotherapy (including infusion or perfusion therapy) or any immunotherapy with interferon and/or interleukins for any type of cancer, with the exception that patients who have received post-lumpectomy radiation therapy for breast cancer are eligible.

_____ 5.6 Patients must have adequate hepatic function documented by a serum bilirubin ≤ 1.5 x the institutional upper limit of normal and liver enzymes (SGOT or SGPT and LDH and alkaline phosphatase) ≤ 2 x the institutional upper limit of normal within 28 days prior to registration. However, if LDH or alkaline phosphatase is above normal, (greater than IULN but less than 2 x IULN) a contrast enhanced CT scan or MRI of liver is required to document the absence of tumor prior to randomization. This scan must be performed within 28 days prior to randomization. **NOTE: No scan is necessary if LDH and alkaline phosphatase are within normal limits.**

Bilirubin _____ IULN _____ Date obtained _____

SGOT/ SGPT (circle one) _____ IULN _____ Date obtained _____

LDH _____ IULN _____ Date obtained _____

Alk Phos _____ IULN_____ Date obtained _____

CT Scan/MRI of liver if clinically indicated (circle one) Date performed _____

_____ 5.7 Patients must have an absolute granulocyte count ≥ 1,500/µl and platelet count ≥ 100,000/µl obtained within 14 days prior to registration.

AGC_____ Date obtained _____

PLTS _____ Date obtained _____

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ 5.8 Patients must have either a serum creatinine ≤ 1.5 mg/dl **or** a calculated creatinine clearance ≥ 75 cc/min using the following formula:

$$\text{Estimated Creatinine Clearance} = \frac{(140 - \text{age}) \times \text{WT (kg)} \times 0.85 \text{ if female}}{72 \times \text{creatinine (mg/dl)}}$$

These tests must have been performed within 28 days prior to registration. (**NOTE**: **Creatinine clearance is not necessary if creatinine levels are normal.)**

Serum creatinine _____ Date obtained _____

OR

Calc creatinine clearance _____

_____ 5.9 Patients must have a CXR or chest CT, and if clinically indicated, a CT scan or MRI of the head performed prior to registration but not more than 4 weeks prior to definitive surgery (lymphadenectomy, satellite/in-transit resection, nodal recurrence resection).

Chest X-ray/Chest CT (circle one) Date performed _____

CT scan/MRI of Head only if clinically indicated (circle one)

Date performed _____

_____ 5.10 Patients must not have evidence of congestive heart failure, symptoms of coronary artery disease, serious cardiac arrhythmia, or evidence of prior myocardial infarction on EKG. The qualifying EKG must have been performed prior to study registration, but no earlier than 28 days prior to the definitive surgery. A normal cardiac stress test within 182 days prior to randomization is required for all patients over 50 years old or those with abnormal EKG or any history of cardiac disease.

EKG _____ Date performed _____

Cardiac Stress Test _____ Date performed _____

Patient Age _____

_____ 5.11 Patients must not have evidence of symptomatic pulmonary disease. PFT's within 182 days prior to registration showing a FEV1 > 2.0 liters or ≥ 75% of predicted are required for patients over 50 or with history of pulmonary symptoms.

Pulmonary Function Test(s) Performed _____ Date obtained _____

FEV1 _____ Predicted FEV1 _____

_____ 5.12 Patients must not have autoimmune disorders, conditions of immunosuppression or treatment with systemic corticosteroids. Patients with known AIDS or HIV-1 associated complex or known to be HIV antibody seropositive or known to be recently PCR + for Hepatitis are not eligible for this study. The severely depressed immune system found in these infected patients and the possibility of premature death would compromise study objectives.

_____ 5.13 Patients must be willing and able to discontinue all antihypertensive medications only if randomized to Arm 2 (beginning 24 hours prior to treatment through treatment Day 5 of each treatment cycle).

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

——— 5.14 All patients registered by Adult Cooperative Groups must be 18 years of age or older.

All patients registered via the Children's Oncology Group (COG) must be between 10 and 18 years of age.

——— 5.15 All patients must have a Zubrod Performance Status of 0 - 1 (see Section 10.1).

——— 5.16 Patients must not be planning to receive concomitant other biologic therapy, radiation therapy, hormonal therapy, other chemotherapy, surgery, or other therapy while on this protocol.

——— 5.17 Patients registered by Adult Cooperative Groups to the study on **May 15, 2003** or later must be willing to participate in minimal residual disease studies (MRD) as outlined in Section 15.0.

Patients registered by Adult Cooperative Groups prior to **May 15, 2003** should be offered participation in the MRD studies.

Patients registered via the Children's Cooperative Group (COG) are **strongly encouraged**, but not required to participate in the MRD studies outlined in Section 15.0.

——— 5.18 Pregnant or nursing women may not participate in this trial because of the increased risk of fetal harm including fetal death from the chemotherapeutic agents. Women/men of reproductive potential may not participate unless they have agreed to use an effective contraceptive method. A beta HCG pregnancy test is required within 14 days prior to registration for women of childbearing potential.

Beta HCG Pregnancy Test _____ Date obtained _____

——— 5.19 No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.

——— 5.20 If Day 14, 28, 56 or 182 falls on a weekend or holiday, the limit may be extended to the next working day.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines.

——— 5.21 Patients must be informed of the investigational nature of this study and sign and give written informed consent in accordance with institutional and federal guidelines.

The Sample Informed Consent document for patient's between 10 and 18 years of age is located in Appendix 19.7.

——— 5.22 At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

6.0 STRATIFICATION FACTORS

6.1 Patients will be randomized to one of the two treatment arms of the study. Patients will be stratified by the following factors:

a. Nodal Stage: N1 or N2 vs N3 (see Section 4.0).

b. Degree of lymph node involvement: micrometastases only vs. any macrometastases (including satellite/intransit metastases, see Section 4.0).

c. Ulceration of the primary tumor: yes vs. no vs. unknown (including unknown primary).

NOTE: Patients with recurrent disease will be stratified with respect to the above factors based on their original disease.

7.0 TREATMENT PLAN

For questions relating to treatment or dose modifications, please contact Dr. Flaherty at 313/576-8715 or Dr. Thompson at 206/598-2514.

7.1 Good Medical Practice

Required prestudy tests are listed in Section 5.0. The following pre-study tests are optional but recommended and should be obtained prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not impact on patient safety in the clinical judgment of the treating physician.

a. Mg++, Ca++

b. Glucose

c. Albumin

d. T4/TSH

e. CPK

f. BUN

g. PT

h. PTT

i. Urinalysis

j. Audiogram

7.2 **ARM 1: One Year High-Dose Interferon Alpha-2b**

AGENT	DOSE†	ROUTE	SCHEDULE	DURATION
Induction Therapy				
Interferon Alpha-2b	20 million units per m^2/day	IV	Days 1 - 5 (M - F)	Weeks 1 - 4
Consolidation/Maintenance Therapy*				
Interferon Alpha-2b	10 million units per m^2/day subcutaneous	SC injection	Days 1, 3, 5 (M,W,F)	Weeks 5 - 52

†Doses must be rounded to the nearest 1.0 million unit.
*Patients who are deemed competent to self administer the subcutaneous maintenance doses of IFN Alfa - 2b may do so following the first 4 weeks of treatment. (See Appendix 19.3 - Self Administration of Interferon.)

NOTE: Corticosteroids and other immunosuppressive medications are contraindicated because of immune suppressive effects. No systemic treatment with steroids (including creams) is permitted. Exception: patients may receive antihistamines if there is no alternative medication.

a. Day 1 of each week of induction therapy should be administered at the registering institution. Days 2 - 5 of interferon administration for Weeks 1 - 4 may be administered at an institution other than the registering institution provided the patient has not encountered any life-threatening or unusual toxicities during Week 1 of treatment and the registering physician still retains primary responsibility for the patient's treatment. Documentation concerning all drugs administered, side effects and tests performed must be forwarded to the registering institution. The registering institution must document any care given at an outside institution. Home Health Agencies (HHA) may be used to treat patients, if the HHA is under the supervision of an approved institution and the nurse treating the patient is supervised by an approved physician.

7.3 **ARM 2: Cisplatin, Vinblastine, Dacarbazine, Interleukin 2 (IL-2), Interferon Alpha-2b and G-CSF**

AGENT	DOSE	ROUTE	SCHEDULE	DURATION
Cisplatin	20 mg/m^2/day	IV over 30 minutes	Days 1 - 4	q 21 days x 3
Vinblastine	1.2 mg/m^2/day	Short IV immediately following cisplatin	Days 1 - 4	q 21 days x 3
Dacarbazine	800 mg/m^2	IV over 1 hour following vinblastine	Day 1 (**only**)	q 21 days x 3
IL-2	9 million international units/m^2/day	Continuous IV over 24 hours	Days 1 - 4 (96 hours)	q 21 days x 3
Interferon Alpha-2b	5 million units/m^2/day	SC	Days 1 - 5 Days 8, 10 and 12	q 21 days x 3
G-CSF	5 µg/kg/day	SC	Days 6 - 15	q 21 days x 3

Cycles will be repeated at 3 week intervals for 3 cycles of treatment. All patients will be admitted to the hospital on the morning of Day 1. Interferon Alpha-2b, the IL-2 infusion and the prehydration for cisplatin should be planned to begin around 3:00 PM. Patients will be discharged after Day 5 with subsequent doses of interferon and G-CSF to be administered in the outpatient setting or at home.

All patients will have renal function tests, blood counts, and a thorough physical examination, including neurological examination, prior to each cycle of biochemotherapy. If abnormalities are found, these parameters will be rechecked on a weekly basis and further therapy will be withheld until laboratory values and performance status return to within the eligibility criteria (i.e., as in Section 5.0). **Patients must have discontinued all antihypertensive therapy at least 24 hours prior to initiation of each cycle.** Antihypertensive therapy may be re-started on Day 6 after the completion of treatment on each cycle at the discretion of the managing physician.

a. **SPECIFIC ADMINISTRATION GUIDELINES FOR CISPLATIN, DACARBAZINE, IL-2 AND INTERFERON ALFA 2-b**

Hydration - Patients will be **prehydrated** with 1,000 ml of D5 1/2 normal saline + 8 meq of $MgSO_4$ given over 3 hours daily prior to cisplatin administration. Hydration will otherwise be with D5 1/2 normal saline plus 20 meq of KCL/L at 100 ml per hour. If urine output is less than 500 cc/8 hour shift, then patients should receive a 500 cc fluid bolus over 30 minutes. If urine output remains unsatisfactory (< 500 cc's over 8 hours) at the time that the cisplatin is due to be administered, patients may receive Lasix 20 mg IV and an additional 500 cc hydration over 1 hour prior to proceeding with cisplatin therapy.

Antiemetics - Patients should receive HT[3] **antiemetics** (ondansetron 32 mg PO or IV or granisitron 1 - 2 mg IV) 30 minutes prior to cisplatin administration Days 1 - 4 and in the AM on Days 5, 6 and if necessary Day 7. Ativan (1mg q 6 hrs), Compazine (10 mg po or 25 mg pr q 6 hours prn) or comparably effective agent, should be given after chemotherapy. **Steroids will not be permitted.**

Cisplatin will be administered in 250 ml of normal saline over 30 minutes daily for 4 days starting on Day 1 of chemotherapy.

Vinblastine will be administered as a short infusion on Days 1 - 4 immediately following cisplatin.

Dacarbazine will be administered in 250 ml of D5W over 1 hour following the vinblastine on Day 1 only. Use of a large vein or indwelling central catheter device will decrease burning and irritation that often accompanies infusion. Further dilution of the drug in any common IV solution may also decrease irritation.

IL-2 will be mixed in 250 ml of D5W and 0.1% Alb and delivered as a continuous intravenous infusion over 24 hours daily for 4 days (96 hours) using a mechanical pump.

Interferon Alpha-2b will be given by subcutaneous injection daily for 5 days along with IL-2 and on Days 8, 10 and 12. Interferon will be administered at the start of the IL-2 infusion for each day and on Day 5 at the end of the 4th 24 hour infusion.

G-CSF will be given subcutaneously on Days 6 - 15. G-CSF will be given daily continuing until the AGC exceeds 10,000/µl on two successive determinations. G-CSF should be discontinued at least 24 hours before the next chemotherapy dose. While the patient is receiving G-CSF, the CBC should be monitored at least twice a week (more frequently if clinically indicated).

b. Venous Access Catheters

Three IV access lines are necessary for this treatment protocol. Triple lumen central venous catheters are strongly recommended. Patients without adequate peripheral venous access should have a triple lumen central venous catheter placed prior to initiating each cycle of therapy. Central venous catheters should be placed preferentially in the subclavian vein. **Infusaports should not be used for IL-2 administration or continuous IV hydration as this may create an unacceptable infection risk;** however, they may be used for administration of the cytotoxic chemotherapy with access needles removed at the end of each day's treatment. Central venous catheters must be removed at the end of each hospitalization. Patients requiring central venous catheters will receive antibiotic prophylaxis with Ciprofloxacin or Keflex 250 mg po BID, Days 1 - 17 of each cycle. If catheter related bacteremia develops, the catheter should be removed and parenteral antibiotic treatment (Vancomycin 1 gm IV q 12 - 24 hours depending on renal function) may be required.

c. All supportive measures consistent with optimal patient care will be given throughout the protocol treatment. Patients requiring other chemotherapy, radiation therapy or immunosuppressive medications including steroids will be removed from protocol treatment. Any exceptions must be discussed with the Study Coordinator.

d. Supportive Care for Constitutional Symptoms

All patients will receive the following on Days 1 - 5 and as indicated on Days 8, 10 and 12 to abrogate toxicity related to IL-2 and interferon alpha-2b.

The following medications are necessary as part of the supportive care:

Acetaminophen: 650 mg PO every 4 hours (total 3,900 mg/day) will be administered 30 - 60 minutes prior to initiation of IL-2/IFN therapy and continued until discharge. Acetaminophen 650 mg should be administered 30 - 60 minutes prior to and every 4 hours x 2 following the interferon alpha-2b injections on Days 8, 10 and 12.

Naproxen: (375 mg) will be administered po q 12 hours for fever and chills days 1-5.

Ranitidine or Nizatidine: (150 mg) po q 12 hours for prophylaxis of gastrointestinal bleeding.

The following medications should be administered as needed:

Meperidine: (25 - 50 mg) IV should be given in the case of severe rigors.

Diphenoxylate: 1 tab po q 4 - 6 hours or supplemented with paregoric.

Loperamide: 5 - 10 ml q 4 - 6 hours PRN will be used for diarrhea.

Diphenhydramine: (25 - 50 mg po) or **Atarax** (25 mg po) may be used for generalized erythematous skin rash and/or pruritus.

Furosemide: (20 - 40 mg) IV/po qd may be administered for symptomatic fluid retention during IL-2 infusion. Routine treatment of asymptomatic fluid retention is unnecessary. Lasix should not be given prior to Cisplatin administration except as noted above under "hydration".

7.4 **Criteria for Removal from Protocol Treatment**

a. Disease Progression (as defined in Section 10.2).

b. Unacceptable toxicity (as defined in Section 8.0).

c. The patient may withdraw from the study at any time for any reason.

d. Completion of therapy.

e. For any treatment delay of > 3 weeks patient may only continue with permission of Study Coordinator.

7.5 All reasons for removal from protocol treatment must be documented on the Adjuvant Melanoma Off Treatment Notice (Form #52588).

7.6 All patients must be followed for 10 years or death, whichever comes first, regardless of whether or not protocol treatment has been discontinued.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATION

8.1 This study will utilize the CTC (NCI Common Toxicity Criteria) Version 2.0 for toxicity and Adverse Event reporting. A copy of the CTC version 2.0 can be downloaded from the CTEP home page (http://ctep.info.nih.gov). **All appropriate treatment areas should have access to a copy of the CTC version 2.0.**

8.2 **ARM 1: One Year High Dose Interferon Alpha-2b**

Induction therapy Weeks 1 - 4 shall be evaluated separately from Consolidation/Maintenance Weeks 5 - 52. A patient requiring dose modification(s) in the first month will therefore receive treatment at Week 5 at full dose. Any doses missed during treatment due to toxicity or patient compliance, should not be made up.

ARM 1 - DOSE MODIFICATION TABLE

	Full Dose	Dose Mod 1	Dose Mod 2	Dose Mod 3
Induction	Weeks 1 - 4			
High Dose IFN Alpha-2b	20 million units/m^2	13.3 million units/m^2	6.6 million units/m^2	Remove from protocol treatment
Consolidation/ Maintenance	Weeks 5 - 52			
High Dose IFN Alpha-2b	10 million units/m^2	6.6 million units/m^2	3.3 million units/m^2	Remove from protocol treatment

ARM 1
TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

TOXICITY	GRADE 2	GRADE 3	GRADE 4
<u>Blood/Bone Marrow</u>			
Leukopenia Thrombocytopenia	Full Dose	Hold therapy*; reduce one dose level	Removal from protocol treatment
Anemia	Hold therapy*; reduce one dose level		
Neutropenia	Full Dose	Full Dose	Reduce one dose level
<u>Cardiovascular</u>			
Arrhythmia Cardiac - Other	Hold therapy until return to normal*; reduce one dose level after formal cardiologic evaluation and clearance	Removal from protocol treatment	Removal from protocol treatment
<u>Gastrointestinal</u>			
Nausea, vomiting and/or diarrhea	Administer supportive care; if persistent for more than 2 weeks reduce one dose level	Hold therapy*; reduce one dose level	Removal from protocol treatment
Weight loss	Hold therapy for weight loss observed over a 1 month period until weight gain or stabilization*		
<u>Hepatic</u>			
ALK PHOS, Bilirubin or SGOT/SGPT	Full Dose	Hold therapy until return to ≤ Grade 1*; reduce one dose level	Removal from protocol treatment
<u>Neurology</u>			
Cognitive disturbance Mood alteration Neuropathy - motor Neuropathy - sensory	Full Dose	Hold therapy*; reduce one dose level (evaluation by specialist)	Removal from protocol treatment
<u>Renal/Genitourinary</u>			
Proteinuria	Full Dose	Hold therapy until return to ≤ Grade 2*; reduce one dose level	Removal from protocol treat ment
Creatinine	Hold therapy*; reduce one dose level	Removal from protocol treatment	Removal from protocol treatment

***PLEASE NOTE:** If a patient experiences any of the toxicities listed in the above table, the patient must have a dose modification as indicated (unless otherwise specified). Treatment must be held until the toxicity returns to institution's normal limits, patient's baseline, or normal limits per the CTC (NCI Common Toxicity Criteria) Version 2.0, then reduce as indicated above. Dose re-escalation will not be attempted following resolution of toxicity that required dose interruption or attenuation.

8.3 **ARM 2: Cisplatin, Vinblastine, Dacarbazine, Interleukin 2 (IL-2), Interferon Alpha-2b and G-CSF**

a. Hematologic Toxicity

TOXICITY	GRADE 3 without fever or bleeding	GRADE 4 Neutropenia; Febrile Grade 3 Neutropenia; Grade 4 Thrombocytopenia or Bleeding with Grade 3 Thrombocytopenia
Week 1 (Day 1 - 5)	No dose reduction required	Hold CVD, IL-2/IFN, resume when Grade 3 or less without bleeding or fever, with full dose chemo and 50% dose reduction in IL-2/IFN from the baseline dose (permanent dose reduction). If the listed toxicities recur, permanently discontinue IL-2/IFN. (Chemotherapy will resume once toxicity resolves to ≤ Grade 3). Patients with unresolved toxicity at the end of Week 1 will have a CBC drawn on Day 8 (see Interferon Dosing Day 8 - 12).
Interferon Dosing: Week 2 (Day 8 - 12)	IFN held*	IFN held*
**Future Chemo-therapy Dosing: Day 22 or later	No dose reduction required	Reduce DTIC and Vinblastine doses by 25% from the baseline dose in subsequent cycles.

*Resume full dose IFN in subsequent cycles.

****Subsequent cycles of therapy will be delayed until ANC and platelets return to eligibility level. If the next cycle is delayed > 2 weeks the patient will be removed from protocol treatment.**

b. Renal/Genitourinary

Creatinine	Drug	Dose
> 1.6 mg/dl	Cisplatin	Hold until ≤ 1.6*

*On Days 1 - 4, the patient should receive a 500 cc normal saline fluid bolus and have creatinine rechecked in four hours. If serum creatinine improves to ≤ 1.6, scheduled cisplatin chemotherapy may proceed. If creatinine remains > 1.6, cisplatin for that day should be held. If creatinine remains > 2.0 despite fluid boluses, cisplatin should be discontinued for the remainder of that cycle. Missed doses of cisplatin should not be made up. Patients should continue on vinblastine, IL-2 and interferon unless Grade 3 nephrotoxicity develops, in which case treatment should be modified as described below. **Subsequent cycles may proceed at full-dose as long as creatinine has returned to ≤ 1.6**.

Grade 3 nephrotoxicity following completion of 5 day treatment course, Weeks 2 and 3 of each cycle, will necessitate a 25% reduction in cisplatin dose from the baseline dose for the subsequent cycle. Patients experiencing repeat Grade 3 nephrotoxicity should have a second 25% reduction in cisplatin from the baseline dose. Patients still experiencing Grade 3 nephrotoxicity despite a 50% reduction in cisplatin from the baseline dose will be removed from protocol treatment.

c. Neurology

Development of neuropathy - motor or sensory of > Grade 2 will require discontinuation of cisplatin. Dacarbazine and vinblastine as well as IL-2 and interferon will continue to be administered.
vPatients experiencing Grade 2 cognitive disturbance or mood alteration during therapy should have IL-2/IFN therapy held until toxicity returns to ≤ Grade 1. IL-2/IFN should then be restarted at a 50% dose reduction for the remainder of this and all subsequent cycles.

Patients experiencing these side effects only during Week 2, require modification of interferon only (50% dose reduction) for the remainder of the current and all subsequent cycles.

Cognitive disturbance or mood alteration from Days 13 on will only require dose modification, as described in Section 8.3n, for subsequent cycles if ≥ Grade 3.

d. Auditory/Hearing

If moderate to severe inner ear/hearing loss occurs, which interferes with communication, the investigators should discuss the treatment options with the patient. Cisplatin therapy may be discontinued or the cisplatin dose may be reduced by 25% from baseline. If the patient requires a hearing aid, cisplatin will be discontinued and an otorhinolaryngologist will examine the patient to exclude other causes for hearing loss. Dacarbazine, vinblastine, IL-2 and interferon therapy will be continued.

e. **Blood Pressure Management: For patients ≥ 40 years old**

Patients must have discontinued any antihypertensive therapy at least 24 hours prior to initiation of each cycle. Blood pressure will be checked every 4 hours for stable patients during IL-2 therapy. Patients experiencing hypotension (as described below) will have SBP and pulse checked at a minimum of every 2 hours. Target minimum systolic blood pressure (SBP) will be 85 for patients under 40 years old with no prior history of cardiac disease or hypertension and 90 for the remainder of the patients. **Cisplatin, vinblastine and interferon will only be administered when patient's SBP > target minimum SBP off of all pressor support.**

Hypotension - Patients over age 40 or with cardiac history or hypertension.

Target SBP for patients ≥ 40 years old is 90.	
SBP < 90, but ≥ 85	Administer NS 250 cc IV bolus over 15 minutes. May repeat x 1. If SBP fails to increase to > 90 hold IL-2 and Interferon until SBP > 90; then resume IL-2 and Interferon at 50% of original dose.
SBP < 85	Hold IL-2 and Interferon. Give fluid boluses as above. Resume IL-2 and Interferon at 50% of original dose when SBP returns to >target SBP.
SBP remains < 85	Hold IL-2 and interferon. Start Dopamine at 2 µg/kg/min and titrate to SBP > target SBP. (Maximum Dopamine dose 6 µg/kg/min.). Resume IL-2 and interferon at 50% of original doses once SBP > 90 off of Dopamine.
SBP fails to return to > 90	Add Neo-synephrine starting at 0.2 µg/kg/min and titrate to keep SBP > 90. Patients requiring both Dopamine and Neo-synephrine will receive no further IL-2 during that cycle. Interferon will be given at 50% of original dose once SBP > 90 off all pressors. For subsequent cycles both IL-2 and interferon will be given at 50% dose reduction from original dose.

Cisplatin, Dacarbazine and Vinblastine will be held until SBP > 90 without pressor support.

If hypotension resolves within 6 hours of scheduled dosing cisplatin, vinblastine and IFN for that particular day can be administered. Otherwise it should be omitted for that particular treatment day.

Patients should be placed on a cardiac monitor while receiving vasopressor support.

Missed IL-2 infusion time will not be made up.

All dose reductions in IL-2 and IFN are permanent.

Patients experiencing hypotension requiring pressor support, despite a 50% reduction in IL-2 and IFN dosages, will continue onstudy, but will receive no additional IL-2. Interferon may continue at 50% of the original dose.

Blood Pressure Management: For patients < 40 years old

Patients must have discontinued any antihypertensive therapy at least 24 hours prior to initiation of each cycle. Blood pressure will be checked every 4 hours for stable patients during IL-2 therapy. Patients experiencing hypotension (as described below) will have SBP and pulse checked at a minimum of every 2 hours. Target minimum systolic blood pressure (SBP) will be 85 for patients under 40 years old with no prior history of cardiac disease or hypertension and 90 for the remainder of the patients. **Cisplatin, vinblastine and interferon will only be administered when patient's SBP > target minimum SBP off of all pressor support.**

Hypotension - Patients under age 40 without cardiac history or hypertension

Target SBP for patients < 40 years old with no cardiac history or hypertension is 85.	
SBP < 85, but ≥ 80	Administer NS 250 cc IV bolus over 15 minutes. May repeat x 1. If SBP fails to increase to > 85 hold IL-2 and Interferon until SBP > 85; then resume IL-2 and Interferon at 50% of original dose.
SBP< 80	Hold IL-2 and Interferon. Give fluid boluses as above. Resume IL-2 and Interferon at 50% of original dose when SBP returns to > 85.
SBP remains < 80	Hold IL-2 and interferon. Start Dopamine at 2 µg/kg/min and titrate to SBP > 85. (Maximum Dopamine dose 6 µg/kg/min.) Resume IL-2 and interferon at 50% of original doses once SBP > 85 off of Dopamine.
SBP fails to return to > 85	Add Neo-synephrine starting at 0.2 µg/kg/min and titrate to keep SBP > 85. Patients requiring both Dopamine and Neo-synephrine will receive no further IL-2 during that cycle. Interferon will be given at 50% of original dose once SBP > 85 off all pressors. For subsequent cycles both IL-2 and interferon will be given at 50% dose reduction from original dose.

Cisplatin, Dacarbazine and Vinblastine will be held until SBP > 85 without pressor support.

If hypotension resolves within 6 hours of scheduled dosing cisplatin, vinblastine and IFN for that particular day can be administered. Otherwise it should be omitted for that particular treatment day.

Patients should be placed on a cardiac monitor while receiving vasopressor support.

Missed IL-2 infusion time will not be made up.

All dose reductions in IL-2 and IFN are permanent.

Patients experiencing hypotension requiring pressor support, despite a 50% reduction in IL-2 and IFN dosages, will continue onstudy, but will receive no additional IL-2. Interferon may continue at 50% of the original dose.

f. Allergic or Vascular Reactions

Cisplatin/DTIC/vinblastine will be discontinued in the event of severe allergic reactions or vascular complications.

g. Hepatic

Bilirubin elevations will only require dose modifications if Grade 4 (greater than 3.0 x normal). Modifications will be as for other Grade 3 toxicities described in Section 8.3n with IL-2/IFN treatment restarted at 50% dose reduction when bilirubin decreases to Grade 3 or less.

h. Gastrointestinal

Patients experiencing Grade 3 nausea and vomiting Days 1 - 4 will have cisplatin and vinblastine held and additional antiemetics administered. If nausea/vomiting resolves to Grade 2 or less within 6 hours of scheduled chemotherapy administration, chemotherapy may proceed for that day at the usual dose. If nausea and vomiting do not respond within 6 hours only vinblastine should be administered for that day. Patients not responding within 6 hours of intended dose, with recurrent Grade 3 toxicity or Grade 4 toxicity will have a 25% reduction in cisplatin for subsequent doses during that cycle. This is a permanent dose reduction.

Patients should not be discharged until ambulatory and taking adequate po without nausea and vomiting. If nausea and vomiting are slow to resolve, daily home IV hydration may be considered. Patients experiencing Grade 3 nausea and Grade 3 or 4 vomiting following appropriate discharge will have dose decreased by 25% in subsequent cycles. Patients experiencing repeat Grade 3 nausea and vomiting despite a reduction in dose should have a second 25% reduction (50% of original dose). Patients still experiencing Grade 3 nausea and vomiting despite a 50% reduction in dose will be removed from protocol treatment.

i. Cardiovascular

Atrial Arrhythmias

Patients receiving IL-2/IFN can occasionally develop atrial arrhythmias, primarily, atrial fibrillation. Patients developing atrial fibrillation, or atrial flutter should have all therapy held and will receive Digoxin (± Verapamil) as needed to control pulse rate. If atrial fibrillation/flutter does not revert to normal sinus rhythm within twenty-four hours, cardioversion should be instituted. IL-2/IFN will be held until atrial fibrillation or flutter resolves, then may be restarted at 50% dosage reduction for the remainder of this and subsequent cycles. Patients experiencing atrial fib/flutter should be on a cardiac monitor during all subsequent IL-2 infusions and should receive Neo-synephrine rather than dopamine, as needed, for blood pressure support. Patients experiencing a subsequent episode of atrial fibrillation/flutter, despite a 50% dose reduction of IL-2/IFN, will be removed from protocol treatment.

Myocarditis

IL-2/IFN can cause subclinical myocarditis (elevated CPK MB) in about 10% of patients. Patients with elevated CPK MB bands will have all treatment held for the remainder of that cycle and IL-2/IFN restarted at a 50% dose reduction for subsequent cycles. CVD may be administered at full-dose in subsequent cycles.

j. Metabolic Acidosis

Patients with serum bicarbonate < 20 should have their hydration switched to D5 1/2 Normal Saline with 1 ampule of bicarbonate/liter at 100 cc/hour. Patients with serum bicarbonate < 18 should have IL-2/IFN therapy held, and should receive 1 ampule of sodium bicarbonate and have their hydration switched to D5 1/2 Normal Saline with 1 ampule of bicarbonate/liter at 100 cc/hour. Serum bicarbonate should be checked at 4 hour intervals and IL-2/IFN restarted at full dose when the bicarb returns to ≥ 18. Falls in serum bicarbonate to < 16 may indicate a serious concomitant problem (e.g., sepsis, bowel ischemia). In this event all therapy should be stopped for the remainder of the cycle and aggressive measures undertaken to restore serum bicarbonate and diagnose etiology. Subsequent cycles may proceed with a 50% reduction in IL-2 and interferon dose.

k. Fever

Patients experiencing fevers to greater than 38.5°C after Day 3 of therapy should have a set of blood cultures drawn from both the central line and peripherally (one set for each day). Patients should be questioned about missing or vomiting up their antipyretics. If unable to take PO medication, antipyretics should be given by suppository. Patients experiencing fevers after completion of IL-2 infusion and unrelated to interferon injections should be presumed to have bacteremia and have blood cultures drawn, receive IV vancomycin and/or other antibiotics as indicated and have central line removed as soon as possible. If also neutropenic (ANC < 500), patients should also receive appropriate antibiotic coverage for gram negative bacteria.

l. Dyspnea

Patients who experience dyspnea may receive O_2 by nasal cannula on a PRN basis.

m. Arthralgias/Myalgias

Dose reductions will be necessary only for Grade 3 toxicity. In the event of Grade 3 toxicity dose modifications will be as described in Section 8.3n.

n. Other Non-hematologic Toxicity

Patients experiencing Grade 3 non-hematologic toxicities while receiving therapy (Days 1 - 5) will have treatment held (both CVD and IL-2/IFN) until toxicity returns to Grade 2 or less. Therapy will then be restarted at full-dose of chemotherapy and a 50% dose reduction of both IL-2 and interferon. This is a permanent dose reduction. Missed IL-2 will not be made up. Missed IFN, vinblastine or cisplatin doses can be given if toxicity resolves to acceptable range within 6 hours of scheduled administration time. If Grade 4 toxicity occurs or Grade 3 toxicity recurs despite dose reduction, no further IL-2/IFN will be administered. Patients will resume CVD during that cycle, once toxicity resolves to Grade 2 or less and continue, and if indicated, subsequent cycles.

Grade 3 toxicity during Week 2 of any cycle will necessitate holding all remaining IFN injections for that cycle. Subsequent interferon will be at full-dose, unless modifications are required as described previously.

Grade 3 toxicity during Week 3 of any cycle **(not described previously)** will necessitate 25% dose reductions in CVD and 50% reductions in IL-2/IFN for subsequent cycles. Weight gain (due to fluid retention) or loss (due to anorexia) should be watched carefully. Additional laboratory studies may be indicated in individual patients. The appearance of any other symptoms which, in the opinion

of the investigator, are drug-related and are hazardous to the patient's well-being is sufficient justification to modify the dosage or omit the drug. Modifications and reasons should be clearly documented on the Study Specific Summary Form.

8.4 Dose adjustments for Toxicities Associated with G-CSF (bone pain, splenomegaly, abnormalities in uric acid concentrations, LDH and alkaline phosphatase, transient elevations of serum creatinine and aminotransferase activity). **Dose modifications for G-CSF toxicity should only be initiated if symptomatic control of the toxicity fails (i.e., analgesics such as acetaminophen or acetaminophen with codeine for myalgias or bone pain, etc.).**

Toxicity Grade	Dose Adjustment
Grade 0 - 1	No change
Grade 2	Decrease G-CSF to 3 µg/kg/d
Grade 3 - 4	Discontinue G-CSF

8.5 For questions relating to treatment or dose modifications, please contact Dr. Flaherty at 313/576-8715 or Dr. Thompson at 206/598-2514.

8.6 Unexpected or fatal toxicities (including suspected reactions) must be reported to the Operations Office, to the Study Coordinator, to the IRB and the NCI. The procedure for reporting adverse reactions is outlined in Section 16.0.

9.0 STUDY CALENDAR S0008 "Phase III Trial of High Dose Interferon Alpha 2-b Versus Cisplatin, Vinblastine, DTIC Plus IL-2 and Interferon in Patients With High Risk Melanoma"

9.1 ARM 1 - One Year High Dose IFN Alpha 2-b

REQUIRED STUDIES	PRE STUDY	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 13	Wk 26	Wk 39	Wk 52	Follow Up ƒ
PHYSICAL															
History and Physical Exam	X	X	X	X	X	X		X		X	X	X	X	X	X
Weight and Performance Status	X	X	X	X	X	X		X		X	X	X	X	X	X
Neuro Exam ∑	X	X													X
Disease Assessment	X										X	X	X	X	X
Toxicity Notation		X	X	X	X	X		X		X	X	X	X	X	X
LABORATORY															
CBC with differential/Platelets	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Creatinine and/or Creatinine Cl	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SGOT/SGPT, Bilirubin, LDH, ALK PHOS	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test §	X														
Special testing of peripheral blood for minimal residual disease (MRD) ß		X≠									X			X	
SUGGESTED LABORATORY∞															
Mg++, CA++, Glucose, Albumin, CPK, PT, PTT, BUN	X														
T4/TSH	X										X	X		XΔ	
Urinalysis	X														
X-RAYS AND SCANS															
CXR or Chest CT	X										X	X	X	X	X
CT or MRI of Head √	X														
CT or MRI of Liver Ω	X														
EKG	X														
PFTs ¶	X														
Cardiac Stress Test £	X														
Audiogram √	X														
TREATMENT															
IFN Alpha 2-b Induction		X	X	X	X										
IFN Alpha 2-b Consolidation/Maintenance (Wks 5 - 52) *						X	X	X	X	X	X	X	X	X	

NOTE: All forms for this study can be found in Section 18.0. Form Submission Guidelines can be found in Section 14.0.

∞ These chemistries are suggested prestudy for good medical practices (see Section 7.1), but are not required during treatment and follow-up for Arm 1 of this study.
§ A beta HCG pregnancy test is required for women of childbearing potential.
√ As clinically indicated.
Ω Contrast enhanced CT or MRI of liver is required if LDH or ALK PHOS are above normal (greater than IULN but less than 2 x IULN).
¶ For patients over 50 years of age or with a history of pulmonary symptoms.
£ For patients over 50 years of age, those with history of cardiac disease or abnormal electrocardiogram.
* IFN Alpha 2-b Consolidation/Maintenance should continue until Week 52 (Monday, Wednesday and Friday of every week).
Δ Obtain at completion of IFN therapy once on Week 52.
ƒ For Labs: Every 3 months until resolution of acute adverse events, or until 24 months after registration, whichever comes first. For Disease Assessment, Toxicity Notation, Neuro Exam, Scans, History and Physical Exam and Weight and Performance Status: Every 3 months until relapse/progression of disease. After relapse, every 6 months to 5 years after registration then annually thereafter until year 10.
ß See Section 5.17. Lavender top to be drawn first then discarded, submit 4 sodium citrate Cell Preparation Tubes (CPT) with 10 ml each (see Section 15.0).
≠ Peripheral blood will be obtained prior to initial treatment (after registration), at Week 13 and then following 52 weeks post initiation of therapy (completion of interferon).
∑ A basic simple neuro exam that is part of physical examination is sufficient.

9.2 ARM 2 - Cisplatin, Vinblastine, DTIC, IL-2, IFN and G-CSF

		CYCLE 1*															
REQUIRED STUDIES	PRE	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Wk	Follow
PHYSICAL	STUDY	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	12	Up *ƒ*
History and Physical Exam	X	X	X	X	X	X											X	X
Weight and Performance Status	X	X															X	X
Neuro Exam ∑	X	X															X	X
Disease Assessment	X																X	X
Toxicity Notation		X	X	X	X	X					X					X	X	X
LABORATORY																		
CBC with differential/Platelets	X	X	X	X	X	X					X					X	X	X
Creatinine and/or Creatinine Cl	X	X	X	X	X	X					X					X	X	X
SGOT, SGPT, Bilirubin, LDH, ALK PHOS ∝	X	X∝		X		X					X					X	X	X
Pregnancy Test §	X																	
residual disease (MRD) ß		X≠															X	X≠
SUGGESTED LABORATORY ∞																		
Mg++, Ca++, Glucose, Albumin, CPK, PT, PTT, BUN	X	X		X		X					X					X	X	X
T4/TSH	X																X	
Urinalysis	X	X															X	
X-RAYS AND SCANS																		
CXR or Chest CT	X																X	X
CT or MRI Head √	X																	
CT or MRI Liver Ω	X																	
EKG	X																	
PFTs ¶	X																	
Cardiac Stress Test £	X																	
Audiogram √	X																	
TREATMENT																		
Cisplatin		X	X	X	X													
Vinblastine		X	X	X	X													
Dacarbazine		X																
IL-2		X	X	X	X													
IFN		X	X	X	X	X			X		X		X					
G-CSF							X	X	X	X	X	X	X	X	X	X		
Supportive Care (see Section 7.3d).		X	X	X	X	X			XΔ		XΔ		XΔ					

NOTE: All forms for this study can be found in Section 18.0. Form Submission Guidelines can be found in Section 14.0.

* **REPEAT CYCLE 1 AS INDICATED (CYCLE = 21 DAYS) FOR A TOTAL OF THREE CYCLES.**

∝ These labs are **optional** for Day 1/Cycle 1, but **required** for Cycle 2 and Cycle 3.

∞ These chemistries are suggested prestudy for good medical practices (see Section 7.1), but are required during treatment and follow-up for Arm 2 of this study.

§ A beta HCG pregnancy test is required for women of childbearing potential.

√ If clinically indicated.

Ω Contrast enhanced CT or MRI of liver is required if LDH or ALK PHOS are above normal (greater than IULN but less than 2 x IULN).

¶ For patients over 50 years of age or with pulmonary symptoms.

£ For patients over 50 years of age, those with history of heart disease or abnormal electrocardiogram.

Δ As needed.

ƒ For Labs: Every 3 months until resolution of acute adverse events, or until 24 months after registration, whichever comes first. For Disease Assessment, Toxicity Notation, Neuro Exam, Scans, History and Physical Exam and Weight and Performance Status: Every 3 months until relapse/progression of disease. After relapse, every 6 months to 5 years after registration then annually thereafter until year 10.

ß See Section 5.17. Lavendar top to be drawn first then discarded, submit 4 sodium citrate Cepp Preparation Tubes (CPT) with 10 ml each (see Section 15.0).

≠ Peripheral blood will be obtained prior to initial treatment (after registration), at Week12 and then following 52 weeks post initiation of therapy (at 12-month follow-up).

∑ A basic simple neuro exam that is part of physical examination is sufficient.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 **Performance Status**: Patients will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.2 **Disease Progression:** Appearance of any new melanoma lesion/site.

10.3 **Disease-Free Survival**: From date of registration to date of first observation of progressive disease or death due to any cause.

10.4 **Time to Death:** From date of registration to date of death due to any cause.

11.0 STATISTICAL CONSIDERATIONS

11.1 The primary objective of this study is to compare the overall survival and disease-free survival between high risk melanoma patients treated with the standard high-dose interferon regimen versus a biochemotherapy regimen of cisplatin, vinblastine, dacarbazine, interferon and interleukin 2. Overall survival will be used for sample size and power estimation.

Based on previous data, the 5-year survival rate for the control arm is estimated to be approximately 40%. Four-hundred and ten eligible patients are targeted over three years. With three additional years' follow-up, the power to detect a survival increase is approximately 0.91 and 0.80 if the true death hazard ratio is 1.53 and 1.42 respectively. With exponential survival distributions, hazard ratios of 1.53 and 1.42 correspond to 5-year survival rates of 55% and 52.5%, respectively in the biochemotherapy arm. The power calculations also assume uniform patient entry and a one-sided logrank test at 0.05 significance level.

11.2 For early reporting, interim analyses will be conducted when 80% of the patients have been accrued, and again when 2/3 of the anticipated deaths in the control arm have been observed. The timing of the latter roughly corresponds to one year after the closure of patient accrual if the event rate is as anticipated. Evidence suggesting early termination of the study would be if the null hypothesis or the alternative hypothesis of a greater than 1.4 control vs. experimental hazard ratio is rejected at a one-sided 0.005 level. The actual decision to terminate the study early will be made by the Southwest Oncology Group Data and Safety Monitoring Committee, and will take into consideration overall survival, disease free survival, and other factors such as toxicities and complications.

The composition of the Data and Safety Monitoring Committee will be according to the current Southwest Oncology Group policy. If the decision is to continue the study to its planned completion and the event rate is as anticipated, the final analysis is targeted at three years after the end of patient accrual.

11.3 With 205 patients per arm, the power to detect an absolute 15% difference in the incidence of any toxicity is at least 0.84. This estimation is based on two-sided 0.05 significance level comparisons without multiple comparison adjustments.

11.4 Analysis will be performed to investigate whether the presence of minimal residual disease (MRD), defined as detection of any one of four melanoma markers (gp-100, MART-1, Tyrosinase, or MAGE-3) by RT-PCR, has predictive value for survival or progression of disease. It is estimated that roughly 40% of the patients will present with MRD in their blood at study entry, potentially representing worse prognosis. If MRD status is determined on 300 patients, accrued over 4 years, with 3 additional years follow up, the power to detect a better prognosis for MRD negative patients is 0.81 if the true death hazard ratio by MRD status is 1.5, assuming a treatment effect with a death hazard ratio of 1.5 favoring the biochemotherapy regimen. If no treatment effect is assumed, the power to detect a better prognosis for MRD negative patients is 0.85 if the true death hazard ratio is 1.5. These power calculations assume an exponential survival distribution, uniform patient entry and a one-sided logrank test at the 0.05 significance level.

Assuming RT-PCR results are available for 300 eligible patients, this will be sufficient to estimate the frequency of MRD at baseline to within ± 6%, (95% confidence interval).

In addition, the relationship between the presence of MRD at baseline and various patient clinical characteristics, (# of involved lymph nodes, ulceration, extracapsular extension), will be explored.

11.5 The effect of treatment on the status of MRD will also be investigated. Assuming an 10% dropout rate at 12 weeks, the power to detect a reduction in the proportion of patients with MRD from 40% at baseline to 25% at 12 weeks will be at least 0.86. However, this is a rough estimate based on an unstratified two-sided 0.05 level McNemar's test. The actual analysis will utilize a test stratified by treatment.

The relationship between MRD status at 12 weeks and subsequent overall survival will also be explored. Depending upon the number of samples obtained at 52 weeks, an attempt will be made to explore the relationships between MRD status at 52 weeks with treatment and overall survival.

12.0 DISCIPLINE REVIEW

12.1 Pathology

a. The goals of this pathology review are:

1. To verify the diagnosis of appropriate stage malignant melanoma, in order to validate patient eligibility; and
2. To record detailed information about morphologic and histologic features of the lesions, which will then be available for analyses of prognosis.

b. Failure to submit the materials necessary for review will render the patient ineligible.

c. The materials to be submitted are as follows:

1. One H&E stained section from each block of the primary lesion which document:

   The character of the vertical component at its site of deepest invasion.
   The radial components.
   The margins of excision.

   NOTE: The "bread loaf" technique is the preferred method for sampling and blocking the gross specimen (see Appendix 19.2).

2. Submit one of the following:

   i. One slide that shows either a macrometastasis in a lymph node or a matted nodal mass.
   ii. Two or more slides of at least two separate positive lymph nodes.
   iii. One slide of in-transit metastasis or satellite.
   iv. One or more representative H&E stained slides that show ulceration of the primary tumor and 1 or more slide(s) of at least one positive node.
   v. One slide showing metastases from the basin of a prior complete lymphadenectomy.

3. Sections of regional lymph nodes, if available.

4. Copy of the corresponding pathology report(s).

5. Copy of the corresponding operative report(s).

6. Southwest Oncology Group Specific Pathology Submission Form (Form #38890).

d. The materials listed above must be submitted within 30 days after the patient is registered on the study to:

Ralph J. Tuthill, M.D.
Department of Pathology
Cleveland Clinic Foundation
One Clinic Center
9500 Euclid Avenue
Cleveland OH 44195-0001

An additional copy of the protocol specific Pathology Submission Form (Form #38890) must be submitted to the Data Operations Center in Seattle each time submissions are made to Dr. Tuthill.

The materials must be identified with a "SWOG Pathology Materials" label on the outside of each package. If this label is missing, the materials will not be reviewed, rendering the patient ineligible. These labels will be provided by the Data Operations Center in Seattle. To obtain labels, please call 206/652-2267 and ask for the Pathology Coordinator.

e. Slides must be labelled to indicate the site from which they were taken.

12.2 All patients registered on this study will undergo a surgical review of the surgical excision.

a. The three goals of this review are:

1. to verify that the excision was done according to the criteria specified in the protocol (Section 19.1); and

2. to evaluate whether all known gross disease was successfully resected as planned; and

3. to confirm that the patient had high risk melanoma.

b. Failure to submit the materials necessary for review will render the patient ineligible.

c. The materials necessary for the surgical review include:

1. Copy of the operative report with detail to document that surgery was performed according to Section 19.1;

2. Copy of corresponding pathology report.

NOTE: Submit operative and pathology reports for all procedures performed for melanoma.

d. The operative reports and corresponding pathology reports are to be submitted within 14 days of registration to the Data Operations Center in Seattle.

12.3 ECOG Investigators Pathology and Surgical Review

a. ECOG Pathology Review:

The slides (outlined in Section 12.1c), the institutional pathology and operative reports, the completed ECOG Pathology Material Submission Form (Form #638), and the Southwest Oncology Group Pathology Submission Form (Form #38890) must be submitted within one month of study entry. The slides and forms are to be sent to:

ECOG Pathology Coordinating Office
Robert H. Lurie Comprehensive Cancer Center
of Northwestern University Medical School
Olson Pavilion - Room 8501
710 North Fairbanks Court
Chicago, IL 60611

Include both the ECOG and Southwest Oncology Group protocol number and patient number. The ECOG Pathology Coordinating Office will forward the slides and a copy of the Southwest Oncology Group Pathology Submission Form (Form #38890) to Dr. Tuthill.

A copy of the completed submission forms will be sent to the ECOG Coordinating Center by the ECOG Pathology Coordinating Office.

b. ECOG Surgical Review:

ECOG Institutions must submit materials as outlined in Section 12.2c to the ECOG Pathology Coordinating Office (at the above address) within 14 days of registration.

Copies of the submitted materials will be forwarded to the ECOG Coordinating Center and to the Southwest Oncology Group Data Operations Center in Seattle by the ECOG Pathology Coordinating Office.

12.4 CALGB Investigator's Pathology and Surgical Review

CALGB Pathology Review:

CALGB institutions are required to submit the slides, pathology and operative reports and Southwest Oncology Group Specific Pathology Submission Form (Form #38890) described in Section 12.1c. These materials must be submitted within 30 days after the patient has been registered, to the address listed in Section 12.1d. The slides must be labeled as described in Sections 12.1d and 12.1e. Failure to submit the materials necessary for review will render the patient ineligible.

CALGB Surgical Review:

CALGB institutions are required to submit a copy of the operative report and corresponding pathology report as described in Section 12.2c. Please label each page of the reports with both the Southwest Oncology Group and CALGB protocol and patient numbers. These materials must be submitted within 14 days of registration to:

Southwest Oncology Group Data Operations Center
Cancer Research And Biostatistics
1730 Minor Avenue, STE 1900
Seattle, WA 98101-1468

12.5 COG Investigator's Pathology and Surgical Review

Please refer to Appendix 19.7c and 19.7d.

13.0 REGISTRATION GUIDELINES

13.1 Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment).

13.2 For either method of registration, the individual registering the patient must have completed the appropriate Southwest Oncology Group Registration Form. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration procedures

a. You may register patients from Member, CCOP and approved Affiliate institutions to a Therapeutics study using the SWOG Registration program. To access the Registration program go to the SWOG Web site (http://swog.org) and click on the *Logon* link to go to the SWOG Members Area logon page (https://swog.org/visitors/logon.asp). This Web program is available at any time except for periods listed **under *Down Times*.** Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at https://swog.org/visitors/logonhelp.asp. After you have logged on, click on the *Clinical Trials* link and then the *Therapeutics Reg* link to go to the Entry Page for the Therapeutics Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files maybe found by clicking on **Starter Kit link at the logon page.**

To register a patient the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN to the institution where a registration is occurring, and

3. You are granted permission to use the Therapeutics Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/450-8088. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Therapeutics Reg program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred, and exactly what you were doing.

b. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate and CCOP Institutions

Registration by phone of patients from member, affiliate and CCOP institutions must be done through the Southwest Oncology Group Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

13.4 For either method of registration, exceptions to Southwest Oncology Group registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

13.5 **REGISTRATION AND RANDOMIZATION - ECOG INVESTIGATORS:**

Submitting Regulatory Documents:

Before an ECOG institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU Regulatory Office
Coalition of National Cancer Cooperative Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19102
FAX: 215/569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.

2. Copy of IRB Informed Consent Document.

NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. a. CTSU or IRB Certification Form.

OR

b. HHS 310 Form.

OR

c. IRB Approval Letter.

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB.

- Full protocol title and number.
- Version Date
- Type of review (full board vs. expedited).
- Date of Review
- Signature of IRB official.

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed http://www.ctsu.org/rss2.0_page.asp. If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1/888-823-5923 or E-mail CTSUContact@westat.com. Monday through Friday, 9:00 a.m. - 6:00 p.m.

Registration/Randomization:

Patients must not start protocol treatment prior to registration.

Treatment should start within five working days of randomization.

Institutions may register eligible patients to this study via the ECOG webpage 24 hours a day, 7 day a week, using the Web-based Patient Registration Program (http://webreg.ecog.org). If you need assistance or have questions, please telephone the Central Randomization Desk at the ECOG Coordinating Center at 617/632-2202. Please note that a password is required to use this program. The following information will be requested: Protocol Number; Investigator Identification (including institution name and/or affiliate and investigator's name), Patient Identification including patient's name or initials and chart number, patient's social security number, patient demographics (sex, birth date, race, nine-digit zip code and method of payment); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 5.0.

13.6 **REGISTRATION AND RANDOMIZATION - COG INVESTIGATRORS**:

Please refer to Appendix 19.7.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Form) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

14.3 Data Submission Procedures.

a. Southwest Oncology Group institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/450-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data.

14.4 ECOG Institutions

Forms submission - The original data forms as listed in Sections 14.6 - 14.14 should be submitted at the required intervals to the Southwest Oncology Group Data Operations Center, Cancer Research And Biostatistics, 1730 Minor Avenue, STE 1900, Seattle, WA 98101-1468. Include the Southwest Oncology Group protocol number and both ECOG and SWOG patient ID numbers on all data forms.

Do not use ECOG forms for this study, with the exception of the ECOG Pathology Materials Submission Form (Form #638), FDA Medwatch Form (Form #3500), and the NCI/CTEP Secondary AML/MDS Report Form.

14.5 CALGB INSTITUTIONS:

CALGB participants should submit the Southwest Oncology Group data forms listed in Sections 14.5 - 14.14 at the required intervals to:

Southwest Oncology Group Data Operations Center
Cancer Research And Biostatistics
1730 Minor Ave, STE 1900
Seattle, WA 98101-1468

Include both the Southwest Oncology Group and CALGB protocol and patient numbers on all data forms.

14.6 WITHIN 14 DAYS OF REGISTRATION:

Submit the following:

a. **S0008** Adjuvant Melanoma Prestudy Form (Form #19207).

b. Operative and Pathology Reports (see Section 12.2).

c. Completed Section 5.0.

14.7 WITHIN 30 DAYS OF REGISTRATION:

Submit pathology materials and all required paperwork per Section 12.0.

Submit an additional copy of the Protocol Specific Pathology Submission Form (Form #38890) to the Data Operations Center in Seattle.

14.8 ARM 1 (HIGH DOSE IFN ALPHA-2b): WITHIN 14 DAYS OF COMPLETING OR DISCONTINUING INDUCTION TREATMENT:

Submit the **S0008 ARM 1, Induction** Treatment and Toxicity Summary Form (Form #31218).

14.9 WITHIN 14 DAYS OF DISCONTINUATION OF PROTOCOL TREATMENTS (BOTH ARMS):

Submit a copy of the Adjuvant Melanoma Off Treatment Notice (Form #52588) documenting reasons off treatment. In addition:

a. **FOR ARM 1 (HIGH DOSE IFN ALPHA-2b)**: Submit a final **S0008** ARM 1, Maintenance Treatment and Toxicity Summary Form (Form #55930) if consolidation/maintenance therapy was given.

b. **FOR ARM 2 (CVD + IFN + IL-2 BIOCHEMOTHERAPY)**: Submit the **S0008** ARM 2, Treatment and Toxicity Summary Form (Form #27082).

14.10 ARM 1: WITHIN 14 DAYS OF 6-MONTH FOLLOW-UP:

Submit a copy of the **S0008** Arm 1, Maintenance Treatment Toxicity Summary Form (Form #55930) if the patient is continuing consolidation/maintenance therapy beyond 6 months.

14.11 WITHIN 4 WEEKS OF KNOWLEDGE OF SECOND PRIMARY MALIGNANCY:

Submit a copy of the Adjuvant Melanoma Follow-Up Form (Form #50219).

14.12 WITHIN 14 DAYS OF RECURRENCE:

If the recurrence happens while the patient is still on treatment, submit Adjuvant Melanoma Off Treatment Notice (Form #52588) and appropriate treatment summary forms per Sections 14.8 and 14.9. If the recurrence happens after off treatment, submit the Southwest Oncology Group Adjuvant Melanoma Follow-Up Form (Form #50219).

14.13 ONCE OFF TREATMENT SUBMIT EVERY 6 MONTHS UNTIL 5 YEARS AFTER REGISTRATION THEN ANNUALLY THEREAFTER UNTIL 10 YEARS AFTER REGISTRATION OR DEATH (WHICHEVER COMES FIRST):

Submit a copy of the Southwest Oncology Group Adjuvant Melanoma Follow-Up Form (Form #50219).

14.14 WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit a copy of the Adjuvant Melanoma Off Treatment Notice (Form #52588) and the appropriate treatment/toxicity summary form/page (if the death occurs while on treatment) or a final Southwest Oncology Group Adjuvant Melanoma Follow-Up Form (Form #50219) (if the death occurs after off treatment). Also, submit a copy of the Notice of Death (Form #49467).

15.0 SPECIAL INSTRUCTIONS

Peripheral blood will be obtained prior to initial treatment (after registration), at Week 13/12 of the two arms (ARM 1 = Week 13 and ARM 2 = Week 12) and then following 52 weeks post initiation of therapy (completion of IFN on ARM 1 and at 12-month follow-up on ARM 2). Specimen shipping kits will be provided by the National Genetics Institute (NGI) and may be requested at the following address (it is recommended that shipping kits be requested approximately 3 days prior to each blood draw):

National Genetics Institute
Catey Watkinson
Sr. Client Service Representative
2440 S. Sepulveda Bl., Suite 130
Los Angeles, CA 90064
Phone: 800/352-7788 Ext. 4125
Fax: 310/996-1070

Specimen Processing and Shipping Instructions

The kits will contain:

- 1 EDTA tube - lavender top
- 4 Cell Preparation tubes (CPTs) - blue tiger top with 8-mL fill volume
- Instructions for collection, centrifugation and shipping
- Pre-paid Airborne waybill

First draw the lavender top tube. This tube will contain the skin plug which expresses the Tyr, Mart and gp100 markers and therefore, must be drawn first and then discarded. Next draw the blue tiger top tubes. PBMCs can be isolated after a single spin. Immediately prior to centrifugation, invert the tubes several times. Spin the blue tiger top tubes at 18 - 25°C for 20 minutes at 2,500 rpm in a swinging bucket (vertical) rotor centrifuge. It must be a swinging bucket rotor or there will not be good separation. After spinning, invert the tubes 5 times. Approximately 30 mL of blood will be drawn from each patient at each time point for PBMC isolation. Ship ambient via overnight delivery (Airborne) to NGI at the address listed above. Specimens should be sent only Monday through Thursday. **Saturday deliveries will not be accepted**. If you have technical questions, please contact Jeff Albrecht (NGI - Manager of Research and Development) at 800/352-7788.

All samples must be submitted with the National Genetics Institute Laboratory Testing Requisition Form (Form #31267). A copy of the National Genetics Institute Laboratory Testing Requisition Form (Form #31267) must be sent at the same time to the Data Operations Center in Seattle.

NOTE: All samples will be discarded by the National Genetics Institution (NGI) after testing.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

For each investigational drug supplied for a study, drug disposition (drug receipt, dispensing, transfer or return) shall be maintained on the NCI Investigational Drug Accountability Record. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the Drug Accountability Record; the SWOG ID # and initials of the subject to whom drug is dispensed, the dose, the date(s) and quantity of drug dispensed to the subject, the date(s) and quantity of drug returned to the NCI or transferred to another NCI-approved protocol, the balance forward, lot number and recorder's initials. These Drug Accountability Records must be readily available for inspection and are open to FDA or NCI inspection at any time.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 2.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 19.8 for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov. An AdEERS report must be submitted to the Southwest Oncology Group Operations Office by one of the following methods:

- Electronically submit the report via the AdEERS Web-based application located at http://ctep.cancer.gov, **or**
- **Only if submitting electronically is not possible**, fax the completed NCI Adverse Event Expedited Report – Single Agent or Multiple Agents – paper template, located at http://ctep.cancer.gov, to 210/677-0006.

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 7 working days of learning of the event.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable must also be reported according to local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.1. If there is any question about the reportability of an adverse event or if on-line AdEERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/450-8808 or adr@swog.org, before preparing the report.

Table 16.1. Expedited reporting requirements for adverse events experienced by patients who have received commercial drugs on this study.

Attribution	**Grade 4**		**Grade 5[a]**	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**AdEERS**	**AdEERS**
Possible, Probable, Definite	**AdEERS**		**AdEERS**	**AdEERS**

AdEERS: Indicates an expedited report is to be submitted using the NCI AdEERS Commercial Drug pathway within 7 working days of learning of the event.

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

f. Reporting secondary AML/MDS/ALL

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported using the NCI/CTEP Secondary AML/MDS Report Form in lieu of AdEERS. The following supporting documentation must also be submitted within 30 days:

- a copy of the pathology report confirming the AML/MDS/ALL diagnosis; and
- (if available) a copy of the cytogenetics report.

Submit the Report and documentationto:

Investigational Drug Branch by fax to 301-230-0159 or mail to P.O. Box 30012 Bethesda, MD 20824-0012	**and**	Southwest Oncology Group ATTN: SAE Program 14980 Omicron Drive San Antonio, Texas 78245-3217

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the AML/MDS Report must be submitted for the most recent trial.

ECOG INSTITUTIONS TOXICITY REPORTING

Toxicity Reporting

All ECOG Investigators are responsible for reporting adverse events according to the NCI guidelines. ECOG participants should employ definitions of adverse events as provided by the Southwest Oncology Group reporting guidelines in Section 16.0. Both 24 hour and written/electronic adverse event reports should be made directly to the Southwest Oncology Group according to the instructions in that section.

Reporting AML/MDS

	NCI/CTEP Secondary AML/MDS Report Form[1]
AML/MDS	X

[1] To be completed within 30 days of diagnosis of AML/MDS that has occurred during or after protocol treatment. A copy is to be sent to ECOG and the Southwest Oncology Group , accompanied by copies of the pathology report (and when available, a copy of the cytogenetic report). ECOG will forward copies to the NCI.

ECOG Telephone Number: 617/632-3610
ECOG Fax Number: 617/632-2990
ECOG Mailing Address: ECOG Coordinating Center
FSTRF
ATTN: Adverse Event
900 Commonwealth Avenue
Boston, MA 02215

NCI Fax Number: 301/230-0159
NCI Mailing Address: Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824

FDA Fax Number: 1/800-332-0178
FDA Mailing Address: MedWatch
5600 Fishers Lane
Rockville, MD 20852-9787

Southwest Oncology Group
Mailing Address: Southwest Oncology Group
Attn: ADR Program
14980 Omicron Drive
San Antonio, Tx 78245-3217

Information on this page has been deleted.

CALGB INSTITUTIONS ADVERSE EVENT REPORTING

CALGB participants should employ definitions of adverse events as provided by the Southwest Oncology Group reporting guidelines in Section 16.0. **Adverse reactions, both written and telephone reports, should be made directly to the Southwest Oncology Group and the NCI according to the instructions in that section**.

17.0 BIBLIOGRAPHY

1. Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alpha-2b adjuvant therapy of high-risk resected cutaneous melanoma. The Eastern Cooperative Oncology Group Trial EST 1684, JCO 14(1);7-17, 1996.

2. Kirkwood JM, Ibrahim J, Sondak V, et al. Preliminary analysis of the E1690/**SWOG-9111**/C9190 intergroup postoperative adjuvant trial of high and low dose IFN∝ 2b (HDI and LDI) in high risk primary and lymph node metastatic melanoma. Proc ASCO 18:537a, 1999.

3. Falkson CI, Ibrahim J, Kirkwood JM, Coates AS, Atkins MB, Blum RH. Phase III trial of dacarbazine versus dacarbazine with interferon ∝-2b versus dacarbazine with tamoxifen versus dacarbazine with interferon ∝-2b and tamoxifen in patients with metastatic malignant melanoma: An Eastern Cooperative Oncology Group Study. JCO 16(5):1743-1751, 1998.

4. Margolin K, Liu PY, Unger JM, et al. Phase II trail of biochemotherapy with ∝-IFN, DTIC, CDDP, and tamoxifen in metastatic melanoma. J Cancer Res Clin Oncol - in press, 1999.

5. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: Analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 17:2105-2116, 1999.

6. Atkins MB, O'Boyle KR, Sosman JA, et al. Multiinstitutional phase II trial of intensive combination chemotherapy for metastatic melanoma. J Clin Oncol 12:1553-1560, 1994.

7. Antoine EC, Benhammouda A, Bernard A, et al. Salpetriere hospital experience with biochemotherapy in metastatic melanoma. Cancer J Sci Am 3:S16-S21, 1997.

8. Richards JM, Mehta N, Ramming K, et al. Sequential chemoimmunotherapy in the treatment of metastatic melanoma. J Clin Oncol 10:1338-1343, 1992.

9. Legha SS, Ring S, Eton O, et al. Development and results of biochemotherapy in metastatic melanoma. The University of Texas M.D. Anderson Cancer Center Experience. Cancer J Sci Am 3:S9-S15, 1997.

10. Keilholz U, Goey SH, Punt CJ, et al. Interferon Alpha-2a and interleukin-2 with or without cisplatin in metastatic melanoma: A randomized trial of the European Organization for Research and Treatment of Cancer Melanoma Cooperative Group. J of Clin Oncol 15(7):2579-2588, 1997.

11. McDermott DF, Mier JW, Lawrence DP, et al. A phase II pilot trial of concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine (CVD), interleukin-2 (IL-2) and interferon alpha-2b (IFN) in patients with metastatic melanoma. Proc ASCO 17:507a.

12. O'Day SJ, Boasberg P, Guo M, et al. Phase II trial of concurrent biochemotherapy (c-BC) with decrescendo interleukin-2 (d-IL-2), tamoxifen, (T), and G-CSF support in patients with metastatic melanoma (MM). Proc ASCO 16:490a, 1997.

13. Flaherty LE, Robinson W, Redman BG, et al. A phase II study of dacarbazine and cisplatin in combination with outpatient administered interleukin-2 in metastatic malignant melanoma. Cancer 71:3520-3525, 1993.

14. Thompson JA, Gold PJ, Markowitz DR, et al. Updated analysis of an outpatient chemoimmunotherapy regimen for treating metastatic melanoma. Cancer J Sci AM 3:529-534, 1997.

15. Atzpodien J, Lopez Hanninen E, Kirchner H, et al. Chemoimmunotherapy of advanced malignant melanoma. Sequential administration of subcutaneous interleukin-2 and interferon-alpha after intravenous dacarbazine and carboplatin or intravenous dacarbazine, cisplatin, carmustine and tamoxifen. European J of Cancer 31A(6):876-881, 1995.

16. Bernengo MG, Doveil GC, Bertero M, et al. Low-dose integrated chemoimmunohormonotherapy with cisplatin, subcutaneous interleukin-2, alpha-interferon and tamoxifen for advanced metastatic melanoma-A pilot study. Melanoma Research 6(3):257-265, 1996.

17. Guida M, Latorre A, Mastria A, et al. Subcutaneous recombinant interleukin-2 plus chemotherapy with cisplatin and dacarbazine in metastatic melanoma. European J of Cancer 32A(4):730-733, 1996.

18. Keilholz U, Conradt C, Legha S, et al. Results of interleukin-2 based treatment in advanced melanoma: A case record-based analysis in 631 patients. J Clin Oncol 16:2921-2929, 1998.

19. Allen IE, Kupelnick B, Kumashiro M. Efficacy of interleukin-2 in the treatment of metastatic melanoma-Systemic review and metastasis-analysis. Cancer Therapeutics 1:168-173, 1998.

20. Legha SS, Ring S, Eton O, et al. Development of biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2 for patients with metastatic melanoma. J Clin Oncol 16:1752-1759, 1998.

21. McDermott DF, Mier JW, Lawrence DP, et al. A phase II pilot trial of concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine (CVD), interleukin-2 (IL-2) and interferon alpha-2b (IFN) in patients with metastatic melanoma. Proc ASCO 17:507a, 1998.

22. Roper M, Smith MA, et al. A phase I study of interleukin-2 in children with cancer. Am J Ped Hem/Onc 14:305, 1992.

23. Bauer M, Reaman GH, et al. A phase II trial of human recombinant interleukin-2 administered as a 4-day continuous infusion for children with refractory neuroblastoma, non-Hodgkin's lymphoma, sarcoma, renal cell carcinoma and malignant melanoma. A Childrens Cancer Group study. Cancer 75:2959, 1995.

24. Kohler PC, Hank JA, et al. Phase I clinical evaluation of recombinant interleukin-2. Prog Clin Res 244:161, 1987.

25. Cavo M, Terragna C, Martinelli G, Ronconi S, Zamagni E, Tosi P, Lemoli RM, Benni M, Pagliani G, Bandini, Tura S. Molecular monitoring of minimal residual disease in patients in long-term complete remission after allogeneic stem cell transplantation for multiple myeloma. Blood 96:355-7, 2000.

26. Sugimoto T, Das H, Imoto S, Murayama T, Gomyo H, Chakraborty S, Taniguchi R, Isobe T, Nakagawa T, Nishimura R, Koizumi T. Quantitation of minimal residual disease in t(8;21)-positive acute myelogenous leukemia patients using real-time quantitative RT-PCR. Am J Hematol 64: 101-106, 2000.

27. Drobyski WR, Endean DJ, Klein JP, Hessner MJ. Detection of BCR/ABL RNA transcripts using the polymerase chain reaction is highly predictive for relapse in patients transplanted with unrelated marrow grafts for chronic myelogenous leukemia. Br J Haematol 98:458-466, 1997.

28. Mackinnon S, Barnett L, Heller G. Polymerase chain reaction is highly predictive of relapse in patients following T cell-depleted allogeneic bone marrow transplantation for chronic myeloid leukemia. Bone Marrow Transplant 17:643-647, 1996.

29. Smith BM, Slade MJ, English J, Graham H, Luchtenborg M, Sinnett HD, Cross NC, Coombes RC. Response of circulating tumor cells to systemic therapy in patients with metastatic breast cancer: comparison of quantitative polymerase chain reaction and immunocytochemical techniques. J Clin Oncol 18: 1432-1439, 2000.

30. Gomella LG, Raj GV, Moreno JG. Reverse transcriptase polymerase chain reaction for prostate specific antigen in the management of prostate cancer. J Urol 158:326-337,1997.

31. Smith B, Selby P, Southgate J, Pittman K, Bradley C, Blair GE. Detection of melanoma cells in peripheral blood by means of reverse transcriptase and polymerase chain reaction. Lancet 338:1227-1229, 1991.

32. Hoon DSB, Bostick P, Kno C, Okamoto T, Wang HJ, Eashoff R, Morton D. Molecular markers in blood as surrogate prognostic Indicators of melanoma recurrence. Cancer Res 60: 2253-2225, 2000.

33. Mellado B, Colomer D, Castel T, Munoz M, Carballo E, Galan M, Mascaro JM, Vives-Corrons JL, Grau JJ, Estape J. Detection of circulating neoplastic cells by reverse-transcriptase polymerase chain reaction in malignant melanoma: association with clinical stage and prognosis. J Clin Oncol 14:2091-2097, 1996.

34. Proebstle TM, Jiang W, Hogel J, Keilholz U, Weber L, Voit C. Correlation of positive RT-PCR for tyrosinase in peripheral blood of malignant melanoma patients with clinical stage, survival and other risk factors. Br J Cancer 82:118-123, 2000.

35. Schittek B, Bodingbauer Y, Ellwanger U, Blaheta HJ, Garbe C. Amplification of MelanA messenger RNA in addition to tyrosinase increases sensitivity of melanoma cell detection in peripheral blood and is associated with the clinical stage and prognosis of malignant melanoma. Br J Dermatol 141:30-36, 1999.

36. Palmieri G, Strazzullo M, Ascierto PA, Satriano SM, Daponte A, Castello G. Polymerase chain reaction-based detection of circulating melanoma cells as an effective marker of tumor progression. Melanoma Cooperative Group. J Clin Oncol 17:304-311, 1999

37. Ghossein RA, Coit D, Brennan M, Zhang ZF, Wang Y, Bhattacharya S, Houghton A, Rosai J. Prognostic significance of peripheral blood and bone marrow tyrosinase messenger RNA in malignant melanoma. Clin Cancer Res 4:419-428, 1998

38. Curry BJ, M, Myers K, Hersey P. Polymerase Chain Reaction Detection of Melanoma cells in the Circulation: Relation to Clinical Stage, Surgical Treatment, and Recurrence from Melanoma. J Clin Oncol 5:1760-1769, 1998.

39. Bostick, PJ, Morton DL, Turner RR, Huynh KT, Wang HJ, Elashoff R, Essner R, Hoon DSB. Prognostic Significance of Occult Metastases Detected by Sentinel Lymphadenectomy and Reverse Transcriptase-Polymerase Chain Reaction in Early-Stage Melanoma Patients. J Clin Oncol 10:3238-3244, 1999.

40. Shivers SC, Wang X, Li W, Joseph E, Messina J, Glass LF, DeConti R, Cruse CW, Berman C, Fenske NA, Lyman GH and Reintgen DS. Molecular staging of malignant melanoma: correlation with clinical outcome. JAMA 28:1410-5, 1998.

18.0 MASTER FORMS SET

18.1 Attached are copies of all data forms which must be completed for this study. The model informed consent form is also included, and must be reviewed and approved by the institutional review board prior to registration and treatment of patients on this study.

18.2 Forms to be used for patients treated on this study include:

a. **S0008** Registration Form (Form #13730). (9/15/07)

b. **S0008** Adjuvant Melanoma Prestudy Form (Form #19207). (6/15/03)

c. Pathology Submission Form (Form #38890). (6/15/03)

d. **S0008** ARM 1, Induction Treatment and Toxicity Summary Form (Form #31218). (5/1/05)

e. **S0008** ARM 1, Maintenance Treatment and Toxicity Summary Form (Form #55930). (5/1/05)

f. **S0008** ARM 2, Treatment and Toxicity Summary Form (Form #27082). (5/1/05)

g. National Genetics Institute Laboratory Testing Requisition Form (Form #31267). (8/15/05)

h. Adjuvant Melanoma Off Treatment Notice (Form #52588). (8/1/00)

i. Southwest Oncology Group Adjuvant Melanoma Follow-Up Form (Form #50219). (8/1/00)

j. Notice of Death (Form #49467). (9/1/03)

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document which are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Readability Statistics:	Flesch Reading Ease	60.9 (targeted above 55)
	Flesch-Kincaid Grade Level	8.2 (targeted below 8.5)

S0008, "Phase III Trial of High Dose Interferon Alpha-2b Versus Cisplatin, Vinblastine, DTIC Plus IL-2 and Interferon in Patients With High Risk Melanoma"

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your family and friends.

You are being asked to take part in this study because you have a type of skin cancer called melanoma.

WHY IS THIS STUDY BEING DONE?

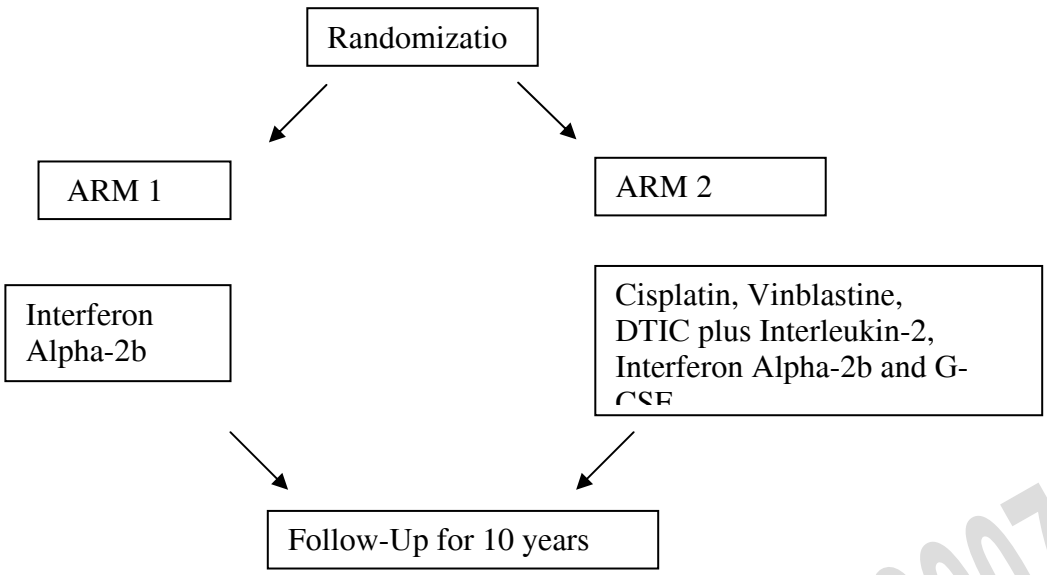
The purpose of this study is to compare the effects (good and bad) on you and your melanoma of high dose interferon alpha-2b alone against the combination of cisplatin, vinblastine, DTIC, interleukin-2, interferon alpha-2b and G-CSF.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 410 people will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

SCHEMA



You will be "randomized" into one of the two study groups described below. Randomization means that you are put into a group by chance: like flipping a coin, you will have an equal chance of being placed in either group. Which group you are put in is done by a computer. Neither you nor the researcher will choose what group you will be in.

If you are placed in Arm 1, you will receive the interferon alpha-2b for 5 consecutive days (Monday - Friday) every week for four weeks given into a vein over 20 minutes and then three times weekly, every other day (Monday, Wednesday, Friday) for 48 weeks by a shot just under your skin.

If you are placed in Arm 2, you will receive the combination of cisplatin, vinblastine, DTIC, IL-2 and interferon alpha-2b which will require a 5- 6 nights stay in the hospital for each cycle. In order for you to receive the study drugs (for Arm 2) you may need a catheter placed into a central vein in your chest. The catheter will be placed in your chest while you are under local anesthesia. One risk of the catheter insertion is the collapse of the lung, which would require the insertion of a special tube into the chest for several days to re-expand the lung. There is also a chance that infection will develop at this site, which would require removal and reinsertion of the catheter and possible treatment with antibiotics. Such an infection can cause additional side effects leading to prolonged hospitalization; however, with the use of oral antibiotics, in a preventative fashion, the chance of infection is uncommon. You will receive DTIC Day 1 only, cisplatin and vinblastine on Days 1 - 4 along with fluids and medicine to prevent side effects. You will also receive IL-2 through the catheter on Days 1 - 4 (total of 96 hours) and interferon alpha-2b as a shot just under the skin Days 1 - 5, 8, 10 and 12 of each treatment cycle. You will also

receive G-CSF as a shot just under the skin to reduce the risk of infection associated with this drug combination. Most likely, the interferon alpha-2b shots on Days 8, 10 and 12 and G-CSF shots (Days 6 - 15) will be given at home. *(1/15/01)* You and your family members will be shown how to give the interferon alpha-2b and G-CSF.

The treatment for this arm of the study will be repeated every 21 days. This 21 day cycle will be repeated for a total of 3 cycles.

You will receive the following drugs as part of your supportive care during your treatment on Days 1 – 5 and as indicated on Days 8, 10 and 12 to help prevent side effects which may be caused by the drugs Interleukin-2 and Interferon Alpha-2b:

- Acetaminophen: This drug will be given every 4 hours on Days 8, 10 and 12 to help lessen the flu-like symptoms you may experience during treatment.

- Naproxen: This drug may be given every 12 hours Days 1 – 5 for fever and chills.

- Ranitidine or Nizatidine: These drugs will be given every 12 hours to help prevent bleeding from the gastrointestinal tract.

The following drugs will be administered as needed during your treatment:

- Meperidine: This drug may be given every 12 hours on Days 1 – 5 in case you experience severe rigors (shivering that may be associated with chills and fever).

- Diphenoxylate and Loperamide: These drugs may be given every 4 – 6 hours to control diarrhea and intestinal cramping.

- Diphenhydramine or Atarax: These drugs may be given for skin rashes ad itching which you may experience during treatment.

- Furosemide: This drug may be given to lessen fluid retention (build-up of water in your body) during the infusion of the drug Interleukin-2.

If your cancer comes back at any time during your treatment, your treatment with these drugs will be discontinued and other treatment alternatives will be discussed with you.

• Procedures that are part of regular cancer care and may be done even if you do not join the study:

You will have blood tests weekly and x-rays/scans before, during and after treatment to see how your disease is reacting to the therapy. The x-rays/scans will include a chest scan, a brain and liver scan if needed, and EKG. Tests to evaluate the adequacy of your heart liver lungs for this therapy will also be performed. You may also have your hearing tested before treatment.

(Paragraph added 12/26/02)

* Procedures that are being investigated in this study:
  As part of this study, you will have blood samples taken from you, approximately 30 ml (about 6 teaspoons) at each blood draw, prior to initial treatment at Week 13 (ARM 1) or Week 12 (ARM 2) and then following 52 weeks after starting treatment. The blood samples will be sent to a special laboratory for scientific testing. The significance of this testing is unknown therefore, the results of this testing will not be reported back to you or your doctors.

(Procedures in the proceeding paragraph are optional for patients registered prior to May 15, 2003.) (Sentence added 12/26/02, date corrected 4/15/03)

HOW LONG WILL I BE IN THE STUDY?

You will be in the study until completion of study or until your doctors think that your disease is getting worse. Your doctors will continue to follow your health status for this study for 10 years.

Your doctors may decide to take you off this study if your disease gets worse despite the treatment; the side effects of the treatment are too dangerous for you; new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious or long-lasting or permanent.

Side effects of the study drugs interferon alpha-2b include:

Arm 1

***Very likely*:**

* **Fever chills and flu-like symptoms.**
* **Loss of appetite.**
* **Nausea, vomiting, diarrhea and abdominal pain.**
* **Fatigue.**
* **Lowered white blood count may increase risk of infection.**
* **Lowered platelets may lead to an increase in bruising or bleeding.**
* **Hair loss.**

Less likely but serious:

* **Drowsiness.**

* **Temporary confusion.**

* **Anxiety, amnesia, irritability, confusion, delusions and depression which can be severe.** *(8/31/07)*

* **Numbness and/or tingling in the hands and/or feet.**

* **Skin rashes.**

* **Inflammation of the pancreas.** *(8/31/07)*

Side effects of the study drugs cisplatin, vinblastine, DTIC, interleukin-2, interferon alpha-2b, and G-CSF include:

Arm 2

Very likely:

* **Fever, chills, and flu-like symptoms.**
* **Loss of appetite.**

* **Fatigue.**

* **Lowered white blood count may increase risk of infection.**

* **Lowered platelets may lead to an increase in bruising or bleeding.**

* **Lowered red blood cells may lead to tiredness or shortness of breath.**

* **Allergic reactions, such as itching and rash, but can be severe or even life threatening.**

* **Loss of appetite and weight loss.**

* **Nausea, vomiting, diarrhea and abdominal pain which may be severe.**

* **Constipation.**

* **Complete hair loss.**

* **Pain in muscles and joints may be severe.**

* **Sores in mouth and throat or on other parts of the body.**

Less likely but serious:

* **Drowsiness.**

* **Irritability, confusion, depression, delusions: because of the possibility that you may become confused as a side effect of the Interleukin-2, you should consider completing a durable Healthcare Power of Attorney that designates who will be able to make decisions about your health care in the event that you are unable to make decisions for yourself.** *(8/31/07)*

* **Skin rashes.**

* **Facial flushing.**

* **Decrease in kidney and liver functions may be severe.**

* **Difficulty with coordination.**

* **Heart problems including abnormal heartbeats, damage to the heart, and in some instances heart attacks.**

* **Numbness, pain or tingling in fingers or toes.**

* **Lowered blood pressure that usually requires drug treatment.**

* **Ringing in the ears and hearing loss.**

* **Collapse of the lung from insertion of catheter in your chest (infection may also develop at this site).**

* **Inflammation in the eye nerve that may cause temporary blindness.**

* **Weight gain from retaining water in your body. Your arms, legs, hands and feet can swell, and the fluid in your lungs may cause shortness of breath.**

* **Inflammation of the pancreas.** *(Added 8/31/07)*

Blood drawing may cause some pain and carries a small risk of bleeding, infection and/or bruising at the puncture. *(Added 12/24//02)*

Reproductive risks: Because the drugs in this study can affect an unborn baby, you should not become pregnant or father a baby while on this study. You should not nurse your baby while on this study. Ask about counseling and more information about preventing pregnancy.

For more information about risks and side effects, ask the researcher or contact your regular doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

We cannot and do not guarantee you will benefit if you take part in this study. The treatment you receive may even be harmful. Your doctors feel that your participation in this study will give you at least as good a chance as you might expect from other treatments. We hope the information learned from this study will benefit other patients with melanoma in the future.

The possible benefits of taking part in the study are the same as receiving either of these treatments without being in the study.

WHAT OTHER OPTIONS ARE THERE?

Instead of being in this study, you have these options:
other types of chemotherapy, radiation or no anti-cancer treatment at this time (with care to help you feel more comfortable).

You can get the same agents treatment for skin cancer without being on this study. All of the treatment on this study may be available at this center or at other locations.

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as: the National Cancer Institute, a qualified representative of the drug manufacturer for Interleukin-2 (Novartis), the Food and Drug Administration, the Eastern Cooperative Oncology Group and the Southwest Oncology Group. *(7/1/01) (8/31/07)*

If we publish the information we learn from this study in a medical journal, you will not be identified by name or in any other way.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds/funds have been set aside to compensate you in the event of injury. *(local institutions must choose the option that best fits the hospital's situation)*

You or your insurance company will be charged for continuing medical care and/or hospitalization.

You will receive no payment for taking part in this study.

Administration of the drug will be (provided free of charge/charged in the usual way). The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be (charged in the usual way/provided at a reduced rate). *(local institutions must choose the option that best fits the hospital's situation)*

Cisplatin, vinblastine, DTIC and interferon alpha-2b are all commercially available. G-CSF and Il-2 are also commercially available; however, G-CSF will be provided by the drug manufacturer for the purpose of this study for those patients whose insurance does not cover the cost of the drug, and IL-2 will be provided by the National Cancer Institute for all patients entered on the study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or a research-related injury, contact the researcher *NAME(S)* at *TELEPHONE NUMBER*.

For questions about your rights as a research participant, contact the *NAME OF CENTER* Institutional Review Board (which is a group of people who review the research to protect your rights) at *TELEPHONE NUMBER*. *[And, if available, list patient representative (or other individual who is not on the research team or IRB).]*

WHERE CAN I GET MORE INFORMATION?

[To IRB/Investigators: Attach information materials and checklist of attachments. Signature page should be at the end of package. You may also wish to include the following informational resources]

You may call the NCI's Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615

Visit the NCI's Web sites…
cancer Trials: comprehensive clinical trials information
http://cancertrials.nci.nih.gov.

CancerNet™: accurate cancer information including PDQ
http://cancernet.nci.nih.gov.

You will get a copy of this form. You may also request a copy of the protocol (full study plan).

SIGNATURE

You are deciding whether or not to take part in this study. If you sign, it means that you have decided to volunteer to take part in this study, and that you have read and understood all the information on this form.

Participant _____ Date _____

(For patients registered prior to May 15, 2003 ONLY) (4/15/03)

I agree to have blood samples sent to a special laboratory for scientific testing.

Yes_____ No_____ Initials_____

For ECOG Participants ONLY *(this section and page added 2/15/04)*

Will any of the samples (e.g., blood, tissue) taken from me be used for other research studies?

There may be a chance that some of your tissue may be left over for future research.

If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. This tissue will only be given to researchers approved by the Eastern Cooperative Oncology Group. Any research done on the tissue must also be approved by the researcher's Institutional Review Board.

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No."

1. **My tissue may be kept for use in research to learn about, prevent, treat, or cure cancer.**

   Yes_____ **No** _____

2. **My tissue may be kept for research about other health problems (for example: causes of diabetes, Alzheimer's disease, and heart disease).**

   Yes _____ No _____

3. **My doctor (or someone from the Eastern Cooperative Oncology Group) may contact me in the future to ask me to take part in more research.**

   Yes _____ **No** _____

19.0 APPENDIX

19.1 Surgical Requirements.

19.2 "Breadloaf" Technique for Sampling Melanoma Specimens.

19.3 Self-Administration of Interferon.

19.4 Sample Orders for Biochemotherapy.

19.5 Neupogen Reimbursement Guidelines.

19.6 Guidelines for Patients on the Self-Administration of G-CSF.

19.7 Children's Oncology Group (COG) Logistical Information.

19.8 Determination of Expedited Adverse Event Reporting Requirements

19.1 SURGICAL REQUIREMENTS

All patients must be free of disease at the time of registration. All surgery is to be completed prior to registration and must the meet the criteria outlined below. Failure to document that surgery meets these criteria will result in the patient being deemed ineligible.

1. Primary Site - These guidelines apply to patients presenting with an intact primary and undergoing sentinel node biopsy or elective or therapeutic lymph node dissection to establish eligibility.

   Primary Excision - All patients enrolled with regional metastases at the time of initial presentation must undergo adequate wide excision of the primary tumor meeting the criteria outlined below. In most cases, this must be a wide excision with 1 cm minimum margins. In all cases, the margins of excision must be histologically free of melanoma (including melanoma in-situ or atypical junctional melanocytic hyperplasia).

   Recurrent Disease - All patients enrolled with regional recurrence after initial presentation must have no evidence of active disease at the primary site or have undergone a re-excision of the primary site that meets the criteria outlined below (including histologically negative margins of excision) prior to registration. Patients presenting with satellite metastases (within 2 cm of the primary) or in/transit metastases (beyond 2 cm from the primary but within the pathway to the regional lymph nodes) are eligible provided that all tumor has been excised with negative margins, they have undergone complete lymph node dissection meeting the criteria outlined below, and they have NOT undergone other therapy for their satellite/in-transit metastases (e.g., limb perfusion).

   a. All sites except head & neck and extremities distal to the wrist or ankle

      The primary melanoma must be excised with at least 1 cm margins of normal skin in all directions, measured either from the edge of the primary tumor or from the edge of the biopsy scar if prior excisional biopsy has been done. The excision should go down to the fascia; including the fascia in the resection is optional. Measurements of margins should ideally be done by the surgeon at the time of wide excision using a ruler; if the measurement is done by the pathologist, allowance of 33% for shrinkage will be made. In addition to the gross margin, a histologically negative margin (including histologic freedom from atypical junctional melanocytic hyperplasia) must be obtained. Failure to document the excision size and margin status will lead to the patient being declared ineligible.

   b. Head & neck, distal extremities

      The primary melanoma must be excised and a histologically negative margin (including histologic freedom from atypical junctional melanocytic hyperplasia) must be obtained. If cosmetically feasible, margins of at least 1 cm are desirable, but not mandatory. Acral-lentiginous melanomas (including subungual primaries) may be resected by any procedure that yields a histologically negative margin. Failure to document the margin status will lead to the patient being declared ineligible.

   c. Non-excisional techniques

      Regardless of site, Mohs chemosurgery or other non-excisional techniques for removing the primary tumor are not acceptable for entry into this study.

2. Regional Lymph Nodes

Regional lymph node dissection is mandatory for all patients enrolled on this trial. **The node dissection must be done in accord with the following guidelines, in order for the patient to be eligible.** Lymph node sampling is not acceptable. Sentinel lymph node biopsy alone, without full lymph node dissection, is not acceptable.

Lymph Node Dissection - All patients must undergo complete lymph node dissection meeting the criteria outlined below within 56 days prior to registration. This includes patients whose diagnosis of regional node involvement was based on positive sentinel nodes. Patients undergoing only sentinel node biopsy, without full node dissection, are ineligible. (For patients with satellite/in-transit metastases, or disease in the regional nodal basin, occurring after prior complete lymphadenectomy, registration must take place within 56 days of complete excision of all recurrent disease.)

Histologic Documentation - Only patients with nodal involvement that has been documented on routine histologic analysis (i.e., hematoxylin and eosin [H&E] stained preparations) are eligible. Patients with nodal metastases that are evident ONLY by immunochemical stains or reverse transcriptase-polymerase chain reaction (RT-PCR) are NOT eligible, regardless of how many nodes are found to have such involvement. (Note: Patients with satellite or in-transit metastases and no evidence of nodal involvement by H&E staining [N2C] are eligible, regardless of whether or not there is immunochemical or RT-PCR evidence of nodal metastases.)

Number of Tumor-involved Nodes - The number of tumor-involved nodes must be documented for all cases. As indicated above, only H&E evidence of involvement is acceptable for determining the number of involved nodes. Patients with confluent nodal involvement that makes determination of the exact number of involved nodes difficult are eligible, and are considered to have "matted nodes" and are classified as N3.

Micrometastases versus Macrometastases - As outlined in Section 4.0, Staging Criteria, the status of regional lymph node involvement will be determined by pathologic assessment and by the clinical presentation of those nodes. Micrometastases are diagnosed by sentinel node biopsy or elective lymph node dissection, and are nonpalpable metastases confined entirely within normal sized nodes. Macrometastases are diagnosed by clinical examination or by the pathologic finding of macroscopic extension of tumor beyond the capsule of the lymph node. Patients with macroscopic extranodal extension are eligible for the trial, and by definition are considered to have macrometastatic involvement (i.e., eligible even if only one tumor-involved node).

a. Head & Neck

A standard radical neck dissection is not required and is discouraged. In cases with clinically negative nodes, less than a full neck dissection is permissible, including modified dissections such as supraomohyoid or posterior triangle dissections. In such cases, the entire triangle should be dissected. Preservation of the internal jugular vein, sternocleidomastoid muscle, and eleventh cranial nerve ("functional neck dissection") should be performed whenever possible. For melanomas of the face, anterior ear and temporal region, consideration should be given to the parotid gland nodes, which should be removed by superficial parotidectomy if prophylactic or therapeutic neck dissection is to be

carried out. The facial nerve (seventh cranial nerve) should be spared unless invaded by tumor. Radionuclide lymphatic drainage scans may be helpful in delineating lymph node groups at risk for tumor involvement.

b. Axilla

Removal of at least the level I and II axillary lymph nodes is the minimum acceptable operation. The minimum borders of the dissection are the latissimus dorsi muscle laterally, the axillary vein superiorly, and the medial border of the pectoralis minor muscle medially. The nerves to the serratus anterior and latissimus dorsi muscle should be identified and preserved if possible. If the primary tumor is on the trunk, consideration should be given to remove the low axillary nodes (at or below the level of the nipple) by following the latissimus dorsi muscle down to its origin on the chest wall and dissecting the node-bearing tissue between it and the serratus anterior muscle.

c. Ilioinguinal

The minimum operation for prophylactic or therapeutic groin node dissections is a superficial inguinal lymph node dissection. A deep (iliac) node dissection is discouraged if the nodes are clinically negative. Removal of the iliac nodes is necessary if these nodes are felt to be involved by pelvic CT scan. The borders of a superficial inguinal node dissection are the adductor muscle medially, the sartorius laterally, the junction of these two muscles caudally, the femoral vessels posteriorly, and the external oblique fascia cranially. Removal of the iliac nodes, if necessary, may be accomplished through the same or a separate incision; "sampling" of the deep nodes rather than a radical dissection is adequate.

d. Other Sites

Lymph node dissections at sites other than those mentioned (e.g., popliteal or epitrochlear) should be carried out only if involvement of the nodes with melanoma is documented or if the primary site lies directly over the node group and node dissection is necessary to allow wide excision.

3. Satellite/In-transit Metastases

Patients who have undergone complete resection of satellite or in-transit lesions are eligible for inclusion in this trial, provided that all evidence of disease has been resected, a full lymph node dissection has been performed, and no other form of treatment for the in-transit metastases (e.g., limb perfusion) has been used.

4. Recurrent Disease

Patients with recurrent disease in the regional nodal basin of a previuos complete lymphadenectomy are eligible for inclusion in this trial provided that all evidence of disease has been resected with pathologically negative margins.

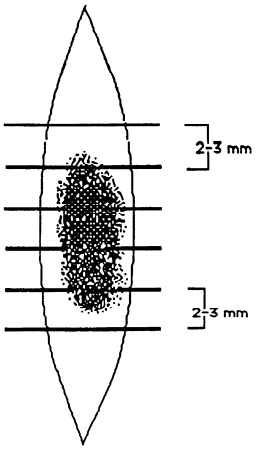
5. Distant Metastases

Patients with any evidence of metastases beyond the regional nodes are ineligible, regardless of the type of metastases or the nature of the surgical treatment.

19.2 "Breadloaf" Technique for Sampling Melanoma Specimens.

"Breadloaf" Technique for Sampling Melanoma Specimens

suggested sampling method for SWOG protocols



This simple method of blocking the gross specimen ensures adequate sampling of cutaneous melanomas. Adequate sampling of the melanoma is important to obtain an accurate microscopic thickness measurement.

19.3 SELF-ADMINISTRATION OF INTERFERON

Patients deemed competent to self administer the Interferon may do so. The hospital or clinic staff will instruct the patient or interested family member in this technique. Patients should be allowed to administer these injections at home when they can independently perform a return demonstration for their instructor. The instructor will note this fact in the patient's record. Adequate contact persons and telephone numbers will be provided so that the patient will always be able to reach someone familiar with this procedure should they need assistance.

Instructions for Self-Administering Medication

1. Preparation

a. Wash hands well. Take required dose of acetaminophen (Tylenol®).

b. Assemble necessary supplies. The Interferon should be kept refrigerated until several minutes before each treatment. You also need a syringe with a needle, at least 3 alcohol prep pads, and a container* for used materials.

_____

*An unbreakable, leak-proof, reclosable container - milk carton, coffee can.

2. Reconstituting the Interferon Powder

a. If this is the first dose that will be coming from a vial, the Interferon powder must be dissolved, using the diluent provided. Snap the plastic cap off both vials, and cleanse both rubber stoppers with an alcohol pad and allow to air dry.

b. There may be a different syringe/needle provided that you will use to reconstitute the Interferon. Open the package containing one of these syringes and attach (or tighten) the appropriate needle to it. Pull back the plunger of the syringe so that the top of it rests right on the line representing the volume of diluent that you are to add to the Interferon powder.

c. Insert the needle through the stopper of the diluent vial, and invert the vial/syringe in front of you at eye level, holding the syringe in your dominant hand and the vial in the other.

d. Inject the air from the syringe into the vial slowly. If you feel like you are forcing it, pull back the plunger to allow some solution into the syringe, then push the remaining air into the vial. Ultimately, your syringe should be filled with diluent solution up to the correct line and no air will be left in the syringe. If you have bubbles, tap the syringe with your finger until they rise to the top, push them up into the vial and recheck the plunger to insure that it is still at the correct volume mark.

e. Withdraw the needle from the diluent vial and insert it into the vial containing the Interferon powder. This time keep the vial on the surface and push the plunger down to inject the diluent into the powder vial. If you meet resistance, allow some air to rise into the syringe before pushing down and expelling the remaining solution into the vial. Eventually, all the solution will be in the vial. Pull back the plunger to return it to the line that is the same as the volume of solution that you injected. This will prevent pressure build-up in the Interferon vial. Remove the needle and discard it appropriately.

f. To help dissolve the Interferon powder, you may need to roll the vial between your palms or swirl the solution around. **DO NOT shake the vial**. Be sure that all the powder is dissolved before proceeding to #3.

3. Withdrawing Your Dose From the Vial

a. Cleanse the rubber stopper of the vial containing the Interferon solution with an alcohol pad and allow to air dry.

b. Open syringe package and needle package (if separate) and attach or tighten needle by twisting until tight. Pull back the plunger to the mark that represents your dose (i.e., 3 mU/0.5 ml, top of plunger should rest at the 0.5 ml mark). This fills the syringe with air in a volume equal to the volume of your dose.

c. Uncap the needle and push it through the stopper, at least half-way into the vial. Now pick up the vial (with syringe/needle in it) with your left hand and turn it upside down, holding it at eye-level, about 12 inches from your face. You should now have the vial in one hand and your other hand free to manipulate the syringe. (Note: Left-handed persons should have the vial in their right hand, so that they can manipulate the syringe with their left hand.)

d. Inject air from the syringe into the vial slowly, and then withdraw the plunger. The syringe will gradually fill with drug solution. Repeat this procedure until only solution is in the syringe, solidly, to the mark that indicates your dose. Withdraw needle and recap it.

4. Administration

a. Thoroughly clean the area to be injected with an alcohol pad. Areas appropriate for this type of injection have been shown to you. A new site should be used for each injection whenever possible.

b. As demonstrated, pinch 1 1/2 to 2 inches of loose skin from the site to be injected.

c. Uncap the needle, and insert the needle approximately 1/4 inch into the skin and push the syringe plunger in all the way, thereby giving the dose of Interferon.

d. Remove needle and wipe injection site with a new alcohol pad, but do not massage the area to any great extent.

e. Carefully recap needle and return needle and syringe to the clinic pharmacy for disposal. If the Interferon vial contains more than one dose, write the date on the label. It is usable for 30 days.

f. If a drug administration diary has been provided, remember to complete it after each dose. Enter the date and time of day given, along with any notable side effects that you may have experienced since the previous dose was given.

19.4 CHEMOTHERAPY-IMMUNOTHERAPY FOR METASTATIC MELANOMA WITH DTIC, CDDP, VBL, IL-2 AND IFN ALPHA

Wt____ kg Height _____ cm BSA _____ m^2

General:	
	Admit
	Dx: Melanoma
	Condition:
	Activity as tolerated, bed rest for SBP < 90
	Weight q am, strict I/O
	Vital signs q4h
	Please call HO for SBP < 90, Temp > 40, confusion, dyspnea, chest pain,
	Diet: House
	Labs: CBC with diff and PLT, lytes, BUN, Creat, Bili qd; Alb, Glu, Mg^{++}, Ca^{++}, ALT, AST, Alk Phos, LDH, CPK, PT/PTT Day 1, 3 and 5; CXR: PA & lateral Day 5.
	Hold IL-2 for Bicarb < 18; call HO.
	Hold CDDP for Creat > 1.6; call HO
	Cardiac Monitor while on pressors
	No procedures requiring IV contrast.
	Hold start of chemotherapy if platelets < 100,000/mm^3, ANC < 1500/mm^3, creatinine ≥ 1.5. Check nadirs (ANC, platelets) and if Grade 4 N/V from previous cycle; and adjust DTIC/Vinblastine or Cisplatin if required.
Meds:	
1.	Naprosyn 375 mg po q12h.
2.	Tylenol 650 mg po/pr q4h
3.	Axid 150 mg po q12h
4.	Benadryl 25 mg po q6h PRN
5.	Halcion 0.125 mg po qhs PRN
6.	Lomotil 1 tab po after each loose stool
7.	Meperidine 25 - 50 mg in 50cc D5W IV over 15 mins q2h PRN sev chill; MR x2 then call HO
8.	Triple lumen CVP line to be inserted by Surg. CVP line dressing changes as per TPN prot. Hep flush for CVP line (10 U/ml, 5ml/port) q shift.
9.	IL-2 (Novartis) 9 MIU/m^2 (18MU = 1.1mg) =____ MIU in 250 cc D5W and 0.1% Alb daily by CIV infus, Days 1 - 4 (96 hrs), begin at 3 PM d 1.
10.	Intron A (Schering) 5MU/m^2 =____ MU sc daily at start of IL-2 infusion for each day Days 1 - 4 and at compl of IL-2 infusion on Day 5
11.	Intron A (Schering) 5MU/m^2 =____ MU sc Days 8,10 and 12. (To be administered as outpt if pt has been discharged)
12.	Transfuse 1U PRBCs over 1 - 2 h for Hgb < 10; 2U for Hgb < 9.
13.	Transfuse 8 units plts over 30 mins for plts < 20,000
14.	No Steroids
15.	Cipro 250 mg po BID for pts with CVP catheters.
16.	IV D5 1/2NS with 20 mEq of KCL/L at 100 ml/hr IV Days 1 - 4 except during periods of prehydration for CDDP

CDDP 20 mg/m^2 =____ mg IV daily, Days 1 - 4 at completion of prehydration. CDDP should be administered in 250 ml of NS over 30 mins. For creatinine > 1.6 give 500 cc NS IV bolus and recheck creatinine in 4 hrs. If creatinine remains > 1.6, hold CDDP for that day. If creatinine > 2.0 despite fluid boluses, further CDDP for this cycle should be withheld.
Vinblastine (1mg/cc) 1.2 mg/m^2 = ____ mg (____cc) IVP daily on Days 1 - 4 immed following CDDP.
DTIC 800 mg/m^2 = _____mg in 250 ml of D5W IV over 1 hour following vinblast on Day 1 only.
Prehydration for CDDP:
1 Liter D5 1/2NS plus 8m Eq Mg So 4 IV over 3 hours starting at 3 PM Day 1; 12 - 3 pm Days 2 - 4.
For UO < 500cc/8hrs, give 500 cc NS IV bolus over 30 mins. Call HO. If UO < 100cc/hr for at least 3 hrs at time that CDDP is due, give lasix 20 mg IV and an additional 500 cc bolus of NS over 1 hr prior to proceeding with CDDP therapy
Antiemetics:
1. Zofran 32 mg IV or PO 30 mins prior to CDDP Day 1 - 4 and qAM Days 5, 6 and, if necessary, 7.
2. Compazine 10 mg po/25 mg pr q 6 h prn nausea or vomiting.
3. Ativan 1 po q 6 hrs; hold for sedation
4. Ativan 1 - 2 mg IV q 6 h PRN Nausea/anxiety.

19.5 REIMBURSEMENT SUPPORT FOR NEUPOGEN® (Filgrastim)

Amgen, the manufacturer of Neupogen® (Filgrastim), has agreed to provide Neupogen reimbursement assistance through its Amgen Reimbursement Hotline for the Phase III trial entitled: **"Phase III Trial of High Dose Interferon vs. Cisplatin, Velban, DTIC + IL-2 and Interferon in Patients with High Risk Melanoma."**

As indicated in Section 7.0 of the protocol (pages 21 - 25), Treatment Plan:

Arm 1 (Interferon alpha 2B x 1 year):

20 MU/m^2 IV M-F x 4 weeks
10 MU/m^2 SC M, W, F x 11 months

Arm 2 (CVD + IL-2/IFN):

Cisplatin 20 mg/m^2 x 4 days
Vinblastine 1.2 mg/m^2 x 4 days
Dacarbazine 800 mg/m^2 x 1 day
IL-2 9 MU/m^2 x 4 days
Interferon alpha 2B 5 MU/m^2 Days 1 - 5, 8, 10, 12
G-CSF 5 µg/kg/d Days 6-15

These uses of Neupogen are within approved FDA labeling. Amgen's Reimbursement Hotline is prepared to assist in providing up-to-date claims advice. The Hotline's services have been expanded specifically for this clinical trial and include:

1. **REIMBURSEMENT SUPPORT**: The Hotline provides assistance relating to claims filing and appeals, and identification of alternative sources of payment (secondary insurer, state programs, and charity programs).

2. **CLAIMS SUPPORT**: The Hotline provides claims appeal support at several different levels, including investigating claims denials and assisting with letter of medical necessity by providing necessary supporting literature.

FOR VERIFICATION OF PATIENT INSURANCE STATUS, REFER TO:

NEUPOGEN® REIMBURSEMENT HOTLINE
Amended 12/26/02Reimbursement Hotline: 1-800/272-9376
Revised 5/30/03Amended 12/26/02Hours: Monday through Friday 9:00 AM - 5:00 PM EST
Revised 5/30/03Amended 12/26/02When calling be prepared with the following information:
Revised 5/30/03Amended 12/26/02 1. Identify yourself as being with the Southwest Oncology Group trial #**S0008**
Revised 5/30/03 2. Name and address of the physician
3. Date of Service
4. Patient name and study ID number
5. Name and address of the insurer
6. Insurer's reason for rejecting claim
7. Copy of the claim
8. Patient consent (study specific consent to share confidential information)
9. Policy ID number
10. Federal Tax ID number

S0008, "PHASE III TRIAL OF HIGH DOSE INTERFERON ALPHA 2-B VERSUS CISPLATIN, VINBLASTINE, DTIC PLUS IL-2 AND INTERFERON IN PATIENTS WITH HIGH RISK MELANOMA."

NEUPOGEN SAMPLE REQUEST

			Date Submitted:				
Requesting Physician:							
Name:			Prof. Designation:				
Mailing/Shipping Address:							
Telephone:		FAX:					
Hospital/Office/Clinic:							
Name:							
Contact Person:		Title:					
Shipping Address:							
Telephone:		FAX:					
DEA #:		Expiration Date:					
	(Number and Photocopy Required)						

REQUEST AND CERTIFICATION

I hereby request that AMGEN furnish me with _____ boxes NDC# _____ at the mailing/shipping address listed on this form. I understand and agree that free sample units furnished in response to this request will only be used in furtherance of the above mentioned trial and are not to be sold, purchased, or traded. I certify that no charge for any such units used in the treatment of any patient will be made, and no bill for or containing any such charge will be submitted to the patient or any third party.

Self-Injection Chart

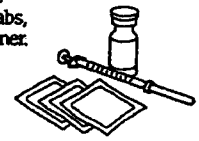
Step-by-step guide to subcutaneous self-injection

Step 1:

Setting up for self-injection

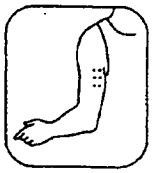
You should find a comfortable, well-lit working place and self-inject at the same time each day

1. Remove medication from refrigerator and let it reach room temperature (do not shake or agitate the vial). Make sure it is the medication your doctor prescribed. Check the expiration date on the vial. Do not use a medication with an expired date. If the medication has particles or is discolored, do not use it and check with a health professional.
2. Clean your work area, preferably with alcohol.
3. Wash your hands with liquid soap.
4. Assemble supplies—vial, sterile disposable syringe, alcohol swabs, puncture-proof disposal container.



Step 2:

Selecting and preparing the injection site

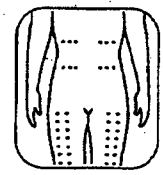


5. Find the site for injection.

a. Back of the arms b. Abdomen, except for the navel and waist c. Upper thighs

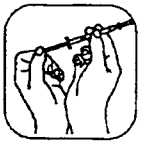
Alternate the injection site each time you inject to avoid soreness at any one site.

6. Clean injection site with an alcohol swab. Use circular motions. Keep the used alcohol swab nearby.

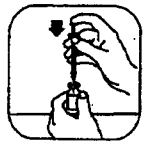


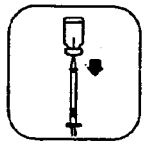
Step 3:

Preparing and injecting the dose



7. Remove the colored cap from the vial, exposing the rubber stopper.
8. Clean the rubber stopper with a fresh alcohol swab, then cover the stopper with the swab.
9. Remove syringe from its packaging. (If the sterile covering is open, dispose of that syringe in the puncture-proof disposal container.)
10. With the needle cover on, pull back the plunger and draw air into the syringe. The amount of air drawn into the syringe should be the same volume as the dose of medication your doctor prescribed.
11. Pull the needle cover *straight* off.
12. While keeping the vial on a flat surface, put the needle straight through the rubber stopper.
13. Push the plunger of the syringe down and inject the air into the vial.





14. Keeping the needle in the vial, turn the vial upside down and make sure that the needle is in the liquid medication.
15. Slowly pull back on the plunger and let the medication enter the syringe, filling up to the dose your doctor prescribed.
16. Check for air bubbles in the syringe. Air bubbles are harmless but can reduce the dose you should be receiving. To remove the air bubbles, gently tap the syringe until the bubbles rise to the top of the syringe barrel. Then push the plunger, forcing the air out of the syringe and once again pull the plunger back to the number that correctly matches the amount of your dose. Double-check for air bubbles. Repeat this procedure if necessary.
17. Double-check for your correct dose.

18. Take the needle out of the vial and hold the syringe in the hand with which you will inject yourself.
19. Use the other hand to pinch a fold of the previously prepared injection site.
20. Hold the syringe the way you would a pencil and insert the needle either straight up and down (90 degree angle) or at a slight angle (45 degrees) to the skin.
21. After the needle is in, let go of the skin. Pull plunger back slightly. If blood appears, do not inject. Withdraw syringe and inject in a different place.
22. Slowly push down on the plunger all the way, until all the medication is gone from the syringe.
23. As you pull the needle out of the skin, place the alcohol swab over the injection site.
24. Place the syringe into the puncture-proof disposal container without replacing the needle cover.

This self-injection guide is a courtesy of your physician and

AMGEN.

Amgen Inc., Amgen Center, Thousand Oaks, CA 91320-1789

PN0064 10M/1-94

Printed in USA

Esquema De Autoinyección

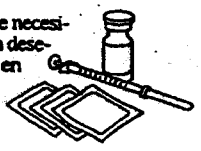
Pasos para la autoinyección subcutánea

Primer Paso

Cómo prepararse para una autoinyección

Debe encontrar un lugar cómodo, bien iluminado donde pueda autoinyectarse cada día a la misma hora.

1. Retire el medicamento de la nevera y deje que adquiera la temperatura del medio ambiente (no agite ni sacuda el frasco). Asegúrese que sea el medicamento recetado por el médico. Verifique la fecha de vencimiento del frasco. No use un medicamento con fecha vencida. Si tiene partículas o presenta decoloramiento, no lo use y hable con su médico o enfermera.
2. Limpie el lugar en donde realizará esta tarea, preferiblemente con alcohol.
3. Lávese las manos con jabón líquido.
4. Coloque todos los materiales que necesitará a la mano: frasco, jeringuilla desechable estéril, gasas empapadas en alcohol, envase resistente a las perforaciones para desechar las jeringuillas usadas.



Segundo Paso

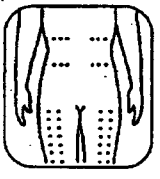
Cómo seleccionar y preparar el área para la autoinyección

5. Seleccione un lugar para inyectarse:

a. la parte posterior de los brazos b. el abdomen, exceptuando la zona del ombligo y la cintura c. la parte superior de los muslos

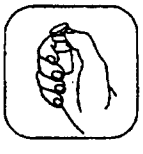
Alterne cada día el lugar en donde se inyectará para evitar sensibilidad al dolor en la zona.

6. Limpie el lugar de la inyección con un algodón con alcohol. Use un movimiento circular. Mantenga el algodón con alcohol usado a la mano.



Tercer Paso

Como preparar y autoinyectarse la dosis



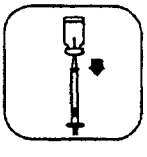
7. Retire la tapa de color del frasco, descubra el tapón de goma.
8. Limpie el tapón de goma con una gasa empapada en alcohol, y luego cubra el tapón con la misma.
9. Saque la jeringuilla de su envoltura (si la cobertura estéril está abierta, descarte en el envase resistente a perforaciones.)

10. Con la cobertura de la aguja todavía en su lugar, jale el émbolo y aspire aire en la jeringuilla. Esta cantidad de aire debe ser igual al volumen de la dosis del medicamento recetado por el médico.
11. Saque la cobertura de la aguja.

12. Con el frasco apoyado en una superficie plana, atraviese la aguja en forma recta sin doblar, a través del tapón de goma.
13. Empuje el émbolo de la jeringuilla e inyecte el aire adentro del frasco.

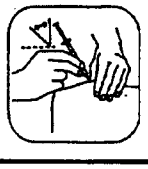
14. Con la aguja aún dentro del frasco, inviértalo y asegúrese de que la aguja esté en el medicamento líquido.
15. Jale lentamente el émbolo para permitir que el medicamento entre en la jeringuilla, y llénela con la dosis recetada por el médico.

16. Verifique si hay burbujas de aire en la jeringuilla. Las burbujas de aire no son peligrosas pero pueden reducir la dosis que usted debe recibir. Para eliminar las burbujas de aire, golpée suavemente la jeringuilla hasta que suban las burbujas al tope del cilindro de la jeringuilla. Entonces, empuje el émbolo para forzar el aire fuera de la jeringuilla y vuelva a jalarlo hasta el número que marca la cantidad de la dosis. Verifique de nuevo si hay burbujas. Repita este procedimiento de ser necesario.

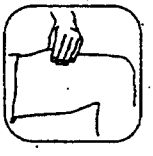


17. Verifique de nuevo si la dosis es correcta.

18. Saque la aguja del frasco y sostenga la jeringa en la mano que usará para inyectarse.
19. Use la otra mano para apretar la zona de la piel previamente preparada para la inyección.
20. Sostenga la jeringuilla de la misma manera que sostiene un lápiz e inserte la aguja ya sea en forma recta (en un ángulo de 90 grados) o inclinada (en un ángulo de 45 grados) en relación con la piel.



21. Una vez que ha penetrado la aguja, afloje la zona de la piel que tenía apretada. Jale el émbolo un poco hacia atrás. Si hay sangre, no inyecte. Retire la jeringuilla e inyecte en otro lugar.
22. Empuje lentamente el émbolo hacia adentro, hasta que todo el medicamento haya desaparecido de la jeringuilla.
23. A medida que saque la aguja de la piel, coloque la gasa de alcohol sobre el lugar de la inyección.
24. Coloque la jeringuilla en un envase resistente a perforaciones sin reemplazar la cobertura de la aguja.



P40056 10M/7-92

Esta guía para la autoinyección es una cortesía de su médico y

AMGEN.

Amgen Inc., Amgen Center, Thousand Oaks, CA 91320-1789

Printed in USA

19.7 Children's Oncology Group (COG) Logistical Information

Participation Procedures

NOTE: Institution's that are members of both the Southwest Oncology Group and COG must register patient's that are less than 18 years of age through COG as outlined below.

COG institutions will not be required to become members of SWOG, but will enroll and follow patients on the above named study solely through their continued affiliation with COG. Any membership action taken by COG that affects an institution's privileges to participate in COG-sponsored research affects participation on **S0008** in the same fashion. Institutional investigators will receive reimbursement for research costs associated with **S0008** from COG in accordance with COG policies and schedules for reimbursement for patients enrolled on therapeutic clinical trials.

a. Enrollment

This protocol must have IRB approval prior to enrollment. Upon receipt of local IRB approval for this study, fax the officially signed IRB approval to the Group Operations Center (GOC) at: 626/445-6715. The *COG IRB Approval Fax Cover Sheet* is required to be faxed with the official approval. A copy of this cover memo can be obtained from the protocol links area of the COG website. After this approval is recorded by GOC staff, the institution will have access to the eRDE enrollment screens. Prior to study enrollment, all patients must have been registered via the eRDE system into the COG Cancer Registry (Diagnosis/Registry). The patient registration application is available 24 hours a day, 7 days a week. The assigned COG patient identification number will be used to identify the patient in all future interactions with the COG. If you have problems with registration, please refer to the online help in the eRDE area of the COG website.

Biopathology Center (BPC) number will be assigned as part of the registration process. Each patient will be assigned only one BPC number per COG Patient ID. Please use this number as part of the labeling information on all banking and biology specimens sent to the Biopathology Center or a COG Reference Laboratory. If you have a question about a patient's BPC Number, please call the Biopathology Center at (800) 347-2486

Once your patient has met eligibility requirements, you will then fax an eligibility worksheet (Section 5.0 of the **S0008** protocol document) to the attention of the **S0008** Research Coordinator at 626/241-1500. Please provide patient information to verify eligibility and the COG registration number. Enrolling institutions must provide the name of a contact person including their phone, fax and email address. After the patient has been enrolled onto the study and has been assigned an SWOG study id number and randomization assignment, Ingrid Shieh will email and fax this information to the designated contact person. The communication will be done through email and will contain the following information:

1. The patient's COG registration number
2. The patient's date of birth
3. The patient's gender
4. The patient's initials
5. The SWOG identification number

6. The patient's treatment assignment designated as "Arm 1 - High dose interferon alpha-2B" or "Arm 2 - Cisplatin, Vinblastine, Dacarbazine, IL-2, interferon alpha-2B and G-CSF."

COG investigators will need to use the Southwest Oncology Group and "Other Group" (i.e., COG in this case) patient numbers in the area provided for such on the Southwest Oncology Group data forms.

For questions regarding enrollment, please contact the **S0008** Research Coordinator at 626/241-1500 or by email at **S0008**@childrensoncologygroup.org.

b. Drug Availability

Cisplatin, vinblastine, DTIC and interferon alpha-2b are all commercially available. G-CSF and IL-2 are also commercially available. However, G-CSF will be provided by the drug manufacturer for the purpose of this study for those patients whose insurance does not cover the cost of the drug (see Appendix 19.5) and IL-2 will be provided by the National Cancer Institute for all patients entered on the study (see Section 3.5).

c. Data Submission

Data Form Submission **-** Data forms should be sent directly from COG institutions to the Southwest Oncology Group Data Operations Center. The protocol, including a copy of the forms set will be posted on the Southwest Oncology Group Website and available to COG institutions via a link from the COG Website in the protocol area for **S0008**.

Surgery Review - The materials required for surgical review are detailed in Section 12.2 of the protocol. These will be submitted from the relevant COG institution directly to the Southwest Oncology Group Data Operations Center.

The original data forms as listed in Section 14.0 should be submitted at the required intervals to the Southwest Oncology Group Data Operations Center. The Southwest Oncology Group study number and COG patient ID number must appear on each page of each form. Individual institutions will be responsible for submitting data directly to the Southwest Oncology Group Data Operations Center.

Attn: Southwest Oncology Group Data Operations Center
Cancer Research And Biostatistics
1730 Minor Ave, STE 1900
Seattle, WA 98101-1468

d. Pathology Submission

COG Institutions will be responsible for submitting pathology materials as outlined in Section 12.1c of the protocol. Follow the instructions for Southwest Oncology Group institutions, but please **forward all pathology review materials to the COG Biopathology Center instead of submitting directly to the reviewer. All materials will be forwarded to the Southwest Oncology Group**.

All materials must be labeled with the patient's study identification numbers (both COG and SWOG patient numbers) and the institutional surgical pathology number found on the corresponding reports.

Please forward materials to:

COG Biopathology Center
Children's Hospital
700 Children's Drive, WA1340
Columbus, OH 43205
Phone: 614/722-2810

e. Minimal Residual Disease (MRD) studies

Patients registered via the COG are encouraged but not required to participate in the MRD studies. Patients who choose to participate in the MRD studies should have specimens submitted as outlined in Section 15.0.

f. Informed Consent

Sample informed consent documents for COG institutions have been included in this appendix.

g. AdEERS Reporting

The COG Study Chair, Dr. Pappo, and COG AdEERS contact person should be included as E-mail recipients of any adverse events submitted via AdEERS. E-mail notifications should be sent to Dr. Alberto Pappo at alberto.pappo@sickkids.ca and COG at **S0008**@childrensoncologygroup.org

h. IRB Approval Tracking for **S0008**

COG will track initial IRB approval and will update continuing IRB approval as these are submitted to the Group Operations Center. The research coordinator for this study will check the initial IRB approval before patient enrollment is attempted. Data on initial approval and continuing IRB approval will be computerized only at the COG Operations Center.

i. On-Site Audit

On site audit of **S0008** patients will take place during the regular COG on-site audit. The **S0008** patients will be recorded in the COG enrollment database and this will be available for selection by the COG audit coordinator. When an **S0008** patient is selected, notification will be sent to the Southwest Oncology Group Operations Office. A representative there will arrange for all submitted data to be copied and sent to the COG audit coordinator within four weeks of the receipt of the request.

The results of the COG on-site audit are recorded on NCI data forms (CTMB database) and available for viewing, if needed, by the Southwest Oncology Group.

j. Study Reports

Reports that will need to be accessed by COG institutions will be provided via a link to the **S0008** protocol abstract page on the COG members Website.

k. Data Transfer

COG funds institutions for providing continued follow-up on therapeutic studies. Every six months on a date to be fixed by mutual agreement between representatives of the Southwest Oncology Group and COG statistics and data centers, the Southwest Oncology Group will transfer patient data consisting of:

1. Patient's SWOG identifier

2. Patient's COG identifier

3. Date of Last Contact as MM/DD/YYYY

4. Patient's Life Status at Last Contact as Alive or Dead

These data will be provided in electronic format to the COG SDC project coordinator.

l. Off Protocol Therapy Follow-Up

Off protocol therapy follow-up must be supplied to the Southwest Oncology Group on the relevant Southwest Oncology Group case report form regardless of whether the patient is being followed on another COG-approved protocol. In particular, follow-up on Southwest Oncology Group data instruments is required for patients who relapse, are removed from protocol therapy and subsequently enrolled on a COG therapeutic protocol. This may result in submission of two sets of data forms for a single patient, with each of the sets of forms being forwarded to different coordinating centers.

m. Questions

Protocol questions (except those that are treatment related), including eligibility, data submission, etc:

Southwest Oncology Group Melanoma Data Coordinator
SWOG Data Operations Center
Cancer Research And Biostatistics
Phone: 206/652-2267

For treatment related questions, please contact the Medical Oncology Study Coordinator listed in the opening paragraph of Section 7.0.

For issues related to data collection, including request for clarification and distribution of data delinquency reports:

S0008
Research Coordinator
COG Operations Office
P.O. Box 60012
Arcadia, CA 91066-6012
Phone: 626/241-1500
E-mail: **S0008**@childrensoncologygroup.org

If the classification of a particular communication cannot be determined, send it to the **S0008** Research Coordinator and he/she will forward it to the relevant person.

SAMPLE INFORMED CONSENT DOCUMENT

S0008, "A Phase III Trial of High Dose Interferon Alpha-2b Versus Cisplatin, Vinblastine, DTIC Plus IL-2 and Interferon in Patients with High Risk Melanoma"

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

WHAT IS THIS STUDY ABOUT?

This study is a clinical trial (a research study involving human patients). Clinical trials only include patients who choose to take part. Please take your time to make your decision. Discuss your decision with your friends and family.

You are being asked to allow your child to participate in this study because your child's doctors have determined that your child has a type of skin cancer called melanoma. This study is for patients with newly diagnosed or recurrent melanomas that have spread to the local nodes with or without distant spread (metastases to lungs, etc.) with or without ulceration of the primary tumor. Patients with this disease have a 50% chance that the disease may return.

Melanoma is a cancerous skin tumor that involves the skin cells that produce the cells that give your skin color.

WHY IS THIS STUDY BEING DONE?

This is a study that was intended for adults with melanoma. However, because melanoma in children is very rare and there are no open clinical trials or proven effective treatments for melanoma in children, the Children's Oncology Group has joined efforts with an adult group called SOUTHWEST ONCOLOGY GROUP (SWOG) which is responsible for this study.

The purpose of this study is to compare the effects (good and bad) of treating melanoma patients with high dose interferon alpha-2b alone against treating patients with a combination of cisplatin, vinblastine, DTIC, interleukin-2, interferon alpha-2b and G-CSF.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 410 patients will participate in this study.

WHAT WILL HAPPEN TO MY CHILD ON THIS STUDY?

Your child will be "randomized" into one of the two study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin; your child will have an equal chance of being placed in either group. The study group your child will be assigned to will be selected by a computer. Neither you nor your child's doctor will choose what group your child will be in.

If your child is place in Arm 1, your child will receive the interferon alpha-2b for 5 consecutive days (Monday – Friday) every week for four weeks. During this four-week period your child will receive interferon alpha-2b intravenously (through a needle in your child's vein) over 20 minutes. After this, your child will receive interferon for 48 weeks. Interferon will be given three times a week, every other day (Monday, Wednesday, Friday) as a shot under his/her skin.

If your child is placed in Arm 2, your child will receive the combination of cisplatin, vinblastine, DTIC, IL-2 and interferon alpha-2b which will require a 5 - 6 night stay in the hospital for each cycle. In order for your child to receive the study drugs (for Arm 2), your child may need a catheter placed into the central vein of his/her chest. The catheter will be placed in his/her central vein while he/she is under local anesthesia. One risk of the catheter insertion is the collapse of the lung, which would require the insertion of a special tube into the chest for several days to re-expand the lung. There is also a chance that infection will develop at this site, which would require removal and reinsertion of the catheter and possible treatment with antibiotics. Such an infection can cause additional side effects leading to prolonged hospitalization; however, with the use of oral antibiotics, in a prevention fashion, the chance of infection is uncommon. Your child will receive DTIC on Day 1 only, cisplatin and vinblastine on Days 1 - 4 along with fluids and medicine to prevent side effects. Your child will also receive IL-2 through the catheter on Days 1 - 4 (total of 96 hours) and interferon alpha-2b as a shot just under the skin on Days 1 - 5, 8, 10 and 12 of each treatment cycle. Your child will also receive G-CSF as a shot just under the skin to reduce the risk of infection associated with this drug combination. Most likely, the interferon alpha-2b shots on Days 8, 10, and 12 and G-CSF shots on Days 6-15 will be given at home. You and your family members will be shown how to give the interferon alpha-2b and G-CSF.

The treatment for this arm of the study will be repeated every 21 days. This 21-day cycle will be repeated for a total of 3 cycles.

Your child will receive the following drugs as part of your child's supportive care during your child's treatment on Days 1-5 and as indicated on Days 8,10 and 12 to help prevent side effects which may be caused by the drugs Interleukin-2 and Interferon Alpha-2b:

- Acetaminophen: This drug will be given every 4 hours on Days 8, 10 and 12 to help lessen the flu-like symptoms your child may experience during treatment.

- Naproxen: This drug may be given every 12 hours Days 1-5 for fever and chills.

- Ranitidine or Nizatidine: These drugs will be given every 12 hours to help prevent bleeding from the gastrointestinal tract.

The following drugs will be administered as needed during you child's treatment:

- Meperidine: This drug may be given every 12 hours on Days 1-5 in case your child experiences severe rigors (shivering that may be associated with chills and fever).

- Diphenoxylate and Loperamide: These drugs may be given every 4-6 hours to control diarrhea and intestinal cramping.

- Diphenhydramine or Atarax: These drugs may be given for skin rashes and itching which your child may experience during treatment.

- Furosemide: This drug may be given to lessen fluid retention (build-up of water in your child's body) during the infusion of the drug Interleukin-2.

If your child's cancer comes back at any time during your treatment, your child's treatment with these drugs will be discontinued and other treatment alternatives will be discussed with you.

- Procedures that are part of regular cancer care may be done even if you do not allow your child to join the study: Your child will have blood tests weekly and x-rays/scans before, during and after treatment to see how your child's disease is reacting to therapy. The x-rays/scans will include a chest scan, a brain and liver scan if needed, and an EKG. Tests to evaluate the adequacy of your child's heart, liver, and lungs for this therapy will also be performed. Your child may also have his/her hearing tested before treatment.

Minimal Residual Disease (MRD) Studies (Optional)

Your child will undergo *(several changes this section 2/15/04)*

During the study, blood samples will be collected to test for Minimal Residual Disease (MRD) to detect small amounts of cancerous cells in the blood. These tests are done to evaluate the progress that the treatment has made in preventing the growth of cancerous cells. The blood samples will be sent to a special laboratory for scientific testing. About 6 teaspoons of blood will be taken before your child's first treatment at Week 13 (ARM1) or Week 12 (ARM2) and 52 weeks after your child has started treatment. Because it is not known how the results of this test will affect your child's treatment, the results of the test will not be given to you or your child's doctors. By conducting these studies, researchers hope to learn more information that will help patients in the future.

Participation in this part of the study is optional. Your child can still participate in the treatment portion of this study. *(changes made to this section 2/15/04)*

Please indicate by initialing below whether you choose to allow your child to participate in the MRD studies.

_____/_____ Yes, I agree to allow my child to participate in the MRD studies.

_____/_____ No, I do not agree to allow my child to participate in the MRD studies.

HOW LONG WILL MY CHILD BE ON THIS STUDY?

Your child will be in this study until completion of the study (52 weeks) or until your child's doctors think that your child's disease is getting worse. Your child's doctors will continue to follow your child's health status for this study for 10 years.

Your child's doctors may decide to take your child off this study if your child's disease gets worse despite the treatment; the side effects of the treatment are to dangerous for your child; new information about the treatment becomes available and this information suggests the treatment will be ineffective of unsafe for your child.

You can remove your child from this study at any time. However, if you consider removing your child from the study, we encourage you to talk to your child's regular physician and to the research physician before making a final decision.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, your child is at risk for the following side effects. You should discuss these side effects with your child's doctor. There also may be other side effects that cannot be predicted. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the drugs are stopped, but in some cases side effects can be serious, long-lasting or permanent.

Side effects of the study drug interferon alpha-2b (Arm 1) include:

Very likely:

- Fever chills and flu-like symptoms.
- Nausea, vomiting, diarrhea and abdominal pain.
- Lowered white blood count may increase risk of infection.
- Hair loss.
- Loss of appetite.
- Fatigue
- Lowered platelets may lead to an increase in bruising or bleeding.

Less likely but serious:

- Drowsiness
- Anxiety, amnesia, irritability, confusion, delusions and depression which can be severe.
- Skin rashes.
- Temporary confusion
- Numbness and/or tingling in the hands and/or feet.
- Inflammation of the pancreas. *(8/31/07)*

Side effects of the study drugs cisplatin, vinblastine, DTIC, interleukin-2, interferon alpha-2b, and G-CSF (Arm 2) include:

Very likely:

- Fever, chills, and flu-like symptoms.
- Fatigue.
- Lowered platelets may lead to an increase in bruising or bleeding.
- Allergic reactions, such as itching and rash, but can be severe or even life threatening.
- Nausea, vomiting, diarrhea and abdominal pain which may be severe.
- Complete hair loss.
- Sores in mouth and throat or on other parts of the body.
- Loss of appetite.
- Lowered white blood count may increase risk of infection.
- Lowered red blood cells may lead to tiredness or shortness of breath.
- Loss of appetite and weight loss.
- Constipation.
- Pain in muscles and joints may be severe.

Less likely but serious:

- Drowsiness
- Skin rashes
- Decrease in kidney and liver functions may be severe.
- Heart problems including abnormal heartbeats, damage to the heart and in some instances heart attacks.
- Lowered blood pressure that usually requires drug treatment.
- Collapse of the lung from insertion of catheter in your child's chest (infection may also develop at this site).
- Weight gain from retaining water in your child's body. Your child's arms, legs, hands and feet may swell, and the fluid in your child's lungs may cause shortness of breath.
- Irritability, confusion, depression, delusions *(8/31/07)*
- Facial flushing
- Difficulty with coordination.
- Numbness, pain or tingling in fingers or toes.
- Ringing in the ears and hearing loss.
- Inflammation in the eye nerve that may cause temporary blindness.
- Inflammation of the pancreas. *(8/31/07)*

Reproductive risks: Because the drugs in the study can affect an unborn baby, your child should not become pregnant or father a baby while on this study.
Blood draw risks: Risks associated with drawing blood are slight, but some risks include: pain, excessive bleeding, fainting or feeling lightheaded, bruising, infection (a slight risk any time the skin is broken).

WILL MY CHILD BENEFIT FROM THIS STUDY?

We cannot and do not guarantee your child will benefit from taking part in this study. The treatment your child will receive may even be harmful. Your doctors feel that your child's participation in this study will give your child at least as good of a chance as your child might expect from other treatments. We hope the information learned from this study will benefit other patients with melanoma.

ARE THERE OTHER TREATMENT OPTIONS?

Yes, there are other options.

Instead of being on this study, your child has these options: other types of chemotherapy, radiation or no anti-cancer treatment at this time (with care to help your child feel more comfortable).

Your child can get the same agents treatment for skin cancer without being on this study. All of the treatments on this study may be available at this center or at other locations.

Please discuss these options with your regular doctor as well as other trusted personal and family advisors.

WILL MY CHILD'S RECORDS BE CONFIDENTIAL?

You may read your child's medical record. The records are available to those caring for your child at this hospital.

Organizations that may inspect/or copy your (your child's) research records for quality assurance and data analysis include:

- The Children's Oncology Group
- The Eastern Cooperative Oncology Group
- The Southwest Oncology Group *(8/31/07)*
- Novartis (the drug manufacturer for Interleukin-2) *(8/31/07)*
- The National Cancer Institute
- The Food and Drug Administration
- The Institutional Review Board of this hospital

Names of participants or material identifying participants (except as described above) will not be released without written permission, unless required by law.

If results of this study are published, your child's identity will remain confidential.

WILL I HAVE TO PAY FOR THIS TREATMENT?

Taking part in this study may lead to added costs to your insurance company. Please ask about any expected added costs or insurance problems. *(sentence removed 2/15/04)*

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate your child in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

Your child will receive no payment for taking part in this study.

(2 paragraphs below added 2/15/04)

Administration of the drug will be (provided free of charge/charged in the usual way). The parts of research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that your child receive certain standard medical tests and examinations. These standard tests and examinations will be (charged in the usual way/provided at a reduced rate). (local institutions must choose the opinion that best fits the hospital's situation)

Cisplatin, vinblastine, DTIC and interferon alpha-2b are all commercially available. G-CSF and IL-2 are also commercially available; however, G-CSF will be provided by the drug manufacturer for the purpose of this study for those patients whose insurance does not cover the cost of the drug, and IL-2 will be provided by the National Cancer Institute for all patients entered on the study.

WHAT ARE MY CHILD'S RIGHTS AS A STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose for your child not to participate in this study. If you decide not to let your child participate, your child will not be penalized and your child will still receive the standard treatment.

If you choose to allow your child to participate, you may discontinue your child's participation in the study at any time. If you discontinue participation in the study, physicians and hospital personnel will still take care of your child.

You also have the right to know about new information that may affect your child's health, welfare, or your willingness to let him/her participate in the study. You will be provided with this information as soon as it becomes available.

Whether you allow your child to participate or not, your child will continue to get the best medical care this hospital can provide.

WHAT IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or an injury related to the research, please call

_____ _____
NAME at TELEPHONE NUMBER

For questions about you rights as a study participant, please call

_____
NAME OF INSTITUTIONAL REVIEW BOARD REPRESENTATIVE*

_____
at TELEPHONE NUMBER

*The Institutional Review Board is a group of people who review the research study to protect your child's rights.

WHERE CAN I GET MORE INFORMATION?

- Call the National Cancer Institute's Cancer Information Service:
  1-800-4-CANCER (1-800-422-6237) OR
  1-800-332-8615 (for the hearing impaired)
- Visit the National Cancer Institute's Web sites:

cancerTrials: http://cancertrials.nci.nih.gov
This site provides comprehensive clinical trials information.

CancerNet™: http:/cancernet.nci.nih.gov

This site provides accurate cancer information including the Physicians Data Query (PDQ). The PDQ is the National Cancer Institute's comprehensive cancer database. It contains peer-reviewed summaries on cancer treatment, screening, prevention, and supportive care; a registry of about 1,700 open and 10,300 closed cancer clinical trials from around the world; and directories of physicians, genetic counselors, and organizations that provide cancer care.

- You will be given a copy of this consent form.
- You will be given a copy of this protocol (complete study plan) upon request.

STATEMENT OF CONSENT

I have already read the above information. I have asked all my questions and I have gotten answers. I agree to enroll my child in this study.

PATIENT NAME _____

_____ _____
SIGNATURE OF PATIENT DATE

_____ _____
SIGNATURE OF PARENT OR GUARDIAN DATE

_____ _____
SIGNATURE OF PHYSICIAN OR RESPONSIBLE INVESTIGATOR DATE

19.8 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.0.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (I, II or III) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events that occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE).* The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE version specified.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event. Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in

- the current NCI Agent-Specific Adverse Event List (for treatments using agents provided under an NCI-held IND);
- the drug package insert (for treatments with commercial agents only);
- Section 3.0 of this protocol.

Step 5: *Review Table 16.1 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.*

NOTE: If no investigational agent was administered, follow the guidelines in Table 16.1.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the agent(s) must be reported according to