Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: November 15, 2007
Effective Date: November 7, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP AND BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK APPROVED AUTOLOGOUS BONE MARROW TRANSPLANT FACILITIES (See Section 19.2 or 19.3, respectively)

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0410**, "Tandem Autologous Stem Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin's Disease (A BMT Study), Phase II." Study Coordinators: E.P. Smith, P.J. Stiff, L.S. Constine, and L.M. Rimsza

REVISION #6

Study Coordinator: Eileen P. Smith, M.D.
Phone: 626/359-8111, ext 63077
Email: esmith@coh.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #6

The protocol referenced above has been revised as follows:

1. (Title page): The version date has been updated (version 11/15/07).

2. (Page 2): The mailing address for Dr. Lisa Rimsza has been corrected. "1501 North Campbell Avenue, Room 5211, Room 245043" has been changed to "1501 North Campbell Avenue, Room *5208*, *PO Box* 245043".

3. (Page 17, Section 5.18, Eligibility Criteria; Fast Fact Sheet): "Patients must have adequate pulmonary function…performed within 28 days prior to initiation of stem cell mobilization" has been changed to "Patients must have adequate pulmonary function…performed *within 42 days prior to registration*". The Fast Fact Sheet has been updated accordingly.

   (*Reason: This change allows centers to know the results of the pulmonary function tests before the patient is enrolled, and allows centers to perform the test after stem cell collection without any adverse impact on patient safety.)*

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to inform the NCI, the BMT CTN, and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
Joseph Unger, M.S.
Tracy Maher
Jeri Jardine
Colleen Allen – BMT-CTN

Southwest
Oncology Group
A National Clinical Research Group

October 1, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP AND BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK APPROVED AUTOLOGOUS BONE MARROW TRANSPLANT FACILITIES (See Section 19.2 or 19.3, respectively)

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0410**, "Tandem Autologous Stem Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin's Disease (A BMT Study), Phase II." Study Coordinators: E.P. Smith, P.J. Stiff, L.S. Constine, and L.M. Rimsza

REVISION #5

Study Coordinator: Eileen P. Smith, M.D.
Phone: 626/359-8111, ext 63077
Email: esmith@coh.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #5

The protocol referenced above has been revised as follows:

1. (Title page): The version date has been updated (version 10/1/07).

2. (Page 38, Section 13.1, Registration Guidelines): "Patients must be registered prior to initiation of treatment (no more than one working day prior to planned start of treatment)" has been changed to "Patients must be registered prior to initiation of treatment (no more than *five* working *days* prior to *the* planned start of treatment)".

3. (Page 41, Section 14.4b, Data Submission Schedule): The **S0410** Registration Form has been removed. (*Reason: The only documents that should be submitted within 14 days of registration are the Advanced Hodgkin's Disease Prestudy Form (Form #34864), Lymphoma Baseline Tumor Assessment Form (Form #48010), completed Section 5.0 of the protocol, and the pathology report confirming histology.)* Subsequent sections have been reorganized.

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to inform the NCI, the BMT CTN, and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
Joseph Unger, M.S.
Tracy Maher
Jeri Jardine
Colleen Allen – BMT CTN

Southwest
Oncology Group
A National Clinical Research Group

Distributed: September 15, 2007
Submitted to CTEP: September 7, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP AND BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK APPROVED AUTOLOGOUS BONE MARROW TRANSPLANT FACILITIES (See Section 19.2 and 19.3, respectively)

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0410**, "Tandem Autologous Stem Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin's Disease (A BMT Study), Phase II." Study Coordinators: E.P. Smith, P.J. Stiff, L.S. Constine, and L.M. Rimsza

REVISION #4

Study Coordinator: Eileen P. Smith, M.D.
Phone: 626/359-8111, ext 63077
Email: esmith@coh.org

IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial activation (for BMT CTN institutions only)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed (for institutions already participating)

( ) No review required

REVISION #4

The protocol referenced above has been revised as follows:

1. (Fast Fact Sheet): The first row under the eligibility column has been revised to be consistent with the language in Section 5.1. "Relapsed or refractory Hodgkin's disease with one of 9 characteristics (Section 5.1)" has been changed to "*Histologically or cytologically confirmed relapsed or refractory Hodgkin's disease*".

2. (Title page): The following changes have been made to this page:
   - The version date has been updated (version 9/7/07).
   - The table of contents has been updated.
   - Participant list: The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) has joined this trial and has been added to the participant list as follows:

     "ALL SOUTHWEST ONCOLOGY GROUP AND *BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK* APPROVED AUTOLOGOUS BONE MARROW TRANSPLANT FACILITIES (See Section 19.2 *and 19.3, respectively*)"

3. (Page 2): The following changes have been made to this page:
   - Dr. Lisa M. Rimsza has replaced Dr. Thomas M. Grogan as the SWOG pathology study coordinator for this trial. Dr. Rimsza's contact information has been added.
   - The contact information for Dr. Ginna G. Laport, the BMT CTN study coordinator for this trial, has been added.

4. (Page 15, Section 5.2, Eligibility Criteria): Section 5.2 has been replaced with the following new eligibility section:

"Patients must have either a unilateral or bilateral (preferred) bone marrow aspirate and biopsy before therapy is initiated. It is highly recommended that a cytogenetic analysis is performed. If performed, cytogenetics must show no abnormalities linked to the diagnosis of myelodysplasia. The timing of the bone marrow aspirate and biopsy must meet at least one of the following criteria:

a. Within 42 days prior to stem cell collection.

b. Within 28 days prior to initiating salvage chemotherapy, provided the bone marrow aspirate and biopsy is negative for Hodgkin's disease and the patient has a response of PR, CRU, or CR to salvage chemotherapy. In this case, the marrow exam does NOT need to be repeated even though it may not fall within 42 days prior to stem cell collection.

c. After stem cell collection and within 28 days prior to starting the transplant procedure, provided the patient did NOT have a marrow exam before salvage chemotherapy and stem cells were collected on the rebound after one of the salvage chemotherapy cycles."

5. (Page 21, Section 7.5a, Treatment Plan): In the first paragraph, first sentence, the melphalan dosing administration instructions have been revised. "Day -1: Intravenous hydration with normal saline at 200 ml/hour…" has been changed to "Day -1: *Recommendations for melphalan administration are as follows:* Intravenous hydration with normal saline at 200 ml/hour…" (*Rationale: The change above was made in order to allow flexibility in the manner in which high dose chemotherapy is mixed and administered at local institutions.)*

6. (Page 25, Section 7.5b.6i.c, Treatment Plan): In the first paragraph, first sentence, the VP-16 dosing administration instructions have been revised. "The method of administration is as per Creger et al." has been changed to "The *recommended* method of *VP-16* administration is as per Creger et al." (*Rationale: The change above was made in order to allow flexibility in the manner in which high dose chemotherapy is mixed and administered at local institutions.)*

7. (Page 26, Section 7.5b.6ii, Treatment Plan): In the fifth paragraph, first sentence, the cyclophosphamide dosing administration instructions have been revised. "The drug should be dissolved at a ratio of…" has been changed to "*Recommendations for cyclophosphamide administration are as follows:* The drug should be dissolved at a ratio of…" (*Rationale: The change above was made in order to allow flexibility in the manner in which high dose chemotherapy is mixed and administered at local institutions.)*

8. (Page 27, Section 7.5c.2, Treatment Plan): In the first paragraph, third sentence, the BCNU dosing administration instructions have been revised. The following sentence has been added: "*Recommendations for BCNU administration are as follows:…"* (*Rationale: The change above was made in order to allow flexibility in the manner in which high dose chemotherapy is mixed and administered at local institutions.)*

9. (Page 27, Section 7.5c.2biii, Treatment Plan): In the first paragraph, first sentence, the VP-16 dosing administration instructions have been revised. "The method of administration is as per Creger et al." has been changed to "The *recommended* method of *VP-16* administration is as per Creger et al." (*Rationale: The change above was made in order to allow flexibility in the manner in which high dose chemotherapy is mixed and administered at local institutions.)*

10. (Page 28, Section 7.5c.2c, Treatment Plan): In the fifth paragraph, first sentence, the cyclophosphamide dosing administration instructions have been revised. "The drug should be dissolved at a ratio of…" has been changed to "*Recommendations for cyclophosphamide administration are as follows:* The drug should be dissolved at a ratio of…" (*Rationale: The change above was made in order to allow flexibility in the manner in which high dose chemotherapy is mixed and administered at local institutions.)*

11. (Page 31, Section 9.0, Cycle 1 Study Calendar): The "¶" footnote explanation has been revised. "Bilateral or unilateral bone marrow aspirate and biopsy must be performed within 42 days prior to stem cell collection" has been changed to "*See Section 5.2".*

12. (Pages 35-36, Section 11.5, Statistical Considerations): The statistical consideration paragraph regarding data and safety monitoring of this study has been revised.

"There is no formal data and safety monitoring committee for Phase II studies. Toxicity and accrual monitoring are done routinely by the Study Coordinator, study Statistician and the Disease Committee Chair. Response monitoring is done by the study Statistician and Study Coordinator. Accrual reports are generated weekly, and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Coordinator monitor toxicities on an ongoing basis."

Has been changed to:

"Toxicity and accrual monitoring are done routinely by the Study Coordinator, Study Statistician and the Disease Committee Chair. Response monitoring is done by the Study Statistician and Study Coordinator. Accrual reports are generated weekly and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Coordinator monitor toxicities on an ongoing basis. *A Data and Safety Monitoring Committee will also oversee the conduct of the study. The Committee consists of four members from outside of the Southwest Oncology Group, three Southwest Oncology Group members, three non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the Southwest Oncology Group Statistical Center, and will meet at the Group's bi-annual meetings as necessary.*"

13. (Page 37, Section 12.5, Discipline Review): Dr. Lisa M. Rimsza has replaced Dr. Thomas Grogan.

14. (Page 38, Section 13.0, Registration Guidelines): The note preceding Section 13.1 has been revised. "This trial can only be conducted at Southwest Oncology Group approved BMT facilities (see Section 19.2)" has been changed to ""This trial can only be conducted at Southwest Oncology Group *or Blood and Marrow Transplant Clinical Trials Network* approved BMT facilities (see *Section* 19.2 *or 19.3, respectively*)."

15. (Pages 39 and 39a, Section 13.4, Registration Guidelines): The BMT CTN registration guidelines have been added. *Subsequent section has been renumbered.* Page 39a was added to prevent repagination.

16. (Pages 40-41, Section 14.0, Data Submission Schedule): The following changes have been made to these pages:
    - Section 14.3c: The BMT CTN data submission procedures have been added.
    - Section 14.6: The instructions for submission of data forms has changed. "IMMEDIATELY AFTER CYCLE 1 HDT…" has been changed to "IMMEDIATELY AFTER *CYCLES 1 AND 2 OF* HDT…" The **S0410** Treatment Form has been updated. Please use Form #55293 instead of Form #64972.
    - Section 14.7: The instructions for submission of data forms has changed. "Two months after the second stem cell infusion" has been changed to "*ONE AND TWO* MONTHS AFTER THE SECOND STEM CELL INFUSION".
    - Section 14.8: A new Section 14.8 has been created with the following new form and instructions: "*TWO MONTHS AFTER THE SECOND STEM CELL INFUSION: Submit the **S0410** Infusion Summary Form (Form # 4533).*" Subsequent sections have been renumbered.
    - Section 14.13: The **S0410** Treatment Form has been updated. Please use Form #55293 instead of Form #64972.

17. (Page 42, Section 16.0, Ethical and Regulatory Considerations): The BMT CTN adverse event reporting procedures have been added.

18. (Page 43, Section 16.1, Ethical and Regulatory Considerations): Formatting changes have been made to this page, but no changes have been made to the content.

19. (Page 44, Section 16.1f, Ethical and Regulatory Considerations): The contact information for reporting secondary AML/MDS to the Investigational Drug Branch has been updated. The address have been removed as submission are preferred via fax only.

20. (Page 48, Section 18.2, Master Forms Set): The following changes have been made to this page:

    - Section 18.2a: The Southwest Oncology Group Registration Form Code Sheet (version 12/08/04) has been updated and replaced with version 10/24/06. It is now listed alongside the **S0410** Registration Form in the Master Forms Set.
    - Section 18.2c: The **S0410** Treatment Form (Form #64972) has been updated and replaced with Form #55293.
    - Section 18.2e: The **S0410** Infusion Summary Form (Form #4533) has been added. Subsequent sections have been reorganized.

21. (Page 49, Model Consent Form, *Notes for Local Institutions): The fifth bullet has been revised.

    "The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and the Southwest Oncology Group."

    Has been changed to:

    "The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form), the Southwest Oncology Group, *and the Blood and Marrow Transplant Clinical Trials Network (if applicable).*"

22. (Page 50, Model Consent Form, *Notes for Local Institutions): Prior to the first bullet on this page the following instructions for BMT CTN institutions have been added:

    "*The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to the BMT CTN.*"

23. (Page 58, Model Consent Form, Will My Medical Information Be Kept Private?): The Blood and Marrow Transplant Clinical Trials Network (BMT CTN) has been added to the list of organizations that may look at and/or copy medical records for research, quality assurance, and data analysis.

24. (Pages 74 & 83, Sections 19.0 & 19.3, respectively, Appendix): The roster of Blood and Marrow Transplant Clinical Trials Network (BMT CTN) approved transplant centers has been added. Repagination was required for pages 74-83.

Institutions must update their local consent forms to include the above information for future registrations. Patients currently being treated on this study should be informed of the changes in the manner determined by the local Institutional Review Board (IRB).

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to inform the NCI, the BMT CTN, and the Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
Joseph Unger, M.S.
Tracy Maher
Jeri Jardine
Colleen Allen – BMT CTN

Southwest
Oncology Group
A National Clinical Research Group

September 1, 2007

TO: ALL SOUTHWEST ONCOLOGY GROUP APPROVED AUTOLOGOUS BONE MARROW TRANSPLANT FACILITIES (SEE SECTION 19.2)

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0410**, "Tandem Autologous Stem Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin's Disease (A BMT Study), Phase II". Study Coordinators: E.P. Smith, P.J. Stiff, L.S. Constine and T.M. Grogan.

MEMORANDUM

Study Coordinator: Eileen P. Smith
Phone number: 626/359-8111 ext.: 63077
E-mail: esmith@coh.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

Bristol-Myers Squibb is allocating supplies of carmustine injection (BiCNU) to patients for drop shipment only. Contact Bristol-Myers Squibb at 800-631-5244, option 1 for details on obtaining carmustine supplies.

Please attach this memorandum to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Joseph Unger, M.S.
Bryan Goldman, M.S.
Jeri Jardine
Tracy Maher

Southwest
Oncology Group
A National Clinical Research Group

November 15, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP APPROVED AUTOLOGOUS BONE MARROW TRANSPLANT FACILITIES (SEE SECTION 19.2)

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0410**, "Tandem Autologous Stem Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin's Disease (A BMT Study), Phase II". Study Coordinators: E.P. Smith, P.J. Stiff, L.S. Constine and T.M. Grogan.

REVISION #3

Study Coordinator: Eileen P. Smith
Phone number: 626/359-8111 ext.: 63077
E-mail: esmith@coh.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #3

The protocol referenced above has been revised as follows:

1. (Fast Fact Sheet): Under prestudy requirements, a new "≤ *28 days prior to stem cell mobilization*" category has been added. Tests required within this time frame are pulmonary function tests (taken from the ≤ 28 days prior to registration category) and MUGA or 2-D Echo (taken from the ≤ 42 days before stem cell collection category).

2. (Title page): The version date has been updated (11/15/06).

3. (Page 16, Section 5.17, Eligibility Criteria): In the second sentence, "...MUGA scan or 2-D echocardiogram must be obtained within 42 days prior to registration" has been changed to "...MUGA scan or 2-D echocardiogram must be obtained within *28 days prior to stem cell mobilization*."

4. (Page 17, Section 5.18, Eligibility Criteria): "Patients must have adequate pulmonary function ...performed within 28 days prior to registration" has been changed to "Patients must have adequate pulmonary function ...performed within 28 days prior to *initiation of stem cell mobilization*."

5. (Page 32, Section 9.0, Study Calendar): The LDH assessments post-transplant (i.e. Days, 7, 14, 21, and 60) have been removed. (*LDH assessments at these timepoints are not necessary for patient care*.)

6. (Page 37, Section 12.5, Discipline Review): The address for the Southwest Oncology Group Lymphoma Repository has been updated.

7. (Page 39, Section 13.3a, Registration Guidelines): In the first sentence of the paragraph that begins "For assistance with points 1 and 2..." the phone number for the Southwest Oncology Group Operations Office has been changed from 210/677-8808 to 210/*450*-8808.

8. (Page 40, Sections 14.2-14.3, Data Submission Schedule): The SWOG data submission procedures have been replaced with updated sections.

9. (Page 41, Section 14.0, Data Submission Schedule): The following changes have been made to this page:

   - Section 14.6: "Immediately after Cycle 1 HDT, immediately after Cycle 2 HDT, and 1 month after stem cell infusion" has been changed to "Immediately after Cycle 1 HDT, immediately after Cycle 2 HDT, and 1 month after *the second* stem cell infusion."
   - Section 14.7: "Two months after stem cell infusion" has been changed to "Two months after *the second* stem cell infusion."
   - Sections 14.6 & 14.12: The **S0410** Treatment Form number has changed from #6760 to #*64972.*
   - Sections 14.6, 14.7, 14.11, & 14.12: The **S0410** Adverse Event Summary Form number has changed from #18970 to #*3502*.

10. (Page 43, Section 16.1e, Ethical and Regulatory Considerations): In the last sentence, the Southwest Oncology Group Operations Office has been changed from 210/677-8808 to 210/*450*-8808.

11. (Page 48, Section 18.1, Master Forms Set): The paragraph that begins, "Attached are copies of all data forms..." has been replaced with the following updated paragraph:

    "*The Model Informed Consent Form is included in this section, preceded by "Notes for Local Institution Consent Form Authors" and "Notes for Local Investigators." The study - as well as the local consent form meeting the guidelines noted in these documents - must be reviewed and approved by the Institutional Review Board prior to registration and treatment of patients on this study*."

12. (Page 48, Section 18.2, Master Forms Set): The sentence "Forms to be used for patients treated on this study" has been replaced with "*This section includes copies of all data forms which must be completed for this study.*" Additionally, the following forms have been updated:

    - Section 18.2c: **S0410** Treatment Form
    - Section 18.2d: **S0410** Adverse Event Summary Form
    - The final form numbers and version dates have been updated.

13. (Pages 76-80, Section 19.2, Southwest Oncology Group Approved Transplant Centers): The Southwest Oncology Group approved bone marrow transplant facilities list has been updated. The following changes have been made:

- Page 76: The H. Lee Moffitt Cancer Center and Research Institute have been added. Also, Henry Ford Hospital, previously approved for only autologous transplants, is now approved for allogeneic transplants.
- Page 77: Formatting changes have been made to this page, but the content remains unchanged.
- Page 78: The Sutter Health Western (Alta Bates Medical Center) listing has been updated to indicate that this institution is an affiliate of UC-Davis.
- Pages 79-80: Formatting changes have been made to these pages, but the content remains unchanged.

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Joseph Unger, M.S.
Bryan Goldman, M.S.
Jeri Jardine
Tracy Maher
Monica Toth

Southwest
Oncology Group
A National Clinical Research Group

August 1, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP APPROVED AUTOLOGOUS BONE MARROW TRANSPLANT FACILITIES (SEE SECTION 19.2)

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0410**, "Tandem Autologous Stem Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin's Disease (A BMT Study), Phase II". Study Coordinators: E.P. Smith, P.J. Stiff, L.S. Constine and T.M. Grogan.

REVISION #2

Study Coordinator: Eileen P. Smith
Phone number: 626/359-8111 ext.: 63077
E-mail: esmith@coh.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #2

The protocol referenced above has been revised as follows:

1. (Fast Fact Sheet): The following changes have been made to this page:
   - Under Cycle 2 High-Dose Therapy, the timing of hydration has been changed from "D -1" to "D -2, -1"
   - Under prestudy requirements, "< 42 days before registration" has been changed to "≤ 42 days before *stem cell collection*".

2. (Title page): The version date has been updated (08/01/06).

3. (Page 14, Section 5.7): In the second sentence, "orchitecture" has been changed to "architecture".

4. (Page 31, Section 9.0): The second sentence under the (**) footnote has been updated. "A minimum of 3.5 x 10^6 CD34+ cells/Kg of actual body weight should be collected for each cycle of high dose therapy" has been changed to "A *total* of 3.5 x 10^6 CD34+ cells/Kg of actual body weight should be collected *for high dose therapy (see Section 7.3)*."

5. (Page 41, Section 14.4a): The form number for the Advanced Hodgkin's Disease Prestudy Form has been changed from "#64486" to "#34864".

6. (Page 48, Section 18.1b): The form number and version date for the Advanced Hodgkin's Disease Prestudy Form have been updated. Form #64486, version 10/15/05 has been changed to Form #34864, version 08/01/06.

7. (Pages 75, 77, 78 and 79, Section 19.2): The Southwest Oncology Group approved bone marrow transplant facilities list has been updated. The following changes have been made:

   - Page 75: Arizona Cancer Center: Dr. Andrew Yeager has replaced Dr. Alan List. The phone and fax numbers have also been updated.
   - Page 75: Columbia University has been removed.
   - Page 77: Louisiana State University Medical Center, Shreveport: The address has been updated. Also, Dr. John W. Hiemenz has replaced Dr. Reinhold Munker.
   - Page 78: University of Arkansas: The address has been updated. Dr. Bart Barlogie has replaced Dr. Sundar Jagannath. The phone and fax numbers have also been updated.
   - Page 79: The University of Illinois Medical Center at Chicago has been added.

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Joseph Unger, M.S.
Bryan Goldman, M.S.
Jeri Jardine
Tracy Maher
Monica Toth

Southwest
Oncology Group
A National Clinical Research Group

July 15, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP APPROVED AUTOLOGOUS BONE MARROW TRANSPLANT FACILITIES (SEE SECTION 19.2)

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0410**, "Tandem Autologous Stem Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin's Disease (A BMT Study), Phase II". Study Coordinators: E.P. Smith, P.J. Stiff, L.S. Constine and T.M. Grogan.

REVISION #1

Study Coordinator: Eileen P. Smith
Phone number: 626/359-8111 ext.: 63077
E-mail: esmith@coh.org

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #1

The protocol referenced above has been revised as follows:

1. (Fast Fact Sheet): Under the ineligibility column, second row, the criteria describing prior malignancy has been revised to match criteria in Section 5.21.

2. (Title page): The version date has been updated (07/15/06).

3. (Page 11, Section 3.2c) In the formulation section, second sentence, "The drug should be reconstituted...in normal saline or D5W" has been changed to "The drug should be reconstituted...in normal saline or D5W *at a ratio of 100 mg of dosage strength cyclophosphamide per 5 mL of diluent*."

4. (Pages 26 & 28, Sections 7.5b.6bii & 7.5c.2, respectively): In the paragraph that begins, "The drug should be dissolved in about 150 mL of saline or D5W and infused IV over an hour", the first sentence has been changed to "The drug should be dissolved *at a ratio of 100 mg of dosage strength cyclophosphamide per 5 mL of diluent* and infused IV over an hour."

5. (Page 27, Section 7.5c.2) In the chemotherapy table that outlines the preparative regimen for BCV chemotherapy, the typo outlining the dose of cyclophosphamide has been corrected: "100 g/kg" has been changed to "100 *mg*/kg".

6. (Page 31, Section 9.0): The following changes have been made to this page:

   - Laboratory: Creatinine clearance, DLCO/FEV_1, and CMV/Hepatitis/Herpes/ Zoster titer at Day 0 have been removed. These tests should only be performed at prestudy.
   - Laboratory: Added a "¶" footnote in the prestudy column for bilateral or unilateral bone marrow aspirate and biopsy. The footnote highlights that the bone marrow aspirate and biopsy must be performed within 42 days prior to stem cell collection.

Please attach this memorandum to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Joseph Unger, M.S.
Bryan Goldman, M.S.
Jeri Jardine
Tracy Maher
Monica Toth

Southwest
Oncology Group
A National Clinical Research Group

October 15, 2005

TO: ALL SOUTHWEST ONCOLOGY GROUP APPROVED AUTOLOGOUS BONE MARROW TRANSPLANT FACILITIES (SEE SECTION 19.2)

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0410**, "Tandem Autologous Stem Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin's Disease (A BMT Study), Phase II". Study Coordinators: E.P. Smith, P.J. Stiff, L.S. Constine and T.M. Grogan.

STATUS NOTICE

Study Coordinator: Eileen P. Smith
Phone number: 626/359-8111 ext.: 63077
E-mail: esmith@coh.org

IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

ACTIVATION

The study referenced above is now open for participation. Entire copies of the protocol are enclosed for your use.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Joseph Unger, M.S.
Bryan Goldman, M.S.
Scott Kurruk
Tracy Maher

SOUTHWEST ONCOLOGY GROUP
PROTOCOL FAST FACT SHEET

THIS FORM HAS BEEN DESIGNED AS A RESOURCE ONLY AND IS NOT INTENDED FOR USE IN THE FULFILLMENT OF PATIENT REGISTRATION AND TREATMENT REQUIREMENTS

S0410

TANDEM AUTOLOGOUS STEM CELL TRANSPLANTATION FOR PATIENTS WITH PRIMARY PROGRESSIVCE OR POOR RISK RECURRENT HODGKIN'S DISEASE (A BMT STUDY).

Treatment initiation Within 5 working days of registration
Drugs Provided: None

TREATMENT:
Collection of PBSC ≤ 6 weeks after completion of the last cycle of salvage chemotherapy
↓
Involved Field Radiation for Residual Tumor > 5 cm after salvage chemotherapy
↓
Cycle 1 High-Dose Therapy

Drugs	Dose	Route	Timing
Melphalan	150 mg/m^2	IV	D -1
PBSC Reinfusion	50% of collected PBSC	IV	D 0

↓
Transplant Center shall choose a single regimen for all patients treated on this protocol who are under the age of 61 (TBI/VP16/CTX or BCV).

Cycle 2 High-Dose Therapy (4-8 weeks after cycle 1)

Drugs	Dose	Route	Timing
TBI	150 cGy x 2 daily		D -8 to -5
VP-16	60 mg/kg	IV	D -4
Cyclophosphamide	100 mg/kg	IV	D -2
PBSC Reinfusion	50% of collected PBSC	IV	D 0

OR

Cycle 2 High-Dose Therapy (4-8 weeks after cycle 1)

Drugs	Dose	Route	Timing
BCNU	150 mg/m^2	IV	D -6, -5, -4
VP-16	60 mg/kg	IV	D -4
Cyclophosphamide	100 mg/kg	IV	D -2
Hydration		IV	D -2, -1
PBSC Reinfusion	50% of collected PBSC	IV	D 0

Eligibility	Ineligibility
Histology or cytologically confirmed relapsed or refractory Hodgkin's disease	Clonal abnormalities detected in the pre-stem cell collection of marrow
Bilateral or unilateral bone marrow aspirate and biopsy	Prior malignancy except for adequately treated basal cell or squamous cell skin cancer, or any other cancer which the patient has been disease free for 5 yrs. Prior history of lymphoma, myelodysplastic syndrome, or leukemia (even if disease free for five years).
Minimum of 3.5 x 10^6 CD34 positive cells/kg collected according to Section 7.4.	Active bacterial, fungal or viral infection
Patients with bulk disease > 5 cm must have received IFRT prior to registration.	Pregnant or nursing female
Must have adequate sections of original diagnostic specimen available for submission	Requires therapy for coronary artery disease, cardiomyopathy, congestive heart failure or arrhythmias
≥ 15 and < 71 years of age	
PS 0 – 2	ANC < 1,500/mcL
Ejection fraction ≥ 45% by MUGA scan or 2-d ECHO with no significant abnormalities if questionable cardiac history	Patients with known HIV or AIDS Not in good medical condition that will permit aggressive HDT.
Adequate pulmonary function measured by a corrected DLCO ≥ 60% or FEV_1 ≥ 60% of predicted	Clinical or laboratory evidence of CNS involvement by Hodgkin's disease

PRESTUDY REQUIREMENTS:
≤ 28 days before registration: H&P/WT/PS; CBC/diff/platelets; bilirubin; alk phos; creatinine/creatinine clearance; EKG; chest x-ray; CT scan chest, abdomen, & pelvis (if negative, studies may have been performed within 42 days)
≤ 42 days before registration: Pulmonary function tests
≤ 28 days prior to initiation of stem cell mobilization: MUGA or 2-D Echo
≤ 42 days before stem cell collection: Bilateral or unilateral bone marrow A&B

*This form has been developed with the support of the SWOG Nurse Oncologists' Committee.

S0410
Activated October 15, 2005
Revised 9/7/07

SOUTHWEST ONCOLOGY GROUP

TANDEM AUTOLOGOUS STEM CELL TRANSPLANTATION FOR PATIENTS WITH PRIMARY PROGRESSIVE OR RECURRENT HODGKIN'S DISEASE (A BMT STUDY), PHASE II

PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP AND BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK APPROVED AUTOLOGOUS BONE MARROW TRANSPLANT FACILITIES (SEE SECTION 19.2 AND 19.3, RESPECTIVELY)

STUDY COORDINATORS:

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AGENTS:

BCNU (Carmustine) (NSC-409962)
Cyclophosphamide (Cytoxan®) (NSC-26271)
Melphalan (NSC-8806)
VP-16 (Etoposide) (NSC-141540)

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(Version Date 11/15/07)

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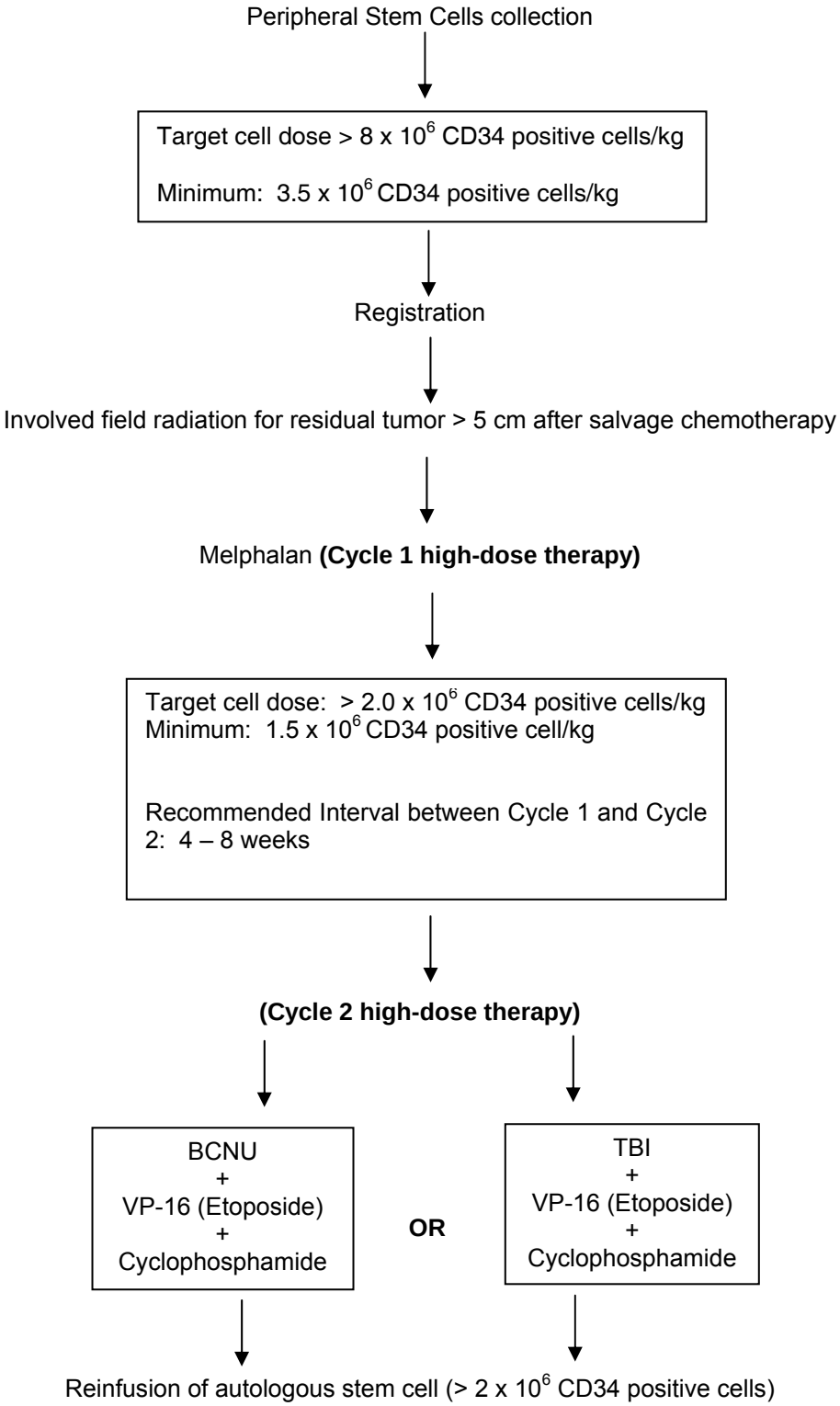
SCHEMA



1.0 OBJECTIVES

1.1 To assess the 2-year progression-free survival (PFS) for patients with primary progressive or recurrent Hodgkin's lymphoma (HL) treated with a tandem transplant program (2 cycles of high dose therapy with autologous stem cell rescue).

1.2 To evaluate the response rate and toxicity in patients with primary progressive or recurrent Hodgkin's lymphoma treated with this regimen.

2.0 BACKGROUND

Hodgkin's lymphoma

Hodgkin's lymphoma is one of the most curable malignancies. Combination chemotherapy with or without radiotherapy result in cures of 60% to 85% of patients with Hodgkin's lymphoma. In the event of failure to completely respond or relapse, the efficacy of secondary therapy is directly related to the duration of initial response. Progression during induction or within 12 months of the completion of treatment has a particularly poor prognosis, with 5-year disease-free survival of 0% and 20%, respectively. A long-term follow-up report from Bonadonna's group confirmed the dismal outcome in these patients. *(1)* At 8 years, the overall survival rate was only 8% in patients who have induction failures after treatment with MOPP-ABVD. Relapses after more durable remissions, those of 12 months or greater, are more amenable to salvage chemotherapy. About half of such patients may enjoy prolonged initial remission. However, in a long term follow up report from NCI, the overall survival was only 24% among patients with long initial remission after re-treatment with MOPP chemotherapy, due to cumulative toxicity. *(2, 19)*

Autologous stem cell transplantation for patients with recurrent or refractory Hodgkin's lymphoma

Despite the lack of randomized Phase III studies, autologous stem cell transplantation has become the treatment of choice for patients who have failed to achieve a first remission with conventional treatment or who have relapsed after achieving an initial remission. Results from single institution studies, as well as cooperative group trials, indicate that various high-dose regimens can result in disease-free survival rates of 30 - 65% in patients who relapse after conventional treatment. *(3 - 6)* Although, these results represent a significant improvement over those obtained with conventional therapy, relapse still occurs in more than 50% of cases.

Investigators from Stanford University have reported the results of a retrospective analysis of patients matched for disease parameters who were treated with either conventional salvage therapy or myeloablative therapy and ASCT. *(7)* In this study the event free survival was superior in the transplant group (27% vs. 53%).

A Phase III trial conducted by the British National Lymphoma Foundation randomized patients with relapsed or refractory Hodgkin's disease to receive mini-BEAM or BEAM with marrow rescue. *(8)* The actuarial 3 year overall survival in this study was significantly better in patients who underwent high-dose chemotherapy (53% vs. 10%). This trial was terminated early because of difficulty in maintaining accrual and superior outcome for patients on the transplant arm.

The German Hodgkin's disease study group and EBMT performed a Phase III randomized study comparing BEAM-HSCT vs. Dexa-BEAM in patients with recurrent Hodgkin's lymphoma. *(9)* The data indicate that the overall survival of patients given either treatment did not differ significantly. In detail, it showed that the overall survival difference was p=0.6229 for the early relapse group, p=0.0878 for the late relapse group, and p=0.4214 for the multiple relapse group. BEAM-HSCT was the favored arm in the first two groups but not the third group, however the tail of all curves had very few patients. Freedom from treatment failure was significantly higher for patients given BEAM-HSCT vs. Dexa-BEAM (55% vs. 34%, p=0.019), while survival for patients followed out to 3 years did not yet show a survival advantage.

Prognostic factors (see Fig 1)

Multiple transplant series have attempted to identify prognostic factors to predict outcome after AHCT. The most consistent adverse prognostic factor was related to the extent of prior treatment. Reports from University of Nebraska Medical Center, MD Anderson, and City of Hope have drawn similar conclusions. *(4, 10, 11)* Multiple salvage attempts not only increase the immediate and long term toxicity after high dose therapy but it may also induce chemo-resistance. In recent years, as AHCT has gained acceptance in the oncology community as a treatment option for patients with refractory or recurrent Hodgkin's disease, many oncologists now refer patients for consideration of transplant at the first sign of treatment failure. Thus, the extent of prior treatment may become an insignificant prognostic factor in the future.

The duration of first remission is the strongest prognostic factor to predict outcome for patients with recurrent Hodgkin's disease treated with conventional salvage chemo/radiation. *(12, 13)* However, contradicting results were reported in the literature for such patients who received AHCT. Reece and colleague reported a significantly superior progression-free survival in first relapse patients with an initial remission duration of $\geq$ 12 months or more (85%, n=23) compared with 48% for those with remission duration < 12 months (n=35). *(3)* Other investigators did not find any impact of remission duration on PFS or OS. *(5, 7, 14, 15)* It is noteworthy that unlike the Vancouver series, many of the long term remitters from other series also had co-existing poor risk features which may account for the difference on the transplant outcome for this group of patients.

In a multi-variate analysis by the Stanford Group in 119 adult patients, symptoms at relapse, extra-nodal involvement of lung or bone marrow at relapse, and more than minimal disease at the time of transplantation were the best predictors of event-free survival. *(5)* The Vancouver group also found the presence of systemic symptoms and extra-nodal disease at relapse adversely affected the transplant outcome. *(3)*

For patients with relapsed Non-Hodgkin's lymphoma, chemo-responsiveness to conventional salvage chemotherapy is routinely used to select patient for high dose therapy. Indeed, patients with chemo-resistant NHL rarely benefit from AHCT but this may not apply to patients with Hodgkin's disease. *(16)* Although a minimal disease state before AHCT has been shown to be predictive in several reports, some patients have achieved long term progression free survival after AHCT even with chemo-refractory disease. Hence, patients with chemo-refractory Hodgkin's disease should not be excluded from AHCT solely based on "chemo-sensitivity."

Indeed, the estimated probability of long-term progression free survival would be approximately 25% for patients with poor risk recurrent Hodgkin's lymphoma (symptoms, extra-nodal involvement or chemo-refractory disease at relapse).

Patients who fail induction therapy have an extremely poor prognosis with further conventional chemotherapy. *(1, 2)* Autologous stem cell transplant improves the survival to 30 - 40%, however, disease progression remains the leading cause of treatment failure.

For patients without poor risk factor at relapse, the estimated 3-years progression free survival was 60%. Again, disease progression accounted for most of the treatment failure.

Figure 1: Adverse prognostic factors for treatment outcome after AHCT for Hodgkin's disease

Vancouver (1st rel only) *(3)*	'B' symptoms at relapse, extranodal disease at relapse, duration of 1st CR < 12 months
Stanford *(5)*	'B' symptoms at relapse, pulmonary/bone marrow involvement, more than minimal disease at AHCT
City of Hope (1st rel only) *(14)*	> 2 prior regimens, extranodal disease at relapse, peripheral stem cell as sole stem cell source
UCHL *(15)*	> 2 prior regimens, Bulky disease > 10 cm, female sex
MD Anderson *(11)*	> 2 prior regimens, extranodal involvement, abnormal performance status, chemorefractory
Boston *(20)*	> 1 extranodal site, ECOG > 0, progressive disease at AHCT
SFGM *(21)*	Extranodal relapse, duration of 1st CR < 12 months
ABMTR (1st rel only) *(22)*	Chemorefractory, abnormal LDH, KPS < 90%

Report from **SWOG-9011** with Prognostic Factor Assessment

In an attempt to evaluate the value of two augmented preparative regimens combined with an autologous bone marrow transplant for the treatment of relapsed/refractory Hodgkin's disease, and to examine prognostic factors for outcome, a Phase II study was performed under the auspices of Southwest Oncology Group. Between April 1990 and December 1995, eighty-one patients with either sensitive or refractory (induction failures or chemoresistant) relapse received etoposide (60 mg/kg), cyclophosphamide (100 mg/kg) and either total body irradiation (12 Gy) if not previously irradiated, or carmustine (15 mg/kg), followed by an ABMT. *(23)* The 5-year PFS and OS for the 74 eligible patients treated at 20 Southwest Oncology Group centers was 41% and 54% respectively, despite a median remission after initial chemotherapy of only 6 months. There was one early treatment related death (1.4%), two late deaths due to lung toxicity, and only one death due to myelodysplasia. There were no differences in PFS or OS based on regimen or chemosensitivity. The Cox prognostic factor analysis determined that > 2 prior regimens, relapse in a radiated field, and extranodal disease were adverse prognostic factors. Among the 46 patients who received prior radiotherapy, the 5-year OS was 38% (95% CI: 14 - 61%) for patients with 2 - 3 adverse factors vs. 60% (95% CI: 42 - 78%) for those with 0 - 1 adverse factors. This study has demonstrated the effectiveness of the augmented preparative regimens for the treatment of relapsed/refractory Hodgkin's Disease, without an increase in regimen-related mortality. However, disease progression after stem cell transplantation still accounted for most of the treatment failure. In this analysis, a poor prognosis group was identified, which would be appropriate to treat with novel therapies. Although the outcomes on good risks patient are very encouraging (5-year overall survival of 60%), there is still room for improvement, in particular, to improve the disease control.

Experience of tandem transplant and high dose sequential therapy for patients with recurrent/refractory Hodgkin's lymphoma

With advances in stem cell mobilization and collection, it has become feasible to perform tandem (double) transplants or sequential high-dose therapy. Desikan, et al, have performed tandem autologous transplants safely in over one thousand patients with multiple myeloma. *(24)* The treatment related death rate is low (< 4%).

Ahmed, et al, have performed tandem transplants on 45 patients with refractory Hodgkin's disease. *(25)* With a median follow-up of four years, the median survival was 45 months. It is worth noting that only 55% of the patients received both planned cycles. Patients were ineligible for second cycle because of toxicity or disease progression. This experience demonstrated the feasibility of tandem (double) transplants in patients with advanced Hodgkin's disease. Furthermore, the preliminary results appear promising.

In a retrospective multi-center study, the Italian Lymphoma Intergroup used a high-dose sequential chemotherapy approach in 110 patients. *(26)* The program was characterized by the sequential administration of high dose cyclophosphamide (7 gm/m^2) followed by peripheral blood progenitor cell harvest, high dose methotrexate (8 gm/m^2) and high dose etoposide (2 gm/m^2) followed by a final intensification with high dose mitoxantrone (60 mg/m^2) + melphalan (180 mg/m^2) with stem cell rescue. At a median follow-up of 3.2 years, the 5-year event-free survival and overall survival was 55% and 69%, respectively. For the 32 patients receiving high dose sequential therapy for first relapse within 1-year, the 5-year event-free survival and overall survival was 63% and 75%, respectively. A prospective study led by the German Hodgkin Lymphoma Study Group is currently evaluating a similar approach in patients with relapsed and refractory Hodgkin's lymphoma. Treatment consisted of two cycles of DHAP, followed by high dose therapy in those patients responding (high dose cyclophosphamide, high dose methotrexate and high dose etoposide). This was followed by one cycle of BEAM supported by peripheral stem cell rescue. The latest interim analysis of this study included 69 patients of whom 16 were primary refractory and 53 were relapsed. The overall response was 80% in relapsed patients and 50% in those with primary refractory disease. *(27)*

Brice, et al, have treated 72 patients with very unfavorable Hodgkin's lymphoma with two cycles of high dose therapy with stem cell rescue. *(28)* The first cycle consists of CBV + mitoxantrone (30 mg/m^2) and the second cycle consists of cytarabine (6 gm/m^2), melphalan (140 mg/m^2) and total body irradiation (12 Gy) or busulfan (12 mg/m^2). Seventy-two percent of patients received both transplants with a response rate of 91%. Two toxic deaths occurred: one from VOD and one from ARDS.

Taken together, these data demonstrate that high dose sequential therapy and tandem transplant are both feasible and effective and may improve the response and transplant outcome for patients with poor risk recurrent or primary refractory Hodgkin's lymphoma.

Rationale of the study design

Experience from City of Hope and cooperative group studies have demonstrated that intensified CBV (BCNU 450 mg/m², cyclophosphamide 100 mg/kg and etoposide (VP-16) 60 mg/kg) or FTBI (1,200 cGy) + VP-16 (60 mg/kg) + cyclophosphamide (100 mg/kg) are highly effective as preparative regimens for patients with advanced Hodgkin's disease undergoing autologous stem cell transplant. *(4, 6)* However, relapses remain a major problem; particularly in patients with poor risk disease.

One possible approach to decrease the relapse rate is to further intensify the regimen, either by increasing the dose of the individual drugs or to add a fourth agent. Phase I studies of CBV combination, performed by Wheeler, et al, suggest that the maximum cumulative doses of cyclophosphamide, BCNU and VP-16 that can be tolerated are in the range of 7,200, 450 and 2,000 mg/m², respectively. *(29)* Further dose intensification would probably be limited by major toxicity. Reece, et al, have added cisplatin as a fourth agent to their preparatory regimen (VP-16 2,400 mg/m², BCNU 500 mg/m², cyclophosphamide 7,200 mg/m² and cisplatin 150 mg/m²). *(30)* Although toxicity remained acceptable, there was no evidence that this regimen was more effective than CBV alone. It is worth noting that the dose of cisplatin used is relatively small in this high-dose therapy setting, but further dose escalation would be limited by toxicity.

Horning, et al, and Jones, et al, have both demonstrated the benefit of cytoreduction with conventional chemotherapy before transplant, concluding that minimal disease status before transplant was an important prognostic factor for FFP, EFS and overall survival in their reports. *(5, 31)* However, repeat cycles of conventional dose salvage chemotherapy might potentially increase the drug resistance of the tumor, and increase transplant related toxicity. In addition, the

efficacy of conventional salvage chemotherapy is also thought to be limited in these aggressive high-risk cases. Another approach is to try to achieve minimal disease state by using a single agent high-dose regimen with G-CSF and/or peripheral stem cell support before proceeding to a "classic transplant" which will then be used as "consolidation".

Melphalan, an alkylating agent, is widely used as a component of conventional salvage chemotherapy (MVP or mini-BEAM) or as a preparatory regimen in stem cell transplant (BEAM or BEM). Russell, et al, have treated 20 patients with single high-dose melphalan (140 - 200 mg/m²) with stem cell support. *(32)* All 20 patients had relapsed/refractory Hodgkin's disease that has been heavily pre-treated by multiple chemotherapeutic regimens. Thirty-three percent of patients achieved complete remission and 56% achieved partial remission, 20% of patients have a durable complete remission. The regimen, as expected, is extremely well tolerated. It is worth noting that a similar regimen (melphalan 200 mg/m²) has been used extensively in patients with multiple myeloma and treatment related death in this group of older higher risk patients is less than 5%.

Most transplant patients relapsed in sites of prior disease and HD is very sensitive to radiation. Both Pezner and Poen suggested that in conjunction with high-dose therapy and autologous bone marrow transplantation, involved field radiotherapy is well tolerated, effectively controls local and regional disease, and may improve survival in selected patients with relapsed or recurrent Hodgkin's lymphoma. *(33, 34)*

Here, we hypothesized that the overall outcome might be improved if a minimal disease status could be achieved before the conventional transplant. Therefore, we will use high-dose melphalan with stem cell support (Cycle 1) as salvage cytoreductive treatment, and after achieving a minimal disease state or maximum debulking of the disease, standard conditioning regimen (CBV or TBI/VP-16/Cy) will be used as "consolidation" followed by second stem cell infusion (Cycle 2).

Experience from a pilot study (City of Hope and Loyola University Medical Center)

Based on the above background, a pilot study was conducted by City of Hope National Medical Center and Loyola University. *(35)* The purpose of the study is to determine the safety and efficacy of a tandem ASCT program for patients with primary progressive or poor risk recurrent Hodgkin's lymphoma.

Between 4/98 and 3/00, 46 patients were enrolled in this Phase I-II study. The 1st cycle consisted of melphalan (150 mg/m^2) alone. The 2nd cycle consisted of of FTBI (1,200 cGy) or BCNU (450 mg/m^2) in combination with VP-16 (60 mg/kg) and cyclophophamide (100 mg/kg). A minimum of 2 x 10^6 CD34 positive autologous stem cells were re-infused after each cycle of therapy. Eligibility criteria included primary progressive (n=28) or recurrent Hodgkin's lymphoma (n=18) with at least one of the following poor prognostic factors: first CR < 12 months (n=15), extranodal disease at relapse (n=4), B symptoms at relapse (n=4), or chemotherapy-refractory disease (n=3). Seven of the 18 had more than one poor risk feature.

Of the 46 enrolled patients (median age 35, range 17-65), five patients did not receive the planned tandem transplants because of inadequate stem cell collection for two transplants in 4 patients and withdrawal from study before the first cycle of high-dose therapy in one patient. Of the 41 patients who received the planned first cycle of high-dose therapy, five developed disease progression before receiving the second cycle of HDCT. Four of these patients proceeded to the second autologous transplant cycle and all of them developed disease progression after the second cycle. One patient elected to receive an allogeneic stem cell transplant and also relapsed after transplant. With a median of 64 days (range 25-105), 41 patients received the second HDCT cycle. Twenty-five patients received the FTBI-based regimen and 16 received the BCNU-based regimen for the second transplant. With a median follow-up of 5 years (range 1.6 - 6.4 years), 24 patients are alive and progression-free at time of last follow-up. Of the 41 patients who received both cycles of high dose therapy, 21 are alive and disease-free. Seventeen patients had disease progression at a median of 4 months post-transplant. Of the 17 patients with progressive

disease, 13 died of Hodgkin's lymphoma and 4 of them are still alive, two having undergone allogeneic HCT from a volunteer matched unrelated donor. Day 100 mortality was 4% with 2 patient deaths from interstitial pneumonitis. Three other patients died of non-relapse causes (1 adenocarcinoma, 1 ruptured aneurysm, 1 cardiac event) while in remission. Late events included the following: one patient who relapsed 7 months after tandem transplant and received further salvage chemotherapy subsequently developed myelodysplasia at 28 months after transplant. One patient developed endometrial carcinoma 4 years after transplant.

Using an intent-to-treat analysis for all 46 patients enrolled on study, the 5-year K-M estimate of overall survival, event-free survival and freedom from progression were 73% (95% CI 60-87), 50% (95% CI 35-64) and 61% (CI 46-76%) respectively. For the 41 patients who received both cycles of HDCT, the K-M 5-year overall survival, event-free survival and freedom from progression were 73% (95% CI 59-88), 52 % (95 % CI 36-68) and 63 % (95% CI 47-79) respectively. The results of this pilot study suggest that for patients with primary progressive or poor risk recurrent Hodgkin's lymphoma, this tandem autologous HDCT program is effective and well tolerated and compares favorably with the conventional single transplant.

We are encouraged by the tolerability of this very intensive regimen and would like to extend this pilot study into a Phase II study in the cooperative group setting to further evaluate the efficacy of this approach. Our goal is to determine if this approach will increase the two-year survival to 60% from the 45% seen in **SWOG-9011** study of a single transplant.

Patients with known HIV infection or AIDS are not eligible for this study. The severely depressed immune system as is found in HIV infected patients and the possibility of premature death would compromise study objectives. Also, pregnant or nursing woman is not eligible due to the potential for congenital abnormalities, and of harm to nursing infants due to this treatment regimen. Due to a higher morbidity and mortality, patients above the age of 70 will be excluded. In general, these patients are treated with reduced intensity transplants at all Southwest Oncology Group institutions.

Inclusion of Women and Minorities:

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects.

3.0 DRUG INFORMATION

3.1 BCNU (1,3-bis (2-chloroethyl)-1-nitrosourea)(NSC-409962)(Carmustine)(BiCNU)

a. DESCRIPTION

BCNU is a lipid soluble agent which has alkylating properties plus an isocyanate metabolite which interferes with DNA and RNA synthesis.

b. TOXICOLOGY

Human Toxicities: The most frequent and most serious toxicity of BCNU is delayed myelosuppression. Pulmonary infiltrates and/or fibrosis, dry cough and difficulty breathing have been reported. Cases of fatal pulmonary toxicity with BCNU have been reported. Nausea and vomiting are very common. A reversible hepatic toxicity is demonstrated by elevated SGOT, alkaline phosphatase and bilirubin.

Renal abnormalities consisting of progressive azotemia, decrease in kidney size and renal failure have been reported. Thrombophlebitis and local ulceration occur if extravasation occurs. Venous pain and flushing during injection and a brownish discoloration of skin on contact have also occurred.

Rapid infusion may produce intensive flushing. Neuroretinitis has been reported. The occurrence of acute leukemia and bone marrow dysplasia have been reported in patients following long-term nitrosourea therapy. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: IV BCNU is rapidly degraded to active metabolites. Sixty to 70% is excreted in the urine in 96 hours and 10% as respiratory CO_2. Because of the high lipid solubility, it crosses the blood-brain barrier readily.

Formulation: BCNU is supplied as a lyophilized powder containing no preservatives. Due to its water insolubility, it is to be reconstituted with the diluent provided (3 ml of absolute ethanol) and then with either 27 ml or 17 ml of sterile water for injection to provide a resulting concentration of 3.3 mg/ml or 5 mg/ml, respectively.

Storage and Stability: Stability upon reconstitution (less than 8% potency lost) is eight hours at room temperature or 24 hours if refrigerated and protected from light. BCNU solution may be further diluted with 500 ml of 5% Dextrose OR sodium chloride injection, USP, and will be stable for 24 hours if refrigerated and protected from light. Unopened vials are stable under refrigeration for two years. BCNU has a low melting point requiring refrigeration at all times prior to reconstitution. Do not use if an oil film is present at the bottom of vial.

Administration: BCNU should be administered by IV. Significant absorption of BCNU to plastics has been documented.

Supplier: BCNU is commercially available and should be purchased by a third party. **This drug will not be provided by the NCI**.

3.2 Cyclophosphamide (Cytoxan®) (NSC-26271)

a. DESCRIPTION

2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxidemonohydrate. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites which cross-link to tumor cell DNA.

b. TOXICOLOGY

Human Toxicology: Toxicity from cyclophosphamide includes bone marrow suppression which usually occurs 10 to 12 days after administration, nausea, vomiting, anorexia, abdominal discomfort, diarrhea, stomatitis, hemorrhagic colitis, jaundice, reversible alopecia, hemorrhagic cystitis which can frequently be prevented with increased hydration, hematuria, ureteritis, tubular necrosis, fibrosis of the bladder, cardiac toxicity which may potentiate doxorubicin-induced cardiotoxicity, anaphylactic reaction, skin rash, hyperpigmentation of the skin and

nails, interstitial pulmonary fibrosis, interstitial pneumonitis, malaise, asthenia SIADH (syndrome of inappropriate ADH secretion) and cross sensitivity with other alkylating agents. Treatment with cyclophosphamide may cause significant suppression of the immune system.

Second malignancies, most frequently of the urinary bladder and hematologic systems, have been reported when cyclophosphamide is used alone or with other anti-neoplastic drugs. It may occur several years after treatment has been discontinued. It interferes with oogenesis and spermatogenesis and may cause sterility in both sexes which is dose and duration related. It has been found to be teratogenic, and women of childbearing potential should be advised to avoid becoming pregnant. Increased myelosuppression may be seen with chronic administration of high doses of phenobarbital. Cyclophosphamide inhibits cholinesterase activity and potentiates effect of succinylcholine chloride. If patient requires general anesthesia within 10 days after cyclophosphamide administration, the anesthesiologist should be alerted. Adrenal insufficiency may be worsened with cyclophosphamide. Cyclophosphamide is excreted in breast milk, and it is advised that mothers discontinue nursing during cyclophosphamide administration. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Cyclophosphamide is activated principally in the liver by a mixed function microsomal oxidase system. PO administration is well absorbed, with bioavailability greater than 75%. Five to twenty-five percent of unchanged drug is excreted in the urine. Several active and inactive metabolites have been identified with variable plasma protein binding. There appears to be no evidence of clinical toxicity in patients with renal failure, although elevated levels of metabolites have been observed.

Formulation: Cyclophosphamide is supplied in 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials as a white powder. The drug should be reconstituted with Sterile Water for Injection, USP, and may be diluted in either normal saline or D5W at a ratio of 100 mg of dosage strength cyclophosphamide per 5 mL of diluent. The PO form is supplied as 50 mg and 25 mg tablets.

Storage and Stability: Although the reconstituted cyclophosphamide is stable for six days under refrigeration, it contains no preservatives and therefore should be used within 6 hours. Tablets are stable at room temperature.

Administration: Cyclophosphamide should be diluted in normal saline or D5W and infused IV. An added dose of IV fluids may help prevent bladder toxicity.

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

3.3 Melphalan - IV (NSC-8806)

a. DESCRIPTION

Chemistry: Melphalan (L-phenylanine mustard) is a bifunctional alkylating agent. It forms covalent linkages with susceptible cellular proteins. It induces formation of DNA interstrand and DNA protein cross-links.

b. TOXICOLOGY

Human Toxicology: Melphalan's major systemic toxicity is bone marrow depression with secondary anemia, leukopenia and thrombocytopenia, usually occurring within three to five weeks of the onset of therapy and lasting four to eight weeks. These effects are exacerbated by prior chemotherapy or radiotherapy. Other side-effects include nausea, vomiting, diarrhea, stomatitis, esophagitis, colitis, increases in liver function and kidney function tests, renal/bladder necrosis, pulmonary fibrosis, respiratory distress, peripheral neuropathy, paresthesia, alopecia, fever and hypersensitivity including edema, rash and anaphylaxis. At high doses, supraventricular arrhythmias, including atrial fibrillation, may occur. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: IV administration of melphalan revealed rapid elimination from plasma with terminal half-life of 1.8 hours. 13% is excreted in the urine. It is rapidly distributed in total body water and eliminated in a biphasic manner. IP administration of 20-30 mg/m^2 revealed a peak concentration in the peritoneal cavity of 6.4 ± 2.4 µg/ml and half-life of 85 ± 30 minutes. The peak plasma concentration was 1.22 µg/ml, and half-life was 86 ± 31 minutes.

Formulation: The drug is available investigationally as an injectable kit. This kit contains an ampule of 100 mg (equivalent) melphalan, a 1 ml ampule of acid-alcohol diluent (containing 0.047 ml 37% HCl, q.s. to 1 ml with alcohol) and a 9 ml ampule of final diluent containing dipotassium phosphate, 108 mg propylene glycol 5.4 ml sterile water for injection q.s. 9 ml. This kit should be stored at room temperature and projected from light.

The 100 mg injectable formulation is put into solution initially with the addition of the 1 ml acid-alcohol diluent. When dissolution is complete, the 9 ml final diluent is added. This final solution has a pH of > 7 and should be used promptly. According to the manufacturer (8.5% hydrolysis 24 hours after mixing) a further dilution in D_5W is also reportedly stable for 24 hours.

Supplier: This drug is commercially available for purchase by a third party. **This drug will not be supplied by the NCI.**

3.4 VP-16 (Etoposide)(VePesid)(Ethylidene-Lignan P.) (NSC-141540)

a. DESCRIPTION

Chemistry: VP-16 is a semi-synthetic podophyllotoxin derivative from the plant podophyllum pletatum, and has antineoplastic properties in experimental animals and in man. The empiric formula $C_{29}H_{32}O_{13}$ has a molecular weight of 588.

Mechanism of Action: The epipodophyllotoxins exert phase specific spindle poison activity with metaphase arrest, but in contrast to the vinca-alkaloids, have an additional activity of inhibiting cells from entering mitosis. Suppression of tritiated thymidine, uridine, and leucine incorporation in human cells in tissue culture suggests effects against DNA, RNA and protein synthesis.

Animal Tumor Data: Significant antitumor effect has been demonstrated in L1210, mouse sarcoma 37 and 180, Walker carcinosarcoma and Erlich ascites tumor. With the L1210 system, activity was schedule-dependent, having greater effect with a twice weekly administration than with daily dosing or the

administration of single large doses. The drug is active given intraperitoneally or orally in L1210. No effect was demonstrated against intracerebrally inoculated L1210.

b. TOXICOLOGY

Animal Toxicology: The predominant toxicities of VP-16 in animal studies involve the hematopoietic system, with toxicity to the liver and GI tract occurring only at doses producing profound myelosuppression. Anemia, leukopenia, and lymphoid involution occur in mice, rats and monkeys. Acute toxicity investigations have been complicated by the toxicity of the solvent system. The LD-50 of the solvent plus drug approached that of the solvent alone. Immunosuppressive effects occur with an inhibition of antibody production in mice and monkeys, and prevention of experimental allergic encephalomyelitis in rats (cell-mediated immunity).

Human Toxicology: Reversible myelotoxicity has been uniformly observed to be the major toxicity of VP-16 and to represent the only clinically significant side effect. Following a single IV injection, peak myelotoxicity occurs at seven to nine days. Following daily IV injections for five to seven days, myelotoxicity is maximal between 12 - 16 days from the initiation of therapy. Bone marrow suppression is mainly manifested as granulocytopenia, with thrombocytopenia and anemia occurring to a lesser extent. Gastrointestinal toxicities including transient modest nausea, vomiting and diarrhea, are common. Other reactions could include aftertaste, rash, pigmentation, pruritis, abdominal pain, constipation and dysphagia. Occasional alopecia is reported. VP-16 does not produce phlebitis or nephrotoxicity. Rarely, anaphylactic-like reactions have been reported, as well as, hypotension. Hypotension can be managed by infusing the drug over at least a 30 minute period. Occasionally, chills, fever, peripheral neurotoxicity, stomatitis, hepatotoxicity, transient cortical blindness and radiation recall dermatitis may be a result of VP-16 administration. The occurrence of acute leukemia has been reported rarely in patients treated with VP-16 in association with other antineoplastic agents. VP-16 can cause fetal harm when administered to pregnant women.

Pregnancy and Lactation: Etoposide can cause fetal harm when administered to a pregnant woman. Etoposide has been shown to be teratogenic in mice and rats. In these studies, etoposide caused dose-related maternal toxicity, embryotoxicity, and teratogenicity. Fetal abnormalities included decrease weight, major skeletal abnormalities, exencephaly, encephalocele, anophthalmia, and retarded ossification. No information is available on 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 IV administration, disposition is biphasic with initial half-life of 1.5 hours and terminal half-life of 4 - 11 hours. Drug does not accumulate in plasma following daily administration of 100 mg/m^2 for 4 - 5 days. Drug crosses blood-brain barrier poorly. Recovery after IV administration of radio-labeled etoposide in the urine ranges from 42 - 67% and feces from 0 - 16%. The mutogenic and genotoxic potential has been established in mammalian cells.

Formulation: 100 mg of VP-16 is supplied as 5 ml of solution in sterile multiple dose vials for injection. The pH of the yellow clear solution is 3 - 4. Each ml contains 20 mg VP-16, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate

80/tween 80, 650 mg polyethylene glycol 300, and 30.5% (v/v) alcohol. VP-16 must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% sodium Chloride Injection, USP. The time before precipitation occurs depends on concentration, however, when at a concentration of 0.2 mg/ml it is stable for 96 hours at room temperature and at 0.4 mg/mL it is stable for 48 hours.

Storage and Stability: The drug is available as a box of 10 vials that are stored at room temperature. Each vial should be kept in the box to protect it from light. VP-16 is less stable in 5% Dextrose injection and precipitation is reported. Capsules must be stored under refrigeration 2° - 8°C (36° - 46°F). The capsules are stable for 24 months under such refrigerated conditions.

Administration: IV. VP-16 has a minimum infusion time of 30 minutes to reduce hypotension.

Supplier: VP-16 is commercially available and should be obtained through a third party. **This drug will not be supplied by the NCI**.

4.0 STAGING CRITERIA

Staging criteria is not applicable to this study.

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) _____

INITIAL REGISTRATION

_____ 5.1 All patients must have histologically or cytologically confirmed relapsed or refractory Hodgkin's disease. All patients must have received systemic chemotherapy as all or part of their initial treatment for Hodgkin's disease.

Re-biopsy at the time of recurrence/progression is **strongly** recommended. If biopsy has not been obtained at the time of disease recurrence/progression, there must be un-equivocal radiological evidence of disease recurrence/progression.

_____ 5.2 Patients must have either a unilateral or bilateral (preferred) bone marrow aspirate and biopsy before therapy is initiated. It is highly recommended that a cytogenetic analysis is performed. If performed, cytogenetics must show no abnormalities linked to the diagnosis of myelodysplasia. The timing of the bone marrow aspirate and biopsy must meet at least one of the following criteria:

a. Within 42 days prior to stem cell collection.

b. Within 28 days prior to initiating salvage chemotherapy, provided the bone marrow aspirate and biopsy is negative for Hodgkin's disease and the patient has a response of PR, CRU, or CR to salvage chemotherapy. In this case, the marrow exam does NOT need to be repeated even though it may not fall within 42 days prior to stem cell collection.

c. After stem cell collection and within 28 days prior to starting the transplant procedure, provided the patient did NOT have a marrow exam before salvage chemotherapy and stem cells were collected on the rebound after one of the salvage chemotherapy cycles.

_____ 5.3 Patients must have had a minimum of 3.5×10^6 CD34 positive cells/kg collected according to guidelines in Section 7.4.

_____ 5.4 Patients with any clonal abnormalities detected in the pre-stem cell collection marrow are not eligible.

_____ 5.5 Patients with bulk disease > 5 cm must agree to receive involved field radiation therapy (IFRT) per Section 7.2.

_____ 5.6 Patients who relapse after achieving a complete remission must complete a minimum of two courses of salvage chemotherapy or a minimum of 2,500 cGy of radiation to determine if they have "sensitive" or "resistant" recurrent disease. The treating physician will determine the salvage regimen. Recommended regimens include ICE or ESHAP.

_____ 5.7 Pathology review: Adequate sections from the original diagnostic specimen must be available for submission for review by the Southwest Oncology Group Lymphoma Laboratory as outlined in Section 12.0. An adequate biopsy requires sufficient tissue to establish the architecture and a REAL or WHO histologic subtype with certainty. Thus, core biopsies, especially multiple core biopsies may be adequate, whereas needle aspirations or cytologies are not adequate.

_____ 5.8 Patients must have a performance status of 0 – 2 according to Zubrod performance criteria (see Section 10.4).

_____ 5.9 Patients must be age 15 or older, and must not have reached 71 years of age (see Section 2.0 for justification).

SWOG Patient No. _____

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

_____ 5.10 Patient must have a chest x-ray within 28 days prior to registration or a chest X-ray that was negative performed within 42 days prior to registration.

Date of chest x-ray _____

_____ 5.11 Patients must have either a CT scan of thorax, abdomen and pelvis within 28 days prior to registration or a CT scan of thorax, abdomen and pelvis which was negative performed within 42 days prior to registration.

Date of CT scan _____

_____ 5.12 Patients must not have clinical or laboratory evidence of central nervous system involvement by Hodgkin's disease. Any lumbar puncture for symptoms at relapse that was performed within 42 days prior to registration must be negative.

Date of lumbar puncture _____

_____ 5.13 Patients must have a good general medical condition that will permit aggressive HDT. Patients must also have a ANC ≥ 1,500/mcL within 28 days prior to registration.

ANC _____ Date _____

_____ 5.14 Patients must have a measured or calculated creatinine clearance ≥ 60mL/minute and serum creatinine ≤ 2 x the institutional upper limit of normal within 28 days prior to registration.

Creatinine Clearance: Measured or calculated (circle one)

Creatinine Clearance _____ Date _____

Serum creatinine _____ Date _____ IULN _____

_____ 5.15 Patients must have adequate hepatic function as measured by a serum bilirubin ≤ 1.5 x the institutional upper limit of normal (unless elevation is greater than this and due to infiltration of the liver by Hodgkin's disease) within 28 days prior to registration.

Liver involvement? YES NO (circle one)

Bilirubin _____ IULN _____ Date _____

_____ 5.16 Patient must be free of active bacterial, fungal, or viral infection.

_____ 5.17 Patients requiring therapy for coronary artery disease, cardiomyopathy, congestive heart failure or arrhythmias are not eligible. If the patient's history is questionable, a MUGA scan or 2-D echocardiogram must be obtained within 28 days prior to initiation of stem cell mobilization. Patients with ejection fractions < 45% will <u>not</u> be eligible.

Ejection fraction by MUGA scan/2-D Echo (circle one) _____

Date of MUGA scan/2-D Echo _____

IULN _____

SWOG Patient No. _____

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

_____ 5.18 Patients must have adequate pulmonary function as measured by a corrected DLCO ≥ 60% or $FEV_1 \geq 60\%$ of predicted performed within 42 days prior to registration.

DLCO or FEV_1 (circle 1)

% Predicted DLCO or FEV_1 _____

Date of DLCO or FEV_1 _____

_____ 5.19 Patients with known HIV or AIDS are not eligible (for justification of this exclusion, see Section 2.0).

_____ 5.20 Pregnant or nursing women are not eligible due the possibility of congenital defects or harm to nursing infants from this treatment regimen (See Section 2.0). Women and men of reproductive potential must have agreed to use an effective contraceptive method.

_____ 5.21 No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, or other cancer for which the patient has been disease free for five years. Patients with a prior history of lymphoma, myelodysplastic syndrome or leukemia are not eligible (even if disease free for five years).

5.22 If Day 28 or 42 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.

_____ 5.23 All patients must be informed of the investigative nature of this study and must sign and given written consent in accordance with institutional and federal guidelines.

_____ 5.24 At the time of patient registration, the treating institution's name and ID number must be provided to the statistical Center 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

Stratification factors are not applicable to this study.

7.0 TREATMENT PLAN

For dosing principles or questions, please consult the Southwest Oncology Group Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38). For treatment or dose modification related questions, please contact Dr. Stiff at 708/327-3101 (email: pstiff@lumc.edu) or Dr. Smith at 626/359-8111 ext.: 63077 (email: esmith@coh.org).

7.1 Good Medical Practice

The following pre-study tests should be obtained within 28 days 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. The Study Coordinator must be contacted if there are significant deviations in the values of these tests.

a. CMV titer

b. Hepatitis profile

c. Herpes simplex/Zoster titer

d. LDH measurement

7.2 Salvage treatment: (radiation/chemotherapy)

All patients who relapse after achieving a complete remission are required to have a minimum of 2 courses of salvage chemotherapy or a minimum of 2,500 cGy of radiation to determine if they have "sensitive" or "resistant" recurrent disease. The treating physician will determine the salvage regimen. Recommended regimens include ICE or ESHAP.

Pre-transplant salvage radiation

Involved field irradiation should be administered before the first cycle of high-dose therapy for any residual tumor that is greater than 5 cm after salvage chemotherapy. No more than two sites may be used to treat disease.

Timing

Involved field radiation should not be given until after completion of stem cells collection.

Portal and treatment Definition

Usually, the radiation portals will include all initial entire involved lymph node regions as defined in the Rye and Ann Arbor Staging Classification. The exceptions are the mediastinum and the bilateral hilar nodes, which should be considered a single region; unilateral iliac nodes, which should be considered a single region; and the preauricular and cervical/supraclavicular which should be considered as two separate regions.

Cervical/Supraclavicular Region

The entire ipsilateral cervical/supraclavicular regions should be treated if individual or confluent nodal masses ≥ 5 cm in largest transverse dimension within this area. If the disease extended to the midline, the bilateral cervical/supraclavicular regions should be treated.

Mediastinum/Hilar region

The mediastinal field should encompass only the residual disease after the salvage chemotherapy and should be a shaped field encompassing the mediastinum, with a 1 cm margin laterally and extending inferiorly to at least 2 cm below the lower extent of disease at presentation, and include the bilateral hilar regions. The entire cardiac silhouette need not be treated, except as noted below. Intrathoracic sites of extralymphatic extension (e.g., lungs, pleura, chest wall, and pericardium) should be excluded.

Axillary Region

The ipsilateral axillary, infraclavicular and supraclavicular areas will be treated. The superior border should at the superior border of the larynx (if supraclavicular adenopathy was present) or the inferior border of the larynx (if there was no supra-clavicular adenopathy).

Para-aortic Region

The width of the para-aortic field should conform to the volume necessary to treat residual disease after both cycles of high dose therapy with 1 – 1.5 cm margins. The superior margin will be matched to the mediastinal field (if treated) or else extend to the top of T10. The inferior margin should be at the L4 - 5 interspace.

Treatment techniques

Radiation therapy will be delivered by standard megavoltage (4-10MV) techniques, utilizing shaped fields with blocks individualized to the specific patient. In general, parallel opposed fields will be most appropriate. The minimum SSD or SAD should be 80 cm. Contiguous sites of bulky involvement should be treated in contiguity unless bulky sites are present on both sides of the diaphragm, in which cases treatment may be administrated sequentially to initial bulky sites on one side of the diaphragm followed by a 1 - 3 week break, then completion of irradiation to the opposite side of the diaphragm. In addition, if treatment to both the retroperitoneal and pelvic nodes is required, this field may be split at the level of the iliac crest and treated sequentially. In the unusual situation in which there may be non-contiguous bulky sites of involvement on the same side of the diaphragm, the intervening lymph node regions should be treated as well.

Dose Definition and Schedule

In general, the total dose should be 18 Gy calculated at the isocenter or through the central axis at the midplane of the patient, 1.8 Gy per fraction, five times per week, all fields treated each day.

Doses are specified as the target dose which will be representative of the dose in the center of the target volume. For the following field arrangements the target dose will be specified as follows: For two opposed coaxial equally weighted beams: On the central ray at the mid-separation of the beams. For an arrangement of 2 or more intersecting beams: At the intersection of the central ray of the beams.

Treatment Modifications

Hematocrit, white blood cell count, and platelet count will be obtained at least weekly during radiation therapy. Treatment may be temporarily interrupted if the white blood count falls below 2,000/mcL and/or platelet fall below 50,000/mcL. Such interruption is discouraged, but if it is considered necessary due to leukopenia or thrombocytopenia, the treatment will be resumed upon recovery.

7.3 Stem cell collection and Cryopreservation of Peripheral Blood Stem Cells:

Prior to transplantation, all patients will have to undergo a collection of adequate numbers of hematopoietic stem cells. Stem cell harvesting may be done after priming with a cytokine (G-CSF, GM-CSF or other factors used singly or in combination according to center preference), or they may be collected following the salvage chemotherapy during the rebound phase with cytokine support. Chemotherapy in combination with growth factors is also allowed.

Stem cells should be collected no longer than six weeks after completion of the last cycle of salvage chemotherapy. Patients will undergo leukapheresis according to standard institutional procedures to collect a minimum of 3.5×10^6 CD34+ cells/Kg of actual body weight with a target dose of 8×10^6 CD34+ cells/Kg of actual body weight (a target of 4×10^6/kg actual body weight for each cycle of high dose therapy).

The collected cells must be cryopreserved according to accepted methods using DMSO alone or DMSO/HES. The stem cells should not be purged or CD34 selected. The collected stem cells will be cryopreserved in two portions and to be re-infused after cycle 1 and cycle 2 high dose therapies. Patients who fail to collect adequate CD34 cells (3.5×10^6/kg actual body weight) will be excluded from the study. The first portion of peripheral stem cell should have approximately 2×10^6 CD34+ cells/Kg of actual body weight (a minimum of 1.5×10^6 CD34+ cells/Kg of actual body weight) and the second portion must have at least 2×10^6 CD34+ cells.

7.4 Overview of Tandem Transplant:

In this study, we intend to treat all patients with two cycles of high dose therapy (tandem transplant). The first cycle of HDT will consist of melphalan alone followed by re-infusion of approximately 1.5×10^6 CD34+ cells. Upon recovery from the first cycle of HDT, patients will be treated with either a total body irradiation-based or BCNU-based high dose regimen (2nd HDT) followed by re-infusion of at least 2×10^6 CD34+ cells. Patients not having previously received mediastinal radiotherapy can be treated with a TBI-based or BCNU based regimen (see Section 7.5c for details). Those who have received previous mediastinal radiotherapy will be treated with BCV (BCNU, Cyclophosphamide and VP-16) regimen. Selected patients will receive involved field radiation upon recovery from initial salvage chemotherapy and completion of stem cells collection but before the first cycle of high dose therapy as defined in Section 7.5. These patients are eligible for the TBI-based regimen, if this is the regimen their center selects for non-previously irradiated, < 60 year old patients. Patients who have received prior involved field radiation as part of salvage therapy will be required at all centers to receive the BCV regimen.

7.5 High Dose Therapy

a. Cycle 1: High Dose Melphalan

Melphalan will be administrated intravenously at a dose of $150 mg/m^2$ on Day –1. Doses will be calculated based on adjusted ideal body weight (see Section 7.5b.6i for calculation instructions).

Day –1: Recommendations for melphalan administration are as follows: Intravenous hydration with normal saline at 200 mL/hour and KCl 15 meq/L will be started. After at least 6 hours of hydration, melphalan 150 mg/m^2 in normal saline at a concentration of 0.4 mg/mL and at a rate of 5 mg/minute with normal saline at rate of 200 mL/hr and KCl 15mEq/L for a total of at least 16 hours. Appropriate intravenous antiemetics will be given.

Day 0: About 50% of the previously collected CD34+ cells (unselected) will be re-infused (minimum of 1.5 x 10^6 CD34 + cells). Stem cells will be thawed and infused according to standard institutional practices beginning at least 24 hours after the completion of melphalan. Pre-medicate with diphenhydramine (Benadryl), mannitol, hydrocortisone, and acetaminophen (Tylenol) as per institutional policy.

b. Cycle 2: TBI or BCNU in combination with high dose etoposide (VP-16) and Cyclophosphamide.

The second transplant may not begin until 28 days after the stem cell infusion (Day 0) of the first cycle.

Each transplant center will need to dedicate themselves to either the TBI regimen for patients who have not received involved field radiation therapy or the BCV regimen for all patients 60 years of age or younger.

OUTLINE OF THE PREPARATIVE REGIMEN: TBI-based regimen (Regimen 1)

1. Schema

Day	
-8	150 cGy TBI x 2
-7	150 cGy TBI x 2
-6	150 cGy TBI x 2
-5	150 cGy TBI x 2
-4	Etoposide (VP-16) (see Section 7.5b.6 for dosing instructions)
-3	Rest
-2	Cyclophosphamide (see Section 7.5b.6 for dosing instructions)
-1	Rest
0	Stem Cell infusion Begin G-CSF (if used)

2. Total Body Irradiation

   i. Total body irradiation (TBI) is to be carried out prior to the administration of the chemotherapeutic agents. TBI should be delivered at an approved Southwest Oncology Group center for TBI (see Section 12.7).

ii. TBI Dose Prescription

The strongly preferred treatment position is AP/PA with lung blocks. Alternatively, the patient may be treated in a lateral posture without lung blocks (see Section 7.5d.6). The radiation will be given in a hyperfractionated schema on Days -8, -7, -6, and -5. The total dose is to be 1,200 cGy, and the minimum number of dose fractions will be 8, given on a b.i.d. basis of 150 cGy per dose. The dose rate shall be between 5 and 20 cGy per minute; however, the dose should be as close to 5 cGy/minute as is reasonably possible. The dose fractions should be separated by 6 hours, however, may be shortened to no less than 5 hours if technically impossible to administer at a six hour interval between fractions. For patients treated in the AP/PA position, the lungs are to be shielded for the final 450 cGy (last three fractions) of radiation using standard lung blocks. Alternatively, partial thickness one HVL lung blocks may be used for the final five fractions. One HVL is defined as that thickness required attenuating the dose 50% at 10 cm under standard conditions.

Guidelines for lung blocks are as follows: the lateral edges should be 1 to 1.5 cm from the inner border of the ribs, the inferior edges are 1 – 1.5 cm from the domes of the apex of the diaphragm, 1 – 1.5 cm below the clavicles and the medial border 2 – 2.5 cm from the lateral edges of the thoracic vertebral bodies. No contouring should be done around the hilum unless there is residual abnormal hilum adenopathy in which case margins should be 1 – 1.5 cm. No boost to the ribs is required.

3. Treatment Volume

The total body will be treated, including the head and feet in one field. Care should be taken to insure that the patient is entirely within the 90% IDL, i.e., not in the penumbra region of the beam.

4. Treatment Dose

The prescription point is defined as the point along the longitude axis of the patient at the midline at the level of the umbilicus. No inhomogeneity corrections will be made in the calculation of the dose to the prescription point. The total absorbed dose along the patient's head to toe axis (line plane) shall be within $\pm$ 10% of the prescribed dose. The dose at selected anatomical points shall be calculated and these calculations are to be submitted as part of the radiation review documentation (see Section 12.4).

i. Head ("Point 1"):

This reference point is defined along the longitudinal axis of the skull at the level of the pituitary fossa. The depth should be taken as midway between the entrance and exit points of the opposed radiation beams.

ii. Neck ("Point 2"):

This reference point is defined along the patient's longitudinal axis at the level of C3/C4. The point is taken to be midway between the entrance and exit point of the beam.

ii. Shoulder ("Point 3"):

This reference point is defined as just inferior to the lateral 1/3 of the clavicle. This point is in the plane midway between the anterior and posterior patient surfaces.

iv. Mid-mediastinum ("Point 4"):

This reference point is defined along the patient's longitudinal axis at the level of the angle of Louis. The reference point is midway between the entrance and exit points of the opposed beams.

v. Hip ("Point 5"):

This reference point is defined along the patient's longitudinal axis in the center of the pelvis at a level which is 1 cm superior to the symphysis pubis.

vi. Knee ("Point 6"):

This reference point is defined along the midline in the midplane of the knee at the level of the middle of the patella.

vii. Ankle ("Point 7"):

This reference point is defined along the midline at the midplane of the ankle at the level of the lateral malleolus.

5. Homogeneity Criterion:

The dose uniformity as measured by the dose to the above reference points (1 – 7) shall be kept within $\pm$ 10% of the prescription dose. If necessary, the treatment technique should be modified using tissue compensation in order to achieve the required uniformity. If used, a complete description of compensation technique and its effects on the prescribed dose and dose distribution shall be reported and submitted as part of the radiation review documentation (see Section 12.4). Skin bolus (such as blanket or other body covers) may be used to bring up the superficial dose to satisfy the homogeneity requirements. The superficial dose shall be determined at a depth of 2 - 3 mm.

i. Treatment Technique:

Equally weighted parallel opposed portals are strongly encouraged. The patient may be treated with the AP, PA fields in the supine, prone, standing or sitting position. Alternatively, the patient may be treated with opposing lateral fields. When treated with lateral fields, the arms will be placed at the patient's side in a

position such that they will compensate for lack of attenuation in the lung. Thermoluminescent dosimeters should be used to monitor the first dose with deviations adjusted to be less than 10% of the plan dose.

ii. Central Axis Dose:

All measurements should be made at the appropriate TBI extended SSD. All institutions participating in this protocol will submit for radiation review, a complete description of the TBI dose calculation techniques (i.e., lateral opposed, four field, with or without compensation) used by that institution (see Section 12.4). The measurements that were made to verify the dose output (cGy per minute or monitor unit) and Percent Depth Dose (or TAR) at the large field size and extended SSD used for TBI would be described and the results included.

Each institution participating in this protocol should submit a detailed description used to calculate and/or measure the doses to the anatomical reference points described previously. This institution should indicate the way in which this method has been verified for extended SSD treatment. For accelerators of 6 MV and above, each participating institution should submit data that demonstrates that the dose to the skin (determine at a depth of 2 – 3 mm) will be within $\pm$ 10% of the prescribed dose for the treatment machine being used. The effect of any routinely used "bolus" should be included.

iii. Normal Tissue Sparing: Lung Dose

For the purposes of this protocol the mid-mediastinum reference point, noted previously, shall be taken as a measure of the lung dose. It is understood that in calculating the dose in this manner the increased dose to parts of the lung due to the reduced lung density is being ignored. However, in addition to the off axis doses specified previously, each institution is asked to calculate a corrected dose to the reference point located in the center of either the right or left lung at the level of the mid-mediastinum. For this purpose a correction factor that accounts for tissue density differences in the chest should be determined. A description of the method used to arrive at the value of the density correction factor should be submitted. This dose will not be taken into account when modifying the treatment technique to satisfy the dose uniformity criteria.

6. Chemotherapy

DRUG	DOSE	ROUTE	DAYS	NOTES
VP-16	60 mg/kg	IV	-4	**Dose based on <u>adjusted</u> ideal body weight (AIBW)**
Cyclophosphamide	100 mg/kg	IV	-2	**Dose based on <u>unadjusted ideal body weight or actual body weight, whichever is less</u>** (See Section 7.5b.6bii)

i. **VP-16 is to be administered as a single infusion on Day -4. The dose is 60 mg/kg and is calculated on <u>adjusted ideal body weight (AIBW)</u>.**

a. Calculation of AIBW:
<u>AIBW = Ideal Body Weight (IBW) + 0.4 (actual body weigh - IBW)</u>

b. <u>Estimation of IBW</u>: Body weight and height are measured directly. An approximate weight for height would be calculated from standard table or equations which reflect ideal "values".

Males IBW = 50 kg + 2.3 kg/inch over 5 feet

Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

c. For patients at or below their IBW, use actual body weight, for the VP-16 dose calculation.

The recommended method of VP-16 administration is as per Creger et al. *(35)* The drug is infused undiluted directly into a port of a double or triple lumen indwelling intravenous catheter, with a total infusion time of 4 hours. The drug is to be drawn into one or more plastic syringes and infused with a syringe infusion pump, placed in an evacuated bottle and infused through a pediatric infusion pump, or infused by gravity without a pump. Thus the dose for a 70 kg patient at his/her IBW would be 4,200 mg. At 20 mg/mL, the volume of VP-16 would be 210 mL. The rate of infusion would thus be 210 mL/240 minutes or 0.875 mL/minute. Appropriate anti-emetics and sedatives should be given before the infusion begins. Before, and 2 hours into, the infusion the patient is to receive 25 mg of diphenhydramine, and 100 mg of hydrocortisone to prevent allergic reactions. If necessary, diuretics may be given. Since in rare cases metabolic acidosis has been observed after high dose VP-16, additional $NaHCO_3$ may be needed. Recommended IV fluids are D5 1/2 normal saline plus 20 mEq of $NaHCO_3$/L plus 30 meq KCL/L at a rate of 2 L/m^2/day.

ii. Cyclophosphamide is administered at a total dose of 100 mg/kg, based on the unadjusted ideal body weight or actual body weight, whichever is less, given in one dose on Day -2. The calculation of the unadjusted ideal body weight is as follows:

Estimation of IBW: Body weight and height are measured directly. An approximate weight for height would be calculated from standard table or equations, which reflect ideal "values".

Males IBW = 50 kg + 2.3 kg/inch over 5 feet

Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

Recommendations for cyclophosphamide administration are as follows: The drug should be dissolved at a ratio of 100 mg of dosage strength cyclophosphamide per 5 mL of diluent, and infused IV over an hour. The following fluid regimen is recommended: D5/.9 normal saline with 30 mEq KCl and 10 mg furosemide per liter at 3 L/m^2 for Day +1 through Day +4 post-BMT. It may be necessary to administer additional diuretics to maintain a diuresis and to keep the patient at dry weight. Additional $NaHCO_3$ may be needed if the patient is undergoing tumor lysis syndrome.

Mesna or continuous bladder irrigation is to be administered along with the high dose cyclophosphamide. The (CBI) is to be given with and for 24 hours after the cyclophosphamide as normal saline at a minimum of 500 mL per hour. Mesna is to be given as per institutional guidelines. Recommended regimen: Mesna to be administered at 40 mg/kg (based on ideal body weight) IV over 15 minutes immediately pre-cyclophosphamide and at 3, 6, 9, 12, 15, 18 and 21 hours later (total of 8 doses), all at the same dose.

c. OUTLINE OF PREPARATIVE REGIMEN: BCV Chemotherapy (Regimen 2)

1. Schema

Day	
-6, -5, -4	BCNU
-4	VP-16
-2	Cyclophosphamide
-1	IV hydration continued
0	Peripheral Stem Cell Re-infusion

2. Chemotherapy

DRUG	DOSE	DAYS	ROUTE
BCNU	150/mg/m^2	-6, -5, -4	IV over 2 hours based on **adjusted ideal body weight (AIBW)**
VP-16	60 mg/kg	-4	IV over 4 hours based on **adjusted ideal body weight (AIBW)**
Cyclophosphamide	100 mg/kg	-2	IV based on unadjusted ideal body weight
IV Hydration continued		-1	

Day –6 a. BCNU: BCNU will be administered intravenously at a dose of 150 mg/m^2 on days -6, -5, and -4. Doses will be calculated based on **adjusted ideal body weight** (see section below). Recommendations for BCNU administration are as follows: The drug should be diluted with normal saline or 5% dextrose/water for a final ethanol concentration of 5-10% and administered over 2 hours. Patients may be premedicated with a sedative and antiemetics at the discretion of the treating physician. All patients are recommended to receive dilantin per institutional guidelines.

Day –4 b. **VP-16 is to be administered as a single infusion on Day -4. The dose is 60 mg/kg and is calculated on adjusted ideal body weight (AIBW).**

i. Calculation of AIBW:

AIBW = Ideal Body Weight (IBW) + 0.4 (actual body weight - IBW)

ii. Estimation of IBW:

Body weight and height are measured directly. An approximate weight for height would be calculated from standard table or equations which reflect ideal "values".

Males IBW = 50 kg + 2.3 kg/inch over 5 feet

Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

iii. For patients at or below their IBW, use actual body weight, for the VP-16 dose calculation.

The recommended method of VP-16 administration is as per Creger et al. *(36)* The drug is infused undiluted directly into a port of a double or triple lumen indwelling intravenous catheter, with a total infusion time of 4

hours. The drug is to be drawn into one or more plastic syringes and infused with a syringe infusion pump, placed in an evacuated bottle and infused through a pediatric infusion pump, or infused by gravity without a pump. Thus the dose for a 70 kg patient at his/her IBW would be 4,200 mg. At 20 mg/mL, the volume of VP-16 would be 210 mL. The rate of infusion would thus be 210 mL/240 minutes or 0.875 mL/minute. Appropriate anti-emetics and sedatives should be given before the infusion begins. Before, and 2 hours into, the infusion the patient is to receive 25 mg of diphenhydramine, and 100 mg of hydrocortisone to prevent allergic reactions. If necessary, diuretics may be given. Since in rare cases metabolic acidosis has been observed after high dose VP-16, additional $NaHCO_3$ may be needed. Recommended IV fluids are D5 1/2 normal saline plus 20 meq of $NaHCO_3$/L plus 30 meq KCl/L at a rate of 2 L/m^2/d.

Day -2 c. **Cyclophosphamide is administered at a total dose of 100 mg/kg, based on the unadjusted ideal body weight or actual body weight, whichever is less given, in one dose on Day -2.** The calculation of the unadjusted ideal body weight is as follows:

Estimation of IBW: Body weight and height are measured directly. An approximate weight for height would be calculated from standard table or equations which reflect ideal "values".

Males IBW = 50 kg + 2.3 kg/inch over 5 feet

Females IBW = 45.5 kg + 2.3 kg/inch over 5 feet

Recommendations for cyclophosphamide administration are as follows: The drug should be dissolved at a ratio of 100 mg of dosage strength cyclophosphamide per 5 mL of diluent, and infused IV over an hour. The following fluid regimen is recommended: D5 1/2 normal saline with 30 meq KCl and 10 mg furosemide per liter at 3 L/m^2 over 24 hours beginning on Day -2 through Day 0, and 2 L/m^2 for Day +1 through Day +4 post-BMT. It may be necessary to administer additional diuretics to maintain a diuresis and to keep the patient at dry weight. Additional $NaHCO_3$ may be needed if the patient is undergoing tumor lysis syndrome.

Mesna or continuous bladder irrigation is to be administered along with the high dose cyclophosphamide. The (CBI) is to be given with and for 24 hours after the cyclophosphamide as normal saline at a minimum of 500 mL per hour. If mesna is to be given, it is administered at 40 mg/kg (based on ideal body weight) IV over 15 minutes immediately pre-cyclophosphamide and at 3, 6, 9, 12, 15, 18 and 21 hours later (total of 8 doses), all at the same dose.

Day –1 d. IV hydration continued.

7.6 Stem Cell Infusion:

Stem Cells will be thawed and infused according to standard institutional practices beginning 36 to 48 hours after the cyclophosphamide. On Day 0, the rest of the 50% of the previously collected CD34+ cells (unselected) will be re-infused (minimum of 2.0×10^6

CD34+ cells). Stem cells will be thawed and infused according to standard institutional practices beginning at least 24 hours after the completion of melphalan. Pre-medicate with diphenhydramine (Benadryl®), mannitol, hydrocortisone, and acetaminophen (Tylenol®) as per institutional policy.

7.7 Supportive Measures:

a. Antibiotics: Decisions regarding antibiotics choices, when hyperalimentation is used and when to use blood products will be determined by each center.

b. Menstruating females should receive an anovulatory agent during the thrombocytopenic period.

c. G-CSF: The use of cytokines such as G-CSF or other investigational agents to facilitate engraftment, is permitted per center studies.

d. Post-transplant consolidative radiation to biopsy proven residual masses is permitted provided the patient has engrafted with a WBC > 3,000/mcL and a platelet count > 100,000/mcL.

7.8 Post Treatment Evaluation

Sixty days following peripheral stem cell transplant, patients will undergo a post-treatment evaluation of disease. Complete disease assessment includes repeat scans used for all measurable disease.

a. CBC with platelet, LDH, creatinine and liver enzymes

b. Repeat of all abnormal pretreatment scans

c. MUGA (if clinically indicated)

d. Pulmonary function tests (If clinically indicated)

e. Bilateral bone marrow aspirate and biopsy, if initially positive.

f. All patients with persistent CT scan abnormalities should undergo a PET or gallium scan examination.

g. For patients who have undergone gallium scanning prior to treatment, repeat gallium is recommended post treatment in those with residual abnormalities. Persistent gallium positively would warrant biopsy and/or alternative imaging technique such as PET scanning.

7.9 Criteria for Removal from Protocol Treatment

a. Documented progression of disease as defined in Section 10.2f.

b. Unacceptable toxicity.

c. Patients who develop hemorrhagic cystitis and/or develop signs or symptoms of congestive heart failure.

d. Completion of both cycles of HDT.

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

f. Interval between first and second cycle of HDT (based on the day of stem cells re-infusion) greater than 60 days.

7.11 All reasons for discontinuation of treatment must be documented in the Off Treatment Notice (Form #61571).

7.12 All patients will be followed for a maximum of seven years or death, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 3.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). **All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.**

8.2 No dosage modifications will be made for BCNU, VP-16, and cyclophosphamide. BCNU and melphalan dose will be calculated on adjusted ideal body weight (IBW) (see Section 7.5b.6i for calculation instructions). As noted in Section 7.5b.6, cyclophosphamide will be calculated on the basis of unadjusted ideal body weight. VP-16 will be calculated on the basis of adjusted ideal body weight.

8.3 Myelodysplasia

All patients who develop one or more cytopenia following achievement of a full engraftment should have a bone marrow examination and cytogenetics to rule out myelodysplasia.

8.4 For treatment or dose modification related questions, please contact Dr. Stiff at 708/327-3101 or Dr. Smith at 626/359-8111 ext.: 63077.

8.5 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 **S0410**, "Tandem Autologous Stem Cell Transplantation for Patients With Primary Progressive or Recurrent Hodgkin's Disease, Phase II Study"

Cycle 1

REQUIRED STUDIES	Pre £ Study	Day -1	Day 0
PHYSICAL			
History and Physical Exam	X		X
Weight and Performance Status	X		X
Tumor Assessment †	X		
Toxicity Notation		X	X
LABORATORY			
CBC/Differential/Platelets	X	X	X
Serum Creatinine/Creatinine clearance	X		
Serum Bilirubin	X		X
DLCO/FEV_1	X		
CMV, Hepatitis, Herpes/Zoster titer	X*		
LDH	X*		X
Unil/Bil bone marrow asp and biop	X¶		
Lumbar puncture	X#		
Materials for pathology review ¥	X		
X-RAYS AND SCANS			
Chest x-ray per Section 5.6	X		
X-rays/scans to evaluate extent of disease †	X		
CT of chest, abdomen, pelvis	X		
EKG	X		
MUGA or 2-d echocardiogram	X#		
TREATMENT			
Stem Cell Harvest **	X		
Melphalan Δ		X	
Stem Cell Transplant &			X

NOTE: The forms to be used for this study may be found in Section 18.0. Forms submission guidelines may be found in Section 14.0.

£ Registration should be completed after minimum cell harvest of 3.5 x 10^6 CD34 + cells/kg and before IFRT (if necessary).
† The same scanning technique as baseline must be used throughout the study to allow uniformity of results.
# If clinically indicated.
* These tests are suggested pre-study for Good Medical Practice.
** Stem cell harvest should be collected no longer than six weeks after completion of the last cycle of salvage chemotherapy. A total of 3.5 x 10^6 CD34+ cells/Kg of actual body weight should be collected for high dose therapy (see Section 7.3). Patients will undergo leukapheresis according to standard institutional procedures. (See Section 7.4)
Δ See Section 7.5a for Melphalan chemotherapy regimen, administration of hydration, premedication, and antiemetics.
& About 50% of the previously collected CD34+ cells (unselected) will be re-infused (minimum of 1.5 x 10^6 CD34 + cells for the first infusion) (see Section 7.5a).
¥ See Section 12.0 for pathology review guidelines.
¶ See Section 5.2.

9.0 STUDY CALENDAR **S0410**, Tandem Autologous Stem Cell Transplantation for Patients With Primary Progressive or Recurrent Hodgkin's Disease, Phase II Study"

Cycle 2

	Ω	£								Δ				√		
REQUIRED STUDIES	Pre	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Day	Pre-Progression	Post-Progression
	Treatment	-8	-7	-6	-5	-4	-3	-2	-1	0	7	14	21	60	Follow Up	Follow Up
PHYSICAL																
History and Physical Exam	X				X			X		X	X	X	X	X	X	X
Weight and Performance Status	X				X			X		X	X	X	X	X	X	X
Tumor Assessment	X†													X†	X†	X†
Toxicity Notation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LABORATORY																
CBC/Differential/Platelets	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Bilirubin	X				X			X		X	X	X	X	X	X	X
Serum Creatinine/Creatinine clearance	X				X			X		X	X	X	X	X	X	X
LDH	X				X			X		X					X	X
Bilat bone marrow asp and biop														Xπ		
Lumbar puncture														X#		
Pulmonary function test														X#		
X-RAYS AND SCANS																
X-rays/scans to evaluate extent of disease	X†													X†	X†	X†
CT of chest, abdomen, pelvis	X													X	X	X
EKG	X													X		
MUGA or 2-d echocardiogram	X#													X#		
TREATMENT*																
Regimen 1 %																
TBI		X	X	X	X											
Etoposide (VP-16)						X										
Cyclophosphamide								X								
Stem Cell Infusion *ƒ*										X						
Regimen 2 Σ%																
BCNU				X	X	X										
Etoposide (VP-16)						X										
Cyclophosphamide								X								
Stem Cell Infusion *ƒ*										X						

NOTE: The forms to be used for this study may be found in Section 18.0. Forms submission guidelines may be found in Section 14.0.

£ The interval between the day of first stem cell re-infusion and the anticipated date of second infusion must be at least 28 days and not exceed 60 days.

Δ Laboratory tests need to be done on day 0 and then three times per week until engraftment then day 14, 21, and 60.

√ At Day 60, patients will undergo complete restaging as outlined in Section 7.9. Follow-up evaluations will occur every 6 months for 2 years and then annually for a total of 7 years. All cases of myelodysplasia and any secondary malignancy are to be reported to the Operations Office as an adverse reaction according to Section 16.0.

† The same scanning technique as baseline must be used to allow uniformity of results.

π Only need be repeated if the patient was bone marrow positive at prestudy.

If clinically indicated.

Ω The timing of pre-treatment assessments are to be no sooner than Day 21 after transplant of Cycle 1 and must be completed before the time limit set in Section 7.5b.

* Each transplant center shall choose a single regimen for all patients treated on this protocol who are under the age of 61. For patients 61 years of age or older or those with prior dose limiting radiation, all will receive the BCV regimen. Patients who have not received prior IFRT will receive the TBI regimen.

% See Section 7.5 for chemotherapy regimen details.

Σ All patients will undergo radiation therapy review as outlined in Section 12.6

ƒ The rest of the previously collected CD34+ cells (unselected) will be re-infused (See Section 7.6).

¥ See Section 12.0

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 **Measurability of Lesions**:

a. **Measurable Disease**: Lesions that can be accurately measured in two dimensions by CT, MRI, medical photograph (skin or oral lesion), plain x-ray, or other conventional technique and a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters ≥ 2 cm. **Note**: CT scans remain the standard for evaluation of nodal disease.

b. **Non-measurable Disease**: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by imaging techniques or disease documented by indirect evidence only (e.g., lab values).

10.2 **Objective Disease Status**: Objective status is to be recorded at each evaluation. All measurable lesions up to a maximum of 6 lesions (largest) should be identified as target lesions at baseline. If there are more than 6 measurable lesions the remaining will be identified as non-target lesions and included as non-measurable disease. The 6 lesions should be selected according to the following features: they should be from disparate regions of the body as possible and they should include mediastinal and retroperitoneal areas of disease if these sites have measurable lesions. Measurements must be provided for target lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

a. **Complete Response (CR)**: Complete disappearance of all measurable and non-measurable disease with the exception of nodes for which the following must be true: for patients with at least one measurable lesion, all nodal masses > 1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤ 1.5 cm in GTD and all nodal masses ≥ 1 cm and ≤ 1.5 cm GTD must have regressed to < 1.0cm in GTD or they must have reduced by 75% in sum of products of greatest diameters (SPD). No new lesions. Spleen and other previously enlarged organs must have regressed in size and must not be palpable. If bone marrow was positive at baseline, it must be negative based on biopsy and aspirate at same site. Normalization of markers. (e.g., LDH definitely assignable to NHL). All disease must be assessed using the same technique as baseline.

b. **Complete Response Unconfirmed (CRU)**: For patients who do not qualify for CR. Complete disappearance of all measurable and non-measurable disease, regressed, non-palpable spleen and other previously enlarged organs, except with one or more of the following features: 1) all residual nodal masses >1.5cm in GTD at baseline reduced by 75% in SPD or 2) bone marrow indeterminate. No new lesions. All disease must be assessed using the same technique as baseline.

c. **Partial Response (PR)**: Applies to patients with at least one measurable lesion that do not quality for a CR or CRU. A 50% decrease in the SPD for up to six identified dominant lesions identified at baseline. No new lesions and no increase in the size of liver or spleen or other nodes. Spleenic and hepatic nodules must have regressed in size by at least 50% in SPD. All disease must be assessed using the same technique as baseline.

d. **Stable**: Does not qualify for CR, CRU, PR, Relapsed/Progressive Disease. All disease must be assessed using the same technique as baseline.

e. **Relapsed Disease**: If a (CR,CRU) was achieved at a previous assessment, a 50% increase in the SPD of target measurable lesions over the smallest sum observed or 50% increase in the GTD of any node greater than 1cm in shortest axis using the same techniques as baseline. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of a new lesion/site. Death due to disease without prior documentation of progression.

f. **Progressive Disease**: If a (CR,CRU) was not achieved at a previous assessment, a 50% increase in the SPD of target measurable lesions over the smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline. Appearance of a new lesion/site. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Death due to disease without prior documentation of progression.

g. **Assessment inadequate, objective status unknown**: Progression has not been documented and one or more target lesions or other sites of disease have not been assessed or inconsistent methods of assessment were used.

Notes: Bone marrow status is evaluated as follows: Positive: Unequivocal cytological or architectural evidence of malignancy. Negative: No aggregates or only a few well-circumscribed lymphoid aggregates. Indeterminate: Does not qualify for either Positive or Negative Status. Note this typically consists of increased number or size of aggregates without cytological or architectural atypia.

10.3 **Best Response**:

a. CR: One objective status of CR documented before relapse.

b. CRU: One objective status of CRU documented before relapse but not qualifying as a CR.

c. PR: One objective status of PR documented before progression but not qualifying as a CR or CRU.

d. Stable: At least one objective status of stable documented at least 6 weeks after registration, not qualifying as anything else above.

e. Increasing Disease: Objective status of progression within 12 weeks of registration not qualifying as anything else above.

f. Inadequate assessment, response unknown: Progression greater than 12 weeks after registration and no other response category applies.

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

GRADE	SCALE
0	Fully active; able to carry on all pre-disease activities 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 all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

3 Capable of only 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.

10.5 **Progression-Free Survival**: From date of randomization to date of first observation of progressive disease (as defined in 10.2f), or death due to any cause.

10.6 **Time to Death**: From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 The primary endpoint is to estimate the 3-year progression-free survival (PFS) for this therapy in the entire group. With an accrual goal of 85 patients accrued over 2 years with 18 months of additional follow-up, we expect to estimate the 2-year PFS to be approximately 60%. A 0.025 one-sided alpha test would have 86% power to detect a 15% increase in PFS as compared to the 2 year PFS seen in **SWOG-9011**. Approximately 40 patients/year will be accrued by SWOG transplant institutions for two years, based on the accrual to **SWOG-9011** and the 25 pts/year enrolled by the COH/Loyola alone in the pilot study that led to this trial. BMT is now considered the standard of care for this patient population.

11.2 A sample size of 85 patients is also sufficient to estimate the probability of any toxicity to within $\pm$ 11%. Any adverse event with at least a 5% probability will be seen at least once (98% chance).

11.3 Following the completion of the study, a prognostic factor model will be developed using the known factors previously reported in the literature, including those identified in **SWOG-9011**. Comparison of clinical outcome based on the prognostic model developed in **SWOG-9011** will also be performed, in an attempt to determine if this tandem transplant approach will be appropriate to pursue in both good and poor risk patients. Pending an analysis of these results, a decision will be made as to whether a Phase III comparison of the tandem transplant approach to a single autograft will be undertaken.

11.4 Data on the rate of treatment-related mortality (within the first 100 days) and of graft failure will be analyzed on the first 20 patients registered. Graft failure will be determined after both transplants are completed, and as defined as either Grade 4 neutrophil count at 28 days post-infusion or Grade 4 platelet count 60 days post-infusion. If greater than 4 patients (> 20%) experience treatment-related death within the first 100 days or if 4 patients (> 20%) experience graft failure, then protocol accrual will be held and consideration will be given to protocol modification or permanently suspending accrual. A termination decision will be made by the Disease Committee Chair in consultation with the study team.

11.5 Toxicity and accrual monitoring are done routinely by the Study Coordinator, Study Statistician and the Disease Committee Chair. Response monitoring is done by the Study Statistician and Study Coordinator. Accrual reports are generated weekly and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Coordinator monitor toxicities on an ongoing basis. A Data and Safety Monitoring

Committee will also oversee the conduct of the study. The Committee consists of four members from outside of the Southwest Oncology Group, three Southwest Oncology Group members, three non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the Southwest Oncology Group Statistical Center, and will meet at the Group's bi-annual meetings as necessary.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review:

All patients registered to this study will undergo pathology review. The purpose of this review is to verify the histologic diagnosis of Hodgkin's lymphoma.

12.2 Specimen Tracking System

All pathology submissions for this protocol must be entered and tracked using the Southwest Oncology Group online specimen tracking system. Southwest Oncology Group Members may log on to the specimen tracking system via the CRA Workbench (https://gill.crab.org/txwb/logon.aspx) using their Southwest Oncology Group roster Identification Numbers and passwords. First-time non-Southwest Oncology Group users must refer to start-up instructions located at https://gill.crab.org/SpecTrack/. In the online Specimen Tracking system laboratory ID numbers are used to identify the laboratories to which specimens are shipped.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

For any questions or problems regarding the Specimen Tracking program, please send an email to technicalquestion@crab.org. A copy of the Shipment Packing List produced by the Specimen Tracking system should be printed and sent with the specimens in a separate resealable bag.

12.3 General Specimen Submission Instructions

a. All submitted specimens must be labeled with the protocol number (**S0410**), SWOG patient number, patient's initials, and date of specimen collection.

b. The Federal guidelines for shipment are as follows:

1. The specimen must be wrapped in an absorbable material.

2. The specimen must be placed in an AIRTIGHT container (like a resealable bag).

3. Pack the resealable bag and specimen in a Styrofoam shipping container.

4. Pack the Styrofoam shipping container in a cardboard box.

5. The cardboard box must be marked as "BIOHAZARD".

12.4 The following materials are to be submitted for review:

a. One representative H&E section and 12 unstained slides from each block of the original diagnostic biopsy. (Note: Needle aspirates are not adequate for this submission. Consult with Dr. Grogan if adequacy of specimen is in question.)

b. One representative paraffin block which will be conserved (no more than eight additional slides will be cut).

c. One copy of pathology report.

12.5 Pathology materials are to be submitted within 30 days of registration to:

Lab # 2 SWOG Lymphoma Repository – University of Arizona
Department of Pathology, Room 5211
P.O. Box 245043
1501 N. Campbell Avenue
Tucson, AZ 85724

Contact: Yvette Frutiger/Lisa M. Rimsza, M.D.
Phone: 520/626-7477
Fax: 520/626-6081
E-mail: frutiger@email.arizona.edu

Failure to submit a registered patient's pathology materials for pathology review will make the patient ineligible.

12.6 Radiation Therapy Review (only for patients receiving TBI-based preparation regimen for Cycle 2)

a. QA Documentation For Total Body Irradiation

An approved TBI benchmark must be on file at QARC before a patient's radiation therapy will be evaluated. The TBI benchmark is available on the QARC website at www.qarc.org. Please contact physics@QARC.org for any technical questions.

b. Radiation Therapy Review - Post-Treatment

Patients receiving RT on this study will have a simple review of the treatment delivered. There is no rapid review in this study. There is no film review required. The following data should be submitted for patients receiving pre-transplant salvage IFRT and/or TBI.

c. Within one week of the completion of radiotherapy the following data shall be submitted:

1. For IFRT submit the RT-2 Radiotherapy Total Dose Record.

2. For TBI submit the QARC Total Body Irradiation Radiotherapy Summary Form.

3. If a technique other than the technique in the approved benchmark is used for this patient, a new benchmark must be completed and approved.

d. For all patients: Submit a copy of the patient’s radiotherapy record, including the prescription and daily and cumulative doses.

e. These data should be sent to the following:

Attention: SWOG Materials
Quality Assurance Review Center
272 West Exchange Street
Providence, RI 02903-1025
Telephone: 401/454-4301
Fax: 401/454-4685
E-mail: SWOG@qarc.org

Questions regarding the dose calculations or documentation should be directed to:

SWOG Protocol Dosimetrist
Quality Assurance Review Center
272 West Exchange Street
Providence, RI 02903-1025
E-mail: physics@QARC.org

f. Questions regarding the delivery of radiation therapy on this study should be directed to:

Louis S Constine, M.D.
University of Rochester
James P. Wilmont Cancer Center
601 Elmwood Avenue, Box 647
Rochester, NY 14642
Phone: 585/275/5622
Fax: 565/275-1531
E-mail: louis_constine@urmc.rochester.edu

13.0 REGISTRATION GUIDELINES

NOTE: This trial can only be conducted at Southwest Oncology Group or Blood and Marrow Transplant Clinical Trials Network approved BMT facilities (see Sections 19.2 and 19.3, respectively).

13.1 Patients must be registered prior to initiation of treatment (no more than five working days prior to the 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 *Patient Reg* link to go to the Entry Page for the Patient 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 may be 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 **Registration, BMT CTN Investigators**

a. Submitting regulatory documents

Before a BMT CTN-affiliated institution may enter patients, protocol specific regulatory documents must be submitted to the BMT Central Office at the following address:

ATTN: Colleen Allen
The EMMES Corporation
401 N. Washington Street, Suite 700
Rockville, MD 20850
Phone: 301/251-1161 x252
Fax: 240/306-0963
Email: callen@emmes.com

b. Required protocol specific regulatory documents

1. Copy of IRB-approved 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.

2. IRB certification form, Protection of Human Subjects: Assurance Identification/Certification/Declaration of Exemption Form (formerly HHS 310 form), or 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

c. BMT CTN registration procedures

1. BMT CTN centers will register the patient first in AdvantageEDC, the BMT CTN electronic data capture system. AdvantageEDC automatically notifies the BMT CTN Data Coordinating Center (DCC) of the registration.

2. The BMT CTN DCC will then register the patient in the SWOG web-based system.

3. The patient will be assigned to a treatment regimen, and the BMT CTN DCC will provide this information to the transplant center.

4. The BMT CTN office will complete the registration process using the SWOG web-based registration system, and will obtain the SWOG patient ID number.

5. Patients must be registered prior to initiation of treatment as outlined in Section 13.1.

13.5 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.

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.

c. BMT CTN Data Submission Procedures

BMT CTN-affiliated institutions should submit the data forms listed in Sections 14.4 – 14.12 at the required intervals to the Southwest Oncology Group Data Operations Center via fax as outlined in Section 14.3b.

14.4 WITHIN 14 DAYS OF REGISTRATION:

Submit the following forms:

a. Advanced Hodgkin's Disease Prestudy Form (Form #34864)

b. Lymphoma Baseline Tumor Assessment Form (Form # 48010)

c. Completed Section 5.0 of the protocol

d. Pathology Report confirming histology

14.5 WITHIN 30 DAYS OF REGISTRATION:

Submit histopathologic materials (one representative H&E section, 10 unstained slides and a paraffin block) along with a copy of the pathology report to the SWOG-Lymphoma Repository (See Section 12.0).

14.6 IMMEDIATELY AFTER CYCLEs 1 AND 2 OF HDT, IMMEDIATELY AFTER CYCLE 2 HDT, AND 1 MONTH AFTER THE SECOND STEM CELL INFUSION**:**

Submit the **S0410** Treatment Form (Form #55293), and the **S0410** Adverse Event Form (Form #3502).

14.7 ONE AND TWO MONTHS AFTER THE SECOND STEM CELL INFUSION:

Submit the **S0410** Adverse Event Form (Form #3502)

14.8 TWO MONTHS AFTER THE SECOND STEM CELL INFUSION:

Submit the **S0410** Infusion Summary Form (Form #4533).

14.9 WITHIN ONE WEEK OF COMPLETION OF RADIATION THERAPY (only for patients receiving the TBI-based preparative regimen for Cycle 2):

Submit materials as specified in Section 12.6c and 12.6d directly to QARC at the address in Section 12.7e.

14.10 WITHIN 14 DAYS OF DISEASE ASSESSMENT:

Submit the Lymphoma Follow-Up Tumor Assessment Form (Form #59058).

14.11 EVERY SIX MONTHS AFTER OFF TREATMENT FOR TWO YEARS AND THEN ANNUALLY THEREAFTER:

Submit a copy of the Follow-Up Form (Form #64587).

14.12 WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit copies of the Off Treatment Notice (Form #8756) and final **S0410** Adverse Event Summary Form (Form #3502).

14.13 WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH;

Submit the **S0410** Treatment Form (Form #55293), **S0410** Adverse Event Form (Form #3502), and the Off Treatment Notice (Form # 8756), if not previously submitted. If death occurs after off treatment, submit the Notice of Death (Form # 49467) and the Follow-Up Form (Form # 64587).

15.0 SPECIAL INSTRUCTIONS

There are no special instructions for this study.

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).

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

Adverse Event Reporting for BMT CTN Institutions

BMT CTN participants should employ definitions of adverse events as provided by the Southwest Oncology Group reporting guidelines in Section 16.1. Both written and telephone reports of adverse reactions should be made directly to the Southwest Oncology Group and the NCI according to the instructions in Section 16.1.

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 timelier monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also **Appendix 19.1** 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

Some adverse events require 24-hour notification (refer to Table 16.1) via AdEERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered electronically into AdEERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1.

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), myelodysplastic syndrome (MDS), and acute lymphocytic leukemia (ALL) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported via the AML/MDS/ALL track in 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 documentation to:

Investigational Drug Branch by fax to 301-230-0159	**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/ALL Report must be submitted for the most recent trial.

17.0 BIBLIOGRAPHY

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18.0 MASTER FORMS SET

18.1 The Model Informed Consent Form is included in this section, preceded by "Notes for Local Institution Consent Form Authors" and "Notes for Local Investigators." The study - as well as the local consent form meeting the guidelines noted in these documents - must be reviewed and approved by the Institutional Review Board prior to registration and treatment of patients on this study.

18.2 This section includes copies of all data forms which must be completed for this study.

a. **S0410** Registration Form (Form #58048) (10/15/05); Southwest Oncology Group Registration Form Code Sheet (10/24/06)

b. Advanced Hodgkin's Disease Prestudy Form (Form #34864) (08/01/06)

c. **S0410** Treatment Form (Form #55293) (9/15/07)

d. **S0410** Adverse Event Summary Form (Form #3502) (11/15/06)

e. **S0410** Infusion Summary Form (Form #4533) (9/15/07)

f. Lymphoma Baseline Tumor Assessment Form (Form # 48010) (10/15/00)

g. Lymphoma Follow-Up Tumor Assessment Form (Form # 59058) (09/01/01)

h. Follow-Up Form (Form # 64587) (09/15/03)

i. Off Treatment Notice (Form # 8756) (09/01/03)

j. Notice of Death (Form # 49467) (09/1/03)

Informed Consent Model for S0410

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

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 that 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.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the Southwest Oncology Group Operations Office.

Readability Statistics:	
Flesch Reading Ease	56.4 (targeted above 55)
Flesch-Kincaid Grade Level	9.4 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form), the Southwest Oncology Group and the Blood and Marrow Transplant Clinical Trials Network (if applicable). *(9/7/07)*

  The "Southwest Oncology Group" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to the Southwest Oncology Group. This includes consent forms for studies where all patients are registered directly through the Southwest Oncology Group Data Operations Office, all intergroup studies for which the registration is being credited to the Southwest Oncology Group (whether the registration is through the SWOG Data Operations Office or directly through

the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to the Southwest Oncology Group.

- The Blood and Marrow Transplant Clinical Trials Network (BMT-CTN) must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to the BMT-CTN. *(added 9/7/07)*
- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

S0410, "Tandem Autologous Stem Cell Transplantation For Patients With Primary Progressive Or Recurrent Hodgkin's Disease"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a kind of cancer called Hodgkin's lymphoma.

Who is doing this study?

The Southwest Oncology Group (SWOG) is sponsoring this trial. SWOG is an adult cancer clinical trials organization. SWOG is funded through the National Cancer Institute, and its network consists of almost four thousand physicians at almost three hundred institutions throughout the United States. Your study doctor has met all requirements to be a member of SWOG and to perform National Cancer Institute-funded research through this Group.

Why is this study being done?

This study is investigational and is being done to find out if a combination of treatments (2 cycles of high dose chemotherapy, each with autologous stem cell rescue) will keep your Hodgkin's lymphoma from getting worse (for any period of time). We also want to compare what kind of side effects this combination of treatments cause and how often they occur. This combination of treatments has not been used to treat a large number of patients with the kind of cancer you have.

How many people will take part in the study?

About 85 people will take part in this study.

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if

you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical History and Physical Exam
- Weight and Performance Status
- Disease Assessment including chest x-ray and/or CT scan.
- Routine laboratory blood tests (to measure your kidney and liver function).
- You will also have your bone marrow examined (called "bone marrow aspiration and biopsy") at the start of this study and if necessary, at Day 60 after stem cell transplant. Your skin over your hipbone will be numbed by a shot of local anesthetic (lidocaine) given just under your skin. A needle will be inserted through the numbed skin and into the hipbone. The bone marrow will be removed by using suction and a twisting motion of the needle. You may have minor discomfort, and minor infection is also possible. Sometimes allergic reactions to the anesthetic may occur. These are regular tests for many patients with lymphoma. The bone marrow will be looked at to find out if any lymphoma cells are present, and to determine the status of normal blood cells.
- Your initial biopsy sample will be sent to our pathology laboratory to confirm your diagnosis.
- If your cancer has returned after a period of complete remission, you will be required to undergo **two courses** of "salvage therapy" (treatment that is given after the cancer has not responded to other treatments) and/or radiation therapy before you can be in this study.
- No longer than six weeks after salvage therapy, you will undergo collection of peripheral blood stem cells by a process called leukapheresis or by bone marrow harvest. Leukapheresis will be done over several hours on several days. Leukapheresis is performed by collecting blood from a vein and processing it through a machine which removes one type of white blood cell (stem cell) which is needed to help produce bone marrow. The rest of the blood is returned to you through another vein. The harvested stem cells will be frozen and stored. These cells will be returned to you after you complete treatment with either radiation, or high dose chemotherapy.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Routine laboratory blood tests (to measure your kidney and liver function).
- Disease Assessment (including chest x-ray and/or CT scans): at Day 60 after stem cell transplant and every 6 months for 2 years, and then annually for 7 years.
- You will require placement of a special central venous catheter. This will be a tube placed into a large vein in the chest. This tube can be of two basic types. (1) It can come out through the skin or (2) be attached to a small chamber with the entire device under the skin. Either one of these central vein catheters will allow the chemotherapy to be dripped in over several hours. In most patients, these can be placed under local anesthesia in an operating room and in most patients, these can remain in place indefinitely. Problems that can be associated with these catheters include pain, bleeding, infection, or clotting. In a minority of patients (< 10%), these problems lead to the catheter being removed.

- The drug melphalan will be used in the first cycle of high dose treatment. You will receive one cycle of melphalan through a catheter over a period of 16 hours. The intravenous drug will be given on the first day of each treatment cycle. Approximately 24 hours after melphalan administration, you will receive an infusion of your own peripheral blood stem cells which had been stored previously. The manner of infusion, and supportive care after the infusion may differ among hospitals.
- After the melphalan regimen, you will be given one of two possible treatments: total body irradiation (TBI) VP16/Cyclophosphamide or BCNU/VP-16/Cyclophosphamide called "BCV." The choice will be made at the time when you are registered for the study. (Your doctor will choose which of these treatment regimens you will receive).
- If your doctor decides, or if you are 61 years of age or older or have already received radiation, you will not receive the TBI. Instead, you will be treated with "BCV". You will begin by receiving a drug called BCNU through the catheter over 2 hours for each of 3 days. On the third day of treatment with BCNU, you will receive another drug called VP-16 through the catheter over 4 hours. The next day, you will receive a third drug called cyclophosphamide through the catheter over 2 hours. To protect your bladder, you will also receive fluids and possibly another drug called mesna.
- With either of these two treatments, approximately two days after you receive the cyclophosphamide, you will receive an infusion of your own peripheral blood stem cells which had been stored previously. The manner of infusion, and supportive care after the infusion may differ among hospitals.
- Before and/or after the infusion you may (at the discretion of your doctor) receive a bone marrow stimulating agent. This will be given either as a shot just under your skin or through your catheter. The time frame of these injections will be determined by your doctor.

When you are finished with the second transplant your health will be re-evaluated by your physician by physical examination every 6 months for a period of two years and then annually thereafter for a total of seven years from the time you started the study. There are circumstances under which your doctor might be required to discontinue your treatment with this drug whether you agree or not. These circumstances include: your tumor 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.

How long will I be in the study?

We think it will take you about 2 months to finish the treatments. You will then return to your doctor about 2 months after you complete your treatment for tests and scans. You will then return for a follow-up visit to your doctor at least every 6 months for two years and then once a year after that. Your doctor may wish to see you more often. We would like to see how you are doing periodically for up to seven years.

The researcher 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. It is unlikely, but the study may be stopped early due to lack of funding.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the experimental surgical technique can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the completion of this experimental surgical technique. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the melphalan chemotherapy treatment include the following:

Likely

- **Lower white blood cell count that may lead to infection**
- **Lower platelets that may lead to bruising or bleeding**
- **Lower red blood counts that may cause you to feel tired or have shortness of breath**
- **Hair loss**

Less Likely

- **Life threatening infections or bleeding**
- **Severe nausea, vomiting, or diarrhea**
- **Severe sores in the mouth, esophagus, or colon**
- **Lung problems, including difficulty breathing and scarring of the lungs**

- **Damage to nerves in the limbs with associated numbness and tingling and/or weakness**
- **Rash**
- **Fever**
- **Swelling**
- **Severe irritation or local tissue death at the site of injection**
- **Loss of menstrual period**
- **Low sperm count**
- **Inability to reproduce**

Rare, but Serious

- **Development of acute leukemia**

Risks and side effects related to the BCNU and Cyclophosphamide include the following:

Likely

- **Fatigue**
- **Lowered white cell counts may increase risk of infection.**
- **Lowered red cell counts may lead to anemia, tiredness or shortness of breath**
- **Lowered platelet may lead to an increase in bruising or bleeding**
- **Diarrhea, abdominal pain, constipation, and difficulty swallowing**
- **Change in taste**
- **Skin: Rash, darkening of the skin, itching, yellowing of skin, discoloration of the skin and nails, flushing**
- **Swelling, redness at IV site**
- **Fever and chills**
- **Hair loss**
- **Sores and/or ulcers and tenderness in mouth or throat or other parts of the body**
- **Abnormal levels in blood chemistry tests that measure liver and kidney function**
- **Eye and vision problems including blindness, and inflammation of the optic nerve and retina**
- **Radiation recall dermatitis**
- **Menstrual changes**
- **Numbness, pain or tingling in fingers or toes**
- **Blood in the urine**

Less Likely

- **Allergic reactions**
- **Bladder pain, scarring of bladder (prevented by drinking 8-10 glasses of water a day and emptying bladder every 2-3 hours on days of treatment)**
- **Scarring of the lungs, shortness of breath, coughing spells**
- **Heart problems or heart failure**

- **Kidney and/or liver damage or failure**
- **Drug interactions with general anesthesia**
- **Loss of fertility, sterility (The ability to have children may be permanently impaired.)**
- **Secondary cancer such as acute leukemia (blood cancer) which may be caused by the drugs you will receive during this treatment**
- **Treatment related death**

Risks and side effects related to the VP-16 (Etoposide) include the following:

<u>Likely</u>

- **Fatigue**
- **Lowered white cell counts may increase risk of infection.**
- **Lowered red cell counts may lead to anemia, tiredness or shortness of breath**
- **Lowered platelet may lead to an increase in bruising or bleeding.**
- **Nausea, vomiting, and diarrhea, abdominal pain, stomach ulcers, constipation, indigestion.**
- **Loss of appetite and weight loss**
- **Change in taste**
- **Difficulty swallowing**
- **Swelling, redness at IV site**
- **Decrease in kidney function which may lead to changes in the balance of chemicals in your blood**
- **Temporary hair loss (not only from the scalp but possibly the underarms, beard, eyelashes, and pubic area)**
- **Numbness, pain or tingling in fingers or toes**
- **General discomfort, weakness, drowsiness**
- **Fluid retention, increased weight gain around the stomach and puffy appearance especially in the face.**
- **Flu-like symptoms: fever, headache, back pain, chills, muscle aches, weakness, loss of appetite, cough, runny nose, general discomfort, sweating, and trouble sleeping.**
- **Increase in blood pressure**
- **Inflammation of the hands and soles of the feet occurs in about ¼ of patients 5-7 days after transplantation. (etoposide)**

<u>Less Likely</u>

- **Sores and/or ulcers and tenderness in mouth or throat or other parts of the body.**
- **Liver toxicity including abnormal levels of blood chemistry tests that measure liver function**
- **Eye and vision problems including blindness and inflammation of the optic nerve**

- **Radiation recall dermatitis**
- **Muscle cramps**
- **Lack of blood supply to the fingers and toes**

<u>Rare but serious</u>

- **Fluid in the lungs**
- **Seizures**
- **Allergic reactions (including potentially severe reactions)**
- **Secondary cancer such as acute leukemia (blood cancer) which may be caused by the drugs you will receive during this treatment**
- **Treatment related death**

Risks and side effects related to the total body irradiation:

The immediate effects of irradiation may include nausea, vomiting, diarrhea, loss of appetite, painful parotid swelling for a few days, and hair loss. The total body irradiation will destroy both the tumor cells and the normal marrow present leading to a disappearance of normal red blood cells, white blood cells and platelets from the blood which will persist until the bone marrow transplantation begins to function. Total body irradiation can result in sterility, i.e., failure to produce a viable egg or sperm. The incidence of this complication is not known at this time.

Radiation therapy may be harmful to an unborn child and has not been proven safe for nursing mothers.

Risks and side effects related to the autologous stem cell infusion:

Side effects of the stem cell infusion are uncommon, and consist primarily of an unusual taste from the preservative, occasional nausea and vomiting, and rarely, fever and chills. In addition, your chest may feel tight for awhile, but that will pass. Although rare, there is a possibility of failure of the transplanted bone marrow to be accepted by your body. This would increase the risk of life threatening infection or bleeding episode.

<u>Reproductive risks</u>: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. You should not nurse your baby while on this study as some drugs (etoposide and cyclophosphamide) have been found in breast milk. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. A pregnancy test may be done before you begin study if you are a woman and there is a chance you could be pregnant.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the combination of treatments will be more useful against Hodgkin's lymphoma compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about the combination of treatments as a treatment for Hodgkin's lymphoma. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study**
- **Taking part in another study**
- **Getting no treatment**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Local Institutional Review Board (IRB)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Southwest Oncology Group
- Blood and Marrow Transplant Clinical Trials Network (BMT CTN) *(added 9/7/07)*

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Administration of the drugs 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)*

Melphalan, VP-16 (etoposide), cyclophosphamide, and BCNU are commercially available.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Southwest Oncology Group Data Operations Center
C/o Cancer Research And Biostatistics
1730 Minor Ave, Suite 1900
Seattle, WA 98101-1468
Patient Registration:
via WebReg at: http://swog.org
(24 hours a day, 7 days a week, excluding downtimes for maintenance)
or call 206-652-2267 (Mon-Fri, 6:30am-4:00pm Pacific Time, excluding holidays)

Southwest Oncology Group Operations Office
14980 Omicron Drive
San Antonio, TX 78245-3217
Phone: (210) 677-8808
Fax: (210) 677-0006

Southwest Oncology Group Registration Form

SWOG Study No.	Registration Step	Assigned Treatment Arm	Activation Date: October 15, 2005
S0410	1	1	Last Amended Date:

Tandem Autologous Stem Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin's Disease (A BMT Study, Phase II)

Patient's Name _____

SWOG Patient ID ☐☐☐☐☐☐

INSTRUCTIONS: All of the information on this Registration Form and the Protocol Eligibility Section must be answered appropriately for a patient to be considered eligible for registration. This Registration Form must be entirely filled out and referred to during the registration. **Do NOT submit this form as part of the patient data.**

Caller's SWOG Roster ID ☐☐☐☐☐

IRB Approval Date ☐☐ / ☐☐ / ☐☐☐☐

SWOG Investigator Number ☐☐☐☐☐

Date Informed Consent Signed ☐☐ / ☐☐ / ☐☐☐☐

Date HIPAA Authorization signed: ☐☐ / ☐☐ / ☐☐☐☐

(Not required for non-American sites)

SWOG Treating Institution Number ☐☐☐☐☐

Projected Start Date of Treatment ☐☐ / ☐☐ / ☐☐☐☐

Radiation Facility Number ☐☐☐☐☐

Planned Radiation Therapy Start Date ☐☐ / ☐☐ / ☐☐☐☐

Radiotherapy Facility _____

Radiation Therapist _____

Patient's Date of Birth: ☐☐ / ☐☐ / ☐☐☐☐

Patient Gender: ☐ Female ☐ Male

Method of Payment: ☐☐

Patient's Ethnicity: ☐

Patient's Race (select all that apply):

☐ White ☐ Native Hawaiian or Other Pacific Islander ☐ American Indian or Alaska Native
☐ Black or African American ☐ Asian ☐ Unknown

If a U.S. resident:

Patient Social Security Number: ☐☐☐ - ☐☐ - ☐☐☐☐

Patient's ZIP Code: ☐☐☐☐☐

Country of Residence (if not USA): _____

If a resident of Canada:

Social Insurance Number: ☐☐☐ - ☐☐☐ - ☐☐☐

Postal Code: ☐☐☐ - ☐☐☐

Southwest Oncology Group Registration Form Code Sheet

Patient's race definitions:

White or Caucasian: a person having origins in any of the original peoples of Europe, Middle East, or North Africa.

Black or African American: a person having origins in any of the black racial groups of Africa.

Native Hawaiian or Other Pacific Islander: a person having origins in any of the original peoples of Hawaii, Guam, Samoa and other Pacific islands.

Asian: a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent. Including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

American Indian or Alaskan Native: a person having origins in any of the original peoples of North, Central or South America, and who maintains tribal affiliations or community attachment.

Patient's ethnicity (Spanish/Hispanic Origin) options:

Unknown
No (not Spanish)
Yes, Mexican
Yes, Puerto Rican
Yes, Cuban
Yes, Central American
Yes, South American
Yes, Other
Yes, NOS

Method of Payment codes:

Private
Medicare
Medicare and Private
Medicaid
Medicaid and Medicare
No insurance (self-pay)
No insurance (no means)
Other, specify at registration
Unknown
Veterans Admin
Military

Other Group codes for use in the Web Registration program:

9977 – ACOSOG
9982 – CALGB
9976 – CTSU
9995 – ECOG
9984 – GOG
9987 – MDACC
9996 – NCCTG
9981 – NCIC
9983 – NSABP
9997 – RTOG

SOUTHWEST ONCOLOGY GROUP
ADVANCED HODGKIN'S DISEASE PRESTUDY FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** ☐

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

PATIENT AND DISEASE DESCRIPTION

Date of First Pathologic Diagnosis: ☐☐ / ☐☐ / ☐☐☐☐

Lymphoma disease status: ☐ Recurrent ☐ Refractory

Histology

☐ Nodular Sclerosis ☐ Mixed Cellularity

☐ Lymphocyte Predominant ☐ Lymphocyte Depleted

☐ Other Hodgkins

Current Stage of Disease: ☐ III ☐ IV

Symptoms: ☐ A (No Symptoms) ☐ B (Fever, Weight Loss, and/or Night Sweats)

Date of initiation of stem cell mobilization: ☐☐ / ☐☐ / ☐☐☐☐

Total CD34+ cells collected: ☐☐.☐ x 10^6 cells/kg actual body weight

Height: ☐☐☐ cm **Weight:** ☐☐☐.☐ kg **BSA:** ☐.☐☐ m^2 **Performance status:** ☐

CURRENT LABORATORY VALUES

Albumin (gm/dl) ☐☐.☐☐ **Hemoglobin (gm/dl)** ☐☐.☐☐

WBC x 10^3 ☐☐☐.☐ **Lymphocytopenia (% of total WBC)** ☐☐

LDH (U/l) ☐☐☐☐ **LDH ULN** ☐☐☐☐ **Serum Beta2 Microglobulin (mg/ml)** ☐☐.☐

PRIOR TREATMENT RELATED TO THIS CANCER

Prior radiation therapy: ☐ No ☐ Yes

Site: _____

Last date of Radiation Therapy ☐☐ / ☐☐ / ☐☐☐☐

Prior systemic therapy: ☐ No ☐ Yes

Treatment Description: _____

Last date of Systemic Therapy ☐☐ / ☐☐ / ☐☐☐☐

Prior surgery: ☐ No ☐ Yes

Last date of Surgery ☐☐ / ☐☐ / ☐☐☐☐

continued on next page

SOUTHWEST ONCOLOGY GROUP
ADVANCED HODGKIN'S DISEASE PRESTUDY FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S | | | | **Registration Step** |

Patient Initials _____ (L, F M)

PROGNOSTIC FACTORS

During initial chemotherapy

Disease progressed: ☐ No ☐ Yes

After initial chemotherapy *(if Yes to the above, then answer No to the following 3 items)*

Patient experienced initial response that lasted ≤ 12 months before disease progression: ☐ No ☐ Yes

Patient experienced CR that lasted ≤ 90 days before disease progression: ☐ No ☐ Yes

Patient experienced PR that lasted ≤ 90 days before disease progression: ☐ No ☐ Yes

At first recurrence/progression

Patient experienced systemic symptoms (i.e. fever, drenching sweats, or weight loss): ☐ No ☐ Yes

Patient showed presence of extra-nodal disease: ☐ No ☐ Yes

Disease relapsed at previously irradiated site(s): ☐ No ☐ Yes

After salvage chemotherapy

Disease was stable or progressed: ☐ No ☐ Yes

Comments:

SOUTHWEST ONCOLOGY GROUP
S0410 TREATMENT FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S0410 **Registration Step** 1

Patient Initials _____ (L, F M)

Institution/Affiliate _____ Physician _____

Time of submission: ☐ End of cycle 1 of high dose therapy
☐ End of cycle 2 of high dose therapy

Instructions: Please complete this form after each cycle of high dose therapy. Please submit stem cell infusion data separately on the S0410 Infusion Summary form. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

STATUS

Date of Last Contact or Death: ☐☐ / ☐☐ / ☐☐☐☐ **Vital Status:** ☐ Alive ☐ Dead
(submit Notice of Death)

Has the patient progressed per the definition in Section 10.0 of the protocol? ☐ No ☐ Yes
(submit Follow Up Form)

TREATMENT

Treatment start date: ☐☐ / ☐☐ / ☐☐☐☐

Date of last treatment: ☐☐ / ☐☐ / ☐☐☐☐

Is patient still on protocol treatment? ☐ No *(submit Off Treatment Notice)* ☐ Yes

First Day of Reporting Interval:

Weight: ☐☐☐.☐ kg **BSA:** ☐.☐☐ m^2 **Performance Status:** ☐

Were there any dose modifications or additions/omissions to protocol treatment?

☐ No
☐ Yes, planned (per protocol guidelines), specify in comments
☐ Yes, unplanned (not per protocol guidelines), specify in comments

Report total dose amount for reporting period:

Cycle 1 of high dose therapy
Melphalan ☐☐☐ mg

Cycle 2 of high dose therapy
TBI ☐☐☐☐ cGy
Etoposide (VP-16) ☐☐☐☐ mg
Cyclophosphamide ☐☐☐☐☐ mg
BCNU ☐☐☐☐ mg

Comments:

SOUTHWEST ONCOLOGY GROUP
S0410 ADVERSE EVENT SUMMARY FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S 0 4 1 0 **Registration Step** 1

Patient Initials _____ (L, F M)

Time of submission: ☐ End of cycle 1 of high dose therapy ☐ End of cycle 2 of high dose therapy ☐ 1 month after the second stem cell infusion ☐ 2 months after the second stem cell infusion

Institution/Affiliate _____ Physician _____

Instructions: Please complete this form after cycle 1 high dose therapy, after cycle 2 high dose therapy, and at 1 month and 2 months after the second stem cell infusion or removal from protocol therapy. Report all adverse events observed. Document the worst Grade seen during the reporting period. Do not code a condition existing prior to registration as an adverse event unless it worsens. Category lists may not include all adverse events from that category. Record any observed adverse events not listed on the blank lines at the end. All dates are MONTH, DAY, YEAR. Explain any blank dates or fields in the **Comments** section. Place an X in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

ADVERSE EVENTS **Reporting period start date:** ☐☐ / ☐☐ / ☐☐☐☐

Reporting period end date: ☐☐ / ☐☐ / ☐☐☐☐

Were adverse events assessed during this time period?

☐ No ☐ Yes, but no reportable adverse events occurred

☐ Yes, and reportable adverse events occurred (report below)

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*		CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
IM00	Allergic reaction/hypersensitivity	☐	☐	FL51	Weight loss	☐	☐
EA30	Tinnitus	☐	☐	SK90	Hair loss/alopecia	☐	☐
HE20	Hemoglobin	☐	☐	SK16	Pruritus/itching	☐	☐
HE00	Leukocytes	☐	☐		Rash: dermatitis associated with radiation		
HE40	Lymphopenia	☐	☐	SKR72	Chemoradiation	☐	☐
HE60	Myelodysplasia	☐	☐	SKR71	Radiation	☐	☐
HE30	Neutrophils/granulocytes	☐	☐	GI01	Anorexia	☐	☐
HE10	Platelets	☐	☐	GI30	Constipation	☐	☐
CA01	Cardiac-ischemia/infarction	☐	☐	GI23	Dehydration	☐	☐
CA50	Hypertension	☐	☐	GI20	Diarrhea	☐	☐
CA51	Hypotension	☐	☐	GI41	Dry mouth/salivary gland	☐	☐
CA06	Left ventricular diastolic dysfunction	☐	☐		Mucositis/stomatitis (functional/symptomatic)		
CA07	Left ventricular systolic dysfunction	☐	☐	GIM52	Pharynx	☐	☐
FL40	Fatigue	☐	☐	GI00	Nausea	☐	☐
FL01	Fever	☐	☐	GI43	Taste alteration (dysgeusia)	☐	☐
FL10	Rigors/chills	☐	☐	GI10	Vomiting	☐	☐
FL30	Sweating	☐	☐	HM25	Hematoma	☐	☐

*** Attribution codes:** 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

continued on next page

SOUTHWEST ONCOLOGY GROUP
S0410 ADVERSE EVENT SUMMARY FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S 0 4 1 0 **Registration Step** 1

Patient Initials _____ (L, F M)

Time of submission: ☐ End of cycle 1 of high dose therapy ☐ End of cycle 2 of high dose therapy ☐ 1 month after the second stem cell infusion ☐ 2 months after the second stem cell infusion

ADVERSE EVENTS, *continued*

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
LI04	Pancreatitis	☐	☐
IN30	Febrile neutropenia	☐	☐
LY01	Edema: head and neck	☐	☐
LY02	Edema: limb	☐	☐
LY03	Edema: trunk/genital	☐	☐
LY04	Edema: viscera	☐	☐
ME04	AST, SGOT	☐	☐
ME05	Bilirubin	☐	☐
ME06	Creatinine	☐	☐
ME31	Glucose, serum-high	☐	☐
ME30	Glucose, serum-low	☐	☐
ME90	Phosphate, serum-low	☐	☐
ME12	Proteinuria	☐	☐
MS09	Fracture	☐	☐
	Mood alteration		
NRM63	Depression	☐	☐
NR50	Neuropathy: motor	☐	☐
NR60	Neuropathy: sensory	☐	☐
NR20	Personality/behavioral	☐	☐

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
NR30	Seizure	☐	☐
EY42	Vision - blurred vision	☐	☐
EY99	Ocular/visual - other specify: _____	☐	☐
	Pain		
PAM02	Bone	☐	☐
PAN37	Head/headache	☐	☐
PAM11	Joint	☐	☐
PAM14	Muscle	☐	☐
PA99	Pain - other specify: _____	☐	☐
LU00	Dyspnea	☐	☐
LU10	Hypoxia	☐	☐
GU53	Renal failure	☐	☐
GU03	Urinary frequency/urgency	☐	☐
SY10	Tumor lysis syndrome	☐	☐
	CTC Adverse Event Term, Other *(specify using CTCAE 3.0 terminology)*		
	_____	☐	☐
	_____	☐	☐
	_____	☐	☐

*** Attribution codes:** 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

Comments: (Please explain any "other" adverse events reported above, e.g., PA99 Pain-other)

SOUTHWEST ONCOLOGY GROUP
S0410 INFUSION SUMMARY FORM

SWOG Patient ID [ ][ ][ ][ ][ ][ ] **SWOG Study No.** [S][0][4][1][0] **Registration Step** [1]

Patient Initials _____ (L, F M)

Institution/Affiliate _____ Physician _____

Instructions: Please complete this form after the second stem cell infusion. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

Date of First Stem Cell Infusion: [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Date of Second Stem Cell Infusion: [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Total Stem Cell Infusion Dose: [ ][ ].[ ] x 10^{6} CD34+ cells/kg

Comments:

SOUTHWEST ONCOLOGY GROUP
LYMPHOMA BASELINE TUMOR ASSESSMENT FORM

SWOG Patient No. ☐☐☐☐☐☐ SWOG Study No. S☐☐☐☐ Protocol Step: 1

Patient Initials _____ (L,F,M)

Institution/Member _____ Physician _____

Groups other than SWOG: Group Name/Study No./Patient No. _____ / _____ / _____

Instructions: Please use black ink. Circle **AMENDED** items in red. Record the requested information for all measurable lesions and all sites of evaluable and non-evaluable disease. Please refer to section 10.1 of the protocol for definitions. If an organ or site has too many measurable lesions to measure at each evaluation, choose three to follow as measurable disease and record the rest as evaluable disease. For measurable lesions, check the RT-No Progression box if the lesion was previously irradiated and has not progressed since.

The same test procedures used for baseline disease assessment must be used for all required subsequent disease assessments.

Site of Target Lesions

	Site of Measurable Lesions	RT-No Progr.	Tumor Measurement (cm)	Assessment Code*	Date of Assessment
L1	_____	☐	☐☐.☐ x ☐☐.☐	☐☐	☐☐ / ☐☐ / ☐☐☐☐
L2	_____	☐	☐☐.☐ x ☐☐.☐	☐☐	☐☐ / ☐☐ / ☐☐☐☐
L3	_____	☐	☐☐.☐ x ☐☐.☐	☐☐	☐☐ / ☐☐ / ☐☐☐☐
L4	_____	☐	☐☐.☐ x ☐☐.☐	☐☐	☐☐ / ☐☐ / ☐☐☐☐
L5	_____	☐	☐☐.☐ x ☐☐.☐	☐☐	☐☐ / ☐☐ / ☐☐☐☐
L6	_____	☐	☐☐.☐ x ☐☐.☐	☐☐	☐☐ / ☐☐ / ☐☐☐☐

	Other Sites of Disease	Extent	Assessment Code*	Date of Assessment
S1	_____	_____	☐☐	☐☐ / ☐☐ / ☐☐☐☐
S2	_____	_____	☐☐	☐☐ / ☐☐ / ☐☐☐☐
S3	_____	_____	☐☐	☐☐ / ☐☐ / ☐☐☐☐
S4	_____	_____	☐☐	☐☐ / ☐☐ / ☐☐☐☐
S5	_____	_____	☐☐	☐☐ / ☐☐ / ☐☐☐☐

List all **negative** diagnostic tests/studies used to evaluate patient for malignancy.

Tests/studies	Date	Tests/studies	Date
_____	☐☐ / ☐☐ / ☐☐☐☐	_____	☐☐ / ☐☐ / ☐☐☐☐
_____	☐☐ / ☐☐ / ☐☐☐☐	_____	☐☐ / ☐☐ / ☐☐☐☐

*** Assessment Codes**:

01-Palpation	05-Endoscopy	14-Radioisotope scan	99-Other (specify below and indicate lesion number)
02-Visualization	10-Plain film/X-ray without contrast	15-Ultrasound	
03-Colposcopy	11-Plain film/X-ray with contrast	20-Histologic confirmation	_____
04-CA-125 assay	12-CT scan	21-Cytologic confirmation	_____
	13-MRI scan		

Notes:

SOUTHWEST ONCOLOGY GROUP
LYMPHOMA FOLLOW-UP TUMOR ASSESSMENT FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** | | | | | | **Registration Step** |

Patient Initials (L, F M) _____ Institution/Affiliate _____ Physician _____

Groups other than SWOG: Group Name/Study No./Patient No. _____ / _____ / _____

Instructions: Please use black ink. Circle **AMENDED** items in red. Record the requested information for all measurable lesions and all sites of evaluable and non-evaluable disease. Please refer to section 10.1 of the protocol for definitions. If an organ or site has too many measurable lesions to measure at each evaluation, choose three to follow as measurable disease and record the rest as evaluable disease. For measurable lesions, check the RT-No Progression box if the lesion was previously irradiated and has not progressed since.

The same test procedures used for baseline disease assessment must be used for all required subsequent disease assessments.

Site of Target Lesions

	Site of Measurable Lesions	RT-No Progr.	Tumor Measurement (cm)	Assessment Code*	Date of Assessment
L1			. x .		/ /
L2			. x .		/ /
L3			. x .		/ /
L4			. x .		/ /
L5			. x .		/ /
L6			. x .		/ /

	Other Sites of Disease	Extent	Assessment Code*	Date of Assessment
S1				/ /
S2				/ /
S3				/ /
S4				/ /
S5				/ /

	New Lesions (Specify Site)	Assessment Code*	Date of Assessment
S1			/ /
S2			/ /

List all **negative** diagnostic tests/studies used to evaluate patient for malignancy.

Tests/studies	Date	Tests/studies	Date
	/ /		/ /
	/ /		/ /

*** Assessment Codes**:

01-Palpation	05-Endoscopy	14-Radioisotope scan	99-Other (specify below and indicate lesion number)
02-Visualization	10-Plain film/X-ray without contrast	15-Ultrasound	
03-Colposcopy	11-Plain film/X-ray with contrast	20-Histologic confirmation	
04-CA-125 assay	12-CT scan	21-Cytologic confirmation	
	13-MRI scan		

SOUTHWEST ONCOLOGY GROUP
FOLLOW UP FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S | | | | **Registration Step** |

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please submit at each follow up after completion of treatment until relapse or progression, at time of relapse or progression, and at protocol-specified intervals after relapse or progression. Also submit at time of diagnosis of second primary. All dates are **MONTH, DAY, YEAR**. Answer all questions and explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle AMENDED items in red.

VITAL STATUS

Vital Status: ☐ Alive ☐ Dead Date of last contact or death: | | / | | / | | | | |

If vital status is Dead, complete and submit Notice of Death form.

DISEASE FOLLOW UP STATUS

Has the patient had a documented clinical assessment for this cancer (since submission of the previous follow-up form)?

☐ No ☐ Yes If Yes, Date of Last Clinical Assessment: | | / | | / | | | | |

NOTICE OF FIRST RELAPSE OR PROGRESSION

Has the patient developed a first relapse or progression that has not been previously reported?

☐ No ☐ Yes If Yes, Date of Relapse or Progression: | | / | | / | | | | |

Site(s) of Relapse or Progression: _____

NOTICE OF NEW PRIMARY

Has a new primary cancer or MDS (myelodysplastic syndrome) been diagnosed that has not been previously reported?

☐ No ☐ Yes If Yes, Date of Diagnosis: | | / | | / | | | | |

New Primary Site: _____

NON-PROTOCOL TREATMENT

Has the patient received any non-protocol cancer therapy (prior to progression/relapse) not previously reported?

☐ No ☐ Yes If Yes, Date of First Non-Protocol Therapy: | | / | | / | | | | |

Agent Name(s): _____

LONG TERM ADVERSE EVENT

Has the patient experienced (prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment) any severe (grade ≥ 3) long term toxicity that has not been previously reported?

☐ No ☐ Yes If Yes, Adverse Events and Grades: _____

Comments:

SOUTHWEST ONCOLOGY GROUP
OFF TREATMENT NOTICE

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** ☐

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: For each registration step, submit this form within 2 weeks after completion (or discontinuation) of treatment.

Systemic Therapy: List regimens, start and end dates. For multidrug regimens, do not list individual drugs separately; end date would be the date all drugs in the regimen were discontinued.

Surgery: List type of surgery, and in the "end date" column, the date of surgery.

Radiation: List sites, start and end dates (inclusive of boosts and implants).

All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section.
Place an [X] in appropriate boxes. Circle **AMENDED** items in red.

Treatment Start Date	Treatment End Date	Regimen or Procedure or Site(s)
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	_____
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	_____
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	_____
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	_____
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	_____

(If more room is needed, please continue on a separate page)

Off Treatment Reason (select one):

- ☐ Treatment completed per protocol criteria
- ☐ Medically required, due to toxicity, specify: _____
- ☐ Patient refused, due to toxicity, specify: _____
- ☐ Patient refused, other than toxicity, specify: _____
- ☐ Progression or relapse. Sites: _____
- ☐ Death (submit Notice of Death form)
- ☐ Other, specify: _____

Off Treatment Date

Date of completion, progression, death or decision to discontinue therapy: ☐☐ / ☐☐ / ☐☐☐☐

Will patient receive further treatment?

☐ No ☐ Yes, specify: _____ ☐ Unknown

Date of Last Contact (or death): ☐☐ / ☐☐ / ☐☐☐☐

Vital Status: ☐ Alive ☐ Dead (submit Notice of Death form)

Comments:

SOUTHWEST ONCOLOGY GROUP
NOTICE OF DEATH

SWOG Patient ID | | | | | | | **Most Recent SWOG Study No.** S | | | | |

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Answer all questions and explain any blank fields or blank dates in the **Comments** section.
Place an [X] in appropriate boxes. Circle **AMENDED** items in red.

Date of Death: | | / | | / | | | | (month / day / year)

CAUSES OF DEATH

Any cancer (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If cancer was the primary cause or if cancer possibly or definitely contributed to death, and the patient had had multiple tumor types, specify those which were causes of death:

☐ Cancer of most recent SWOG study, specify cancer: _____

☐ Cancer of other SWOG study, specify cancer: _____

☐ Other cancer, specify: _____

Toxicity from disease related treatment (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If Primary Cause, Contributory or Possible, specify treatment and toxicity:

Non-cancer and non-treatment related causes (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If Primary Cause, Contributory or Possible, specify:

Autopsy? ☐ No ☐ Yes ☐ Unknown

Source(s) of death information:

☐ Autopsy report
☐ Medical record / Death certificate
☐ Physician
☐ Relative or friend
☐ Other, specify: _____

Comments:

19.0 APPENDIX

19.1 Determination of Expedited Adverse Event Reporting Requirements

19.2 Southwest Oncology Group Approved Transplant Centers

19.3 Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Approved Transplant Centers

19.1 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 (1, 2, or 3) 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 Tables 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: 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 the instructions above.

19.2 Southwest Oncology Group Approved Transplant Centers

SOUTHWEST ONCOLOGY GROUP
APPROVED BONE MARROW TRANSPLANT FACILITIES

Membership	Institution	BMT Director/Contact	Phone/Fax	Approved For
MEM	**Arizona Cancer Center** BMT Program 1501 North Campbell Ave. Tucson, AZ 85724-0001	Andrew Yeager, M.D.	P: (520) 626-0662 F: (520) 626-8944	Allogeneic Autologous
Affiliate	**Baylor College of Medicine** **Stem Cell Transplant Program** **The Methodist Hospital** 6565 Fannin Street Houston, TX 77030-2707	Helen E. Heslop, M.D., Director (Affiliate of UTMB Galveston)	P: (832) 824-4670 F: (832) 825-4668	Allogeneic Autologous
CCOP	**Blood & Marrow Transplant** **Group of Georgia/** **Northside Hospital** 960 Johnson Ferry Rd. , Suite 400 Atlanta, Georgia 30342	Daniel G. Connaghan, M.D. (Component of Atlanta Regional CCOP)	P: (404) 255-1930 F: (404) 459-8510	Allogeneic Autologous
MEM	**Boston Univ. Med. Ctr.** BMT Program 80 E. Concord St., Room E124 Boston, MA 02118	Douglas Faller, M.D., Ph.D.	P: (617) 638-4173 F: (617) 638-4176	Autologous
MEM	**City of Hope National** **Medical Center** BMT Program 1500 E. Duarte Rd. Duarte, CA 91010-0269	Stephen J. Forman, M.D.	P: (626) 359-8111 ext. 62403 F: (626) 301-8256	Allogeneic Autologous
MEM	**City of Hope -- Samaritan** **Bone Marrow Transplantation** **Program** 1111 E. McDowell Rd. Suite 12 B Phoenix, AZ 85006	Jeffrey R. Schriber, M.D.	P: (602) 239-4526 F: (602) 239-3592	Allogeneic Autologous
MEM	**Cleveland Clinic** **Foundation** BMT Program One Clinic Center 9500 Euclid Avenue Cleveland, OH 44195-0001	Brian J. Bolwell, M.D.	P: (216) 444-6922 F: (216) 444-9774	Allogeneic Autologous
CCOP	**Columbia River CCOP** **Good Samaritan Hospital** **& Medical Center** BMT Program, M215 1015 NW 22nd Avenue Portland, Oregon 97210	Keith S. Hansen, M.D.	P: (503) 280-1223 F: (503) 528-5252	Autologous

Membership	Institution	BMT Director/Contact	Phone/Fax	Approved For
AFFIL	**Comprehensive Cancer Institute** **Oncology Specialties, PC** 201 Sivley Road SE Huntsville, AL 35801	John M. Waples, M.D. (Affiliate of UTHSC-San Antonio)	P: (256) 705-4224 F: (256) 517-6588	Autologous
CCOP	**Dayton CCOP** **Miami Valley Hospital** BMT Program 1 Wyoming Street Dayton, OH 45409	Burhan Yanes, M.D.	P: (513) 223-2183	Autologous
CCOP	**DeKalb Medical Center** 2665 North Decatur Road Suite 140 Decatur, GA 30033	Richard S. Leff, M.D.	P: (770) 496-5555 F: (770) 939-2887	Autologous
MEM	**Fred Hutchinson Cancer Research Center** BMT Program 1124 Columbia Street Seattle, WA 98104-2015	Fred R. Appelbaum, M.D. (Component of PSOC)	P: (206) 667-4412 F: (206) 667-6936	Allogeneic Autologous
CCOP	**Greenville CCOP** BMT Program 65 International Drive Greenville, SC 29615	Jeffrey K. Giguere, M.D.	P: (864) 987-7000 F: (864) 987-1257	Autologous
CCOP	**Hawaii CCOP** **St. Francis Medical Ctr.** BMT Program 2228 Liliha Street Suite 208 Honolulu, HI 96817-0166	Livingston M.F. Wong, M.D.	P: (808) 523-0166 F: (808) 528-4940	Allogeneic Autologous
MEM	**H.Lee Moffitt Cancer Center & Research Institute** BMT Program 12902 Magnolia Dr. Tampa, FL 33612	Claudio Anasetti, M.D.	P: (813) 745-7202 F: (813) 745-3071	Allogeneic Autologous
MEM	**Henry Ford Hospital** BMT Program 2799 W. Grand Blvd. Detroit, MI 48202-2608	Nalini Janakiraman, M.D.	P: (313) 916-3820 F: (313) 916-7911	Allogeneic Autologous
CCOP	**Indiana Blood & Marrow** Transplantation/St. Francis Hospital 1600 Albany Street Beech Grove, Indiana 46107	James M. Thompson, D.O. (Component of Dayton CCOP)	P: (317) 929-3400 F: (317) 929-1113	Allogeneic Autologous
Affiliate	**John Muir Medical Ctr.** BMT Program 110 La Casa Via, Suite 200 Walnut Creek, CA 94598	Robert S. Lowitz, M.D. & Dan Ben-Zeev, M.D. (Affiliate of UC-Davis)	P: (925) 939-9610 F: (925) 939-9630	Autologous
CCOP	**Kansas City Blood and Marrow Transplant Program at St. Luke's Hospital** 6601 Rockhill Road Kansas City, MO 64131	Leslie Herst, Executive Director (Component of Kansas City CCOP)	P: (816) 823-0555 F: (816) 823-0563	Allogeneic Autologous
MEM	**LDS Hospital of Utah** BMT Program 325 8th Avenue Salt Lake City, UT 84143	Clyde D. Ford, M.D. (Component of Utah)	P: (801) 535-8166 F: (801) 535-4143	Allogeneic Autologous

Membership	Institution	BMT Director/Contact	Phone/Fax	Approved For
MEM	**Louisiana State University Medical Center**-BMT Program Feist-Weiller CC Bone Marrow Unit 1501 Kings Hwy P.O. Box 33932 Shreveport, LA 71130-3932	John W. Hiemenz, M.D.	P: (318) 675-5972 F: (318) 675-4338	Allogeneic Autologous
CCOP	**LSU New Orleans CCOP** **Louisiana State University School of Medicine-**BMT Program 1542 Tulane Ave. New Orleans, LA 70112-2865	Robert W. Veith, M.D.	P: (504) 568-5151 F: (504) 568-3531	Allogeneic Autologous
MEM	**Loyola University** BMT Program Bldg. 54, Suite 067 2160 South 1st Ave. Maywood, IL 60153-5500	Patrick J. Stiff, M.D.	P: (708) 327-3148 F: (708) 327-3219	Allogeneic Autologous
MEM	**Medical University of South Carolina, Hollings Cancer Center** Blood and Marrow Transplant Program 261 Calhoun Street, Suite 302 P.O. Box 250187 Charleston, SC 29425	Debra A. Frei-Lahr, M.D.	P: (843) 792-4271 F: (843) 792-0644	Allogeneic Autologous
Affiliate	**Memorial Medical Center** BMT Program c/o Debbie Echols, R.N. 2700 Napoleon Avenue, Box 7 New Orleans, LA 70115	Todd Roberts, M.D. (Affiliate of LSU Shreveport)	P: (504) 897-4274 F: (504) 896-5153	Autologous
CCOP	**Northwest CCOP** **St. Joseph Medical Ctr** BMT Program 1717 South J Street Tacoma,WA98405	Jay P. Klarnet, M.D.	P: (253) 627-4123 F: (253) 627-8377	Autologous
MEM	**Oregon Health Sciences University** BMT Program 3181 SW Sam Jackson Park Rd. Portland, OR 97201-3098	Richard T. Maziarz, M.D.	P: (503) 494-1551 F: (503) 494-1552	Allogeneic Autologous
CCOP	**Providence Portland** Medical Center 4805 Northeast Glisan St. Portland, OR 97213-2967	Stacy Lewis, M.D. (Under Columbia River CCOP)	P: (503) 203-1000 F: (503) 203-1010	Autologous
Affiliate	**Scripps Clinic** BMT Program MS312 10666 North Torrey Pines Road La Jolla, CA 92037	James R. Mason, M.D. (Affiliate of City of Hope)	P: (858) 554-8597 F: (858) 554-8946	Allogeneic Autologous
Affiliate	**St. Joseph's Hospital** BMT Program P.O. Box 5600 Orange, CA 92613-5600	Leonard S. Sender, M.D. (Affiliate of UCLA)	P: (714) 771-8921 F: (714) 744-8799	Allogeneic Autologous

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MEM	**St. Louis University Medical Center** BMT Program 3635 Vista Ave. at Grand Blvd. P.O. Box 15250 St. Louis, MO 63110-0250	Paul J. Petruska, M.D. (Interim BMT director)	P: (314) 268-5451 F: (314) 773-1167	Allogeneic Autologous
Affiliate	**St. Luke's Regional Mt. States Tumor Institute** BMT Program 100 E. Idaho Boise, ID 83712-6223	William H. Kreisle, M.D. (Affiliate of Utah)	P: (208) 381-2712 F: (208) 381-3276	Autologous
Affiliate	**Stanford University Hospital** BMT Program 300 Pasteur Drive Stanford, CA 94305	Robert Negrin, M.D. (Affiliate of City of Hope)	P: (650) 723-0822 F: (650) 725-8950	Allogeneic Autologous
Affiliate	**Sutter Health Cancer Research Group-Eastern Div.** (Sacramento Reg Onc) BMT Program 5275 F. Street Sacramento, CA 95819-3295	Vincent Caggiano, M.D. (Affiliate of UC-Davis)	P: (916) 454-6500 F: (916) 454-6501	Autologous
Affiliate	**Sutter Health Western (Alta Bates Medical Center)** 2450 Ashby Avenue Berkeley, CA 94705	Jeffrey L. Wolf, M.D. (Affiliate of UC-Davis)	P: (510) 204-6401 F: (510) 204-6440	Allogeneic Autologous
MEM	**Swedish Hospital Med. Ctr. Tumor Institute** BMT Program 1221 Madison Street Seattle, WA 98104	Erin D. Ellis, M.D. (component of PSOC)	P: (206) 386-2323 F: (206) 386-2729	Autologous
Affiliate	**Southwest Cancer and Research Center** University Medical Center Blood & Marrow Transplant Program 602 Indiana Avenue Lubbock, TX 79415	Everardo Cobos, M.D. (Affiliate of San Antonio)	P: (806) 743-3134 F: (806) 775-8593	Autologous
Affiliate	**Thompson Cancer Survival Center**/BMT Program 1915 White Avenue Knoxville, TN 37916	Richard T. Grapski, M.D. (Affiliate of San Antonio)	P: (865) 541-1812 F: (865) 541-1162	Autologous
MEM	**Tulane University** Medical Ctr. BMT Program 1430 Tulane Avenue New Orleans, LA 70112	Hana Safah, M.D.	P: (504) 585-6070 F: (504) 585-6077	Allogeneic Autologous
MEM	**University of Arkansas** BMT Program 4301 W. Markham Street, Slot 816 Little Rock, AR 72205-7101	Bart Barlogie, M.D., Ph.D.	P: (501) 526-2873 F: (501) 526-2273	Allogeneic Autologous
MEM	**University of California, Davis** BMT Program Division of Hem/Onc 4501 X Street Sacramento, CA 95817	Carol M. Richman, M.D.	P: (916) 734-3772 F: (916) 734-7946	Autologous

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MEM	**University of California, Irvine Medical Center** BMT Program 101 The City Drive, Rt. 81, Bldg. 23 Orange, CA 92668	Randall Holcombe, M.D.	P: (714) 456-5152 F: (714) 456-7142	Autologous
MEM	**University of Colorado Cancer Center** BMT Program Box B-190, UCHSC 4200 East 9th Avenue Denver, CO 80262-0001	John Sweetenham, M.D.	P: (303) 372-9000 F: (303) 372-9003	Autologous Allogeneic
CCOP	**University of Illinois Medical Center at Chicago** Stem Cell and Bone Marrow Transplant Program Section of Hematology Oncology Rm. 820E (M/C 713) 840 Wood St. Chicago, IL 60612-7323		P: (312) 413-8750 (312) 413-4826, or (312) 996-2088 F: (312) 413-8626	Autologous Allogeneic
MEM	**University of Kansas Medical Center** BMT Program 39th & Rainbow Blvd. Kansas City, KS 66103-3337	Barry Skikne, M.D.	P: (913) 588-6077 F: (913) 588-3996	Allogeneic Autologous
MEM	**University of Kentucky** Lucille P. Markey Cancer Ctr. BMT Program 800 Rose Street Lexington, KY 40536-0093	Edward H. Romond, M.D.	P: (859) 323-8043 F: (859) 257-7715	Allogeneic Autologous
Affiliate	**University of Louisville Hospital** Blood and Marrow Transplant 530 South Jackson Street Louisville, KY 40202		P: (502) 562-3484 F: (502) 562-3538	Allogeneic Autologous
MEM	**University of Michigan** BMT Program F 7828 Mott University of Michigan 1500 E. Medical Center Drive Ann Arbor, MI 48109-0247	James Ferrara, M.D. & Joseph Uberti, M.D., Ph.D.	P: (734) 615-1340 or (734) 936-8456 F: (734) 615-3947 or (734) 936-8788	Allogeneic Autologous
MEM	**University of Mississippi Medical Center** BMT Program 2500 North State Street Jackson, MS 39216-4505	Carolyn L. Bigelow, M.D. Joe C. Files, M.D.	P: (601) 984-5615 P: (601) 984-5626 F: (601) 984-5689	Allogeneic Autologous
MEM	**University of Oklahoma** BMT Program P.O. Box 26901 Oklahoma City, OK 73190-0001	George B. Selby, M.D.	P: (405) 271-4022 F: (405) 271-3020	Allogeneic Autologous
MEM	**University of Rochester Medical Center** 601 Elmwood Avenue Box 610 Rochester, NY 14642	Gordon Phillips, M.D.	P: (585) 275-4099 F: (585) 273-1042	Allogeneic Autologous
MEM	**University of Southern California (USC)** Norris Cancer Hospital BMT Program Suite 162 Los Angeles, CA 90033	Dan Douer, M.D.	P: (323) 865-3950 F: (323) 865-0060	Autologous

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MEM	**University of Texas Health Science Center at San Antonio** BMT Program 7703 Floyd Curl Drive San Antonio, TX 78284-0001	Cesar O. Freytes, M.D.	P: (210) 617-5268 F: (210) 617-5271	Allogeneic Autologous
MEM	**University of Texas MD Anderson Cancer Center Department of Blood and Marrow Transplant** 1515 Holcombe Blvd. Houston, TX 77030	Sergio A. Giralt, M.D. (Medical Director) Sherry H. Sorensen, RN (Nurse Manager)	P: (713) 794-1034 F: (713) 792-8314 P: (713) 792-2088 F: (713) 745-1829	Allogeneic Autologous
MEM	**University of Utah Health Sciences Ctr** BMT Program Room 4C464 SOM Salt Lake City, UT 84132-0001	Finn Petersen, M.D.	P: (801) 585-3229 F: (801) 585-3432	Allogeneic Autologous
MEM	**University of Washington Medical Center** BMT Program 1959 NE Pacific Street Seattle, WA 98195	Oliver W. Press, M.D., Ph.D. (component of PSOC)	P: (206) 667-1872 F: (206) 667-1874	Allogeneic Autologous
CCOP	**Virginia Mason CCOP** The Mason Clinic C2-S BMT Program 1100 9th Avenue P.O. Box 900 Seattle, WA 98111-0900	Joellen Nicholson, M.D.	P: (206) 223-6194 F: (206) 223-6914	Allogeneic Autologous
MEM	**Wayne State University** Harper-Grace Hospitals BMT Program P.O. Box 02188 Detroit, MI 49201-1998	Roy D. Baynes, M.D.	P: (313) 966-7021 F: (313) 966-7656	Allogeneic Autologous
CCOP	**Wichita CCOP** Cancer Center of Kansas BMT Program 818 N. Emporia, Suite 403 Wichita, KS 67214-3728	David B. Johnson, M.D.	P: (316) 268-5784 F: (316) 291-7855	Allogeneic Autologous
MEM	**Wilford Hall U.S.A.F. Medical Center** BMT Program Dept. of Hematology-Medical Onc. 2200 Bergquist Drive, Suite 1 Lackland AFB, TX 78236-5300	David W. Ririe, M.D.	P: (210) 292-7312 F: (210) 292-7317	Allogeneic Autologous

19.3 Blood and Marrow Transplant Clinical Trials Network (BMT CTN) Approved Transplant Centers

1. Case Western Reserve University Consortium including: Case Western Reserve University, Ohio State, Oregon Health Sciences University, and Washington University of St. Louis
2. City of Hope National Medical Center
3. Dana-Farber Cancer Institute
4. Duke University Medical Center
5. Fred Hutchinson Cancer Research Center
6. Johns Hopkins University
7. Memorial Sloan-Kettering Cancer Center
8. Pediatric Blood and Marrow Transplant Consortia (PBMTC)
9. Stanford University Medical Center
10. University of California at San Diego/SCRIPPS (Consortium)
11. University of Florida
12. University of Michigan Comprehensive Cancer Center
13. University of Minnesota
14. University of Nebraska Medical Center
15. University of Pennsylvania – Abramson Cancer Center
16. University of Texas, MD Anderson Cancer Center