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September 1, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL SWOG MEMBER, NCORP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Hita, Protocol Coordinator (E-mail: sjhita@swog.org)

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Chairs: Drs. A.S. Advani, and L.C. Michaelis.

STATUS NOTICE

Study Chair: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.org

IRB Review Requirements
(√) Expedited review allowed

Status Change
(√) Closure: Permanent

PERMANENT CLOSURE

The above-referenced study will be permanently closed to accrual **effective September 15, 2017 at 11:59 p.m. Pacific.**

This memorandum serves to notify the NCI and the SWOG Statistical and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
James Geerlof – B.M.S.
John Lee – B.M.S.

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206-342-1616 FAX

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M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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October 15, 2016

TO: ALL SWOG MEMBER, NCORP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Hita, Protocol Coordinator (E-mail: sjhita@swog.org)

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Chairs: Drs. A.S. Advani, and L.C. Michaelis.

MEMORANDUM

Study Chair: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.org

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform sites of the ongoing accrual needs for the above-referenced study.

Currently the study requires at least 14 additional, eligible patients to reach full accrual. Many sites have expressed concern over screening patients for the study, as CTSU currently reflects accrual as being nearly complete; however, these additional 14 eligible patients are still needed to complete accrual. Once the additional 14 eligible patients

have been accrued, SWOG will send a notification to sites and provide approximately 2 week's advanced notice prior to permanently closing the study to accrual, in order to allow sites to complete registration of any patients that have already begun the screening process at that time.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Linda Fischer– B.M.S.

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
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503-346-8038 FAX

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4201 Medical Dr
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210-614-8808
210-614-0006 FAX

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206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: October 1, 2016
CTEP Submission Date: September 12, 2016

TO: ALL SWOG MEMBER, NCORP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Hita, Protocol Coordinator (E-mail: sjhita@swog.org)

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Chairs: Drs. A.S. Advani, and L.C. Michaelis.

REVISION #9

Study Chair: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.org

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
  (√) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

REVISION #9

The primary purpose of this revision is to allow intergroup enrollment of patients from Alliance and ECOG-ACRIN via the Clinical Trials Support Unit (CTSU) to the above-referenced protocol. For this reason, the protocol has been updated as follows:

1. The Version Date has been updated.

2. Title Page: Alliance and ECOG-ACRIN have been added to the participants list and may now register patients via CTSU. Dr. Ehab Attallah has been added as the ECOG-ACRIN Champion for the study.

3. Table of Contents: The Table of Contents has been updated.

4. CTSU Table: The Cancer Trials Support Unit (CTSU) Address and Contact Information Table has been added as Page 4. The remainder of the protocol has been repaginated.

5. Section 13.0: The registration guidelines have been updated to include instructions for registering patients via CTSU.

The following additional changes have been made:

1. Title Page: Anna Moseley has replaced Shannon McDonough in the biostatisticians list.

2. Section 3.3c: This section has been updated to indicate that both the SWOG ID and BMS ID numbers will be needed for initial orders. The e-mail address for re-supply orders has been updated to Sashin.Bhuta@bms.com.

3. Section 5.0: The e-mail address leukemiaquestion@crab.org has been added for eligibility questions.

4. Study Calendar: A note has been added at the end of the footnotes for each calendar indicating that, unless indicated otherwise in the protocol, scheduled procedures and assessments must follow established SWOG guidelines. The url for the guidelines has been included.

5. Section 14.4 5: The AML Disease Assessment Form number has been removed, per current SWOG format standards.

6. Section 18.0: Section 18.1, The Determination of Expedited Adverse Event Reporting Requirements appendix, is no longer necessary for this study, so has been removed. As a result, the study has no associated appendix and so Section 18.0 has been completely removed from the protocol.

7. Instances of “Southwest Oncology Group” have been updated to “SWOG” throughout the protocol.

8. Will My Medical Information be Kept Private?: The Cancer Trials Support Unit (CTSU) has been added to the list of institutions that may access patient records.

9. Notes for Local Investigators, Page 2: The notes have been updated to the current standard NCI-approved language.

10. Who is Doing This Study?: This section has been removed, as it is no longer relevant/correct.

11. Instances of “Southwest Oncology Group” have been updated to “SWOG” throughout the consent form.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Linda Fischer– B.M.S.

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
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503-346-8038 FAX

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4201 Medical Dr
Suite 250
San Antonio, TX 78229
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210-614-0006 FAX

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1730 Minor Ave
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Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: December 15, 2015
E-mailed Date: December 14, 2015

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Cara Laubach, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Chairs: Drs. A.S. Advani, and L.C. Michaelis.

MEMORANDUM

Study Chair: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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- HOLIDAY CLOSURE

The purpose of this memorandum is to notify sites that due to BMS holiday closure, Pravastatin orders must be received using the Drug Order Form for Pravastatin posted on the SWOG protocol abstract page (www. swog.org) by **December 16, 2015**. **Any orders received after December 16, 2015 will not be processed until January 8, 2016**.

Additionally, please note that the contact email address for Initial and Re-supply orders of Pravastatin is: Sashin.Bhuta@bms.com. For initial orders, please note that both the SWOG study ID (**S0919**) **and** the BMS ID (CV123-285) will be required and must be recorded in the subject line of the e-mail request.

If you have questions regarding Pravastatin Drug Orders, please contact: Sashin Bhuta at 609/897-2828.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Anna Moseley, M.S.
Louise Highleyman
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Barbara Skinn – B.M.S.

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Charles D. Blanke, MD
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MC: L586
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4201 Medical Dr
Suite 250
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1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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July 1, 2015

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Cara Laubach, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Chairs: Drs. A.S. Advani, and L.C. Michaelis.

MEMORANDUM

Study Chair: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

The purpose of this memorandum is to notify sites that the distribution method for Pravastatin has changed and a new Drug Order Form for Pravastatin has been posted on the SWOG protocol abstract page (www. swog.org).

Additionally, please note that the contact email address for Initial and Re-supply orders of Pravastatin has changed to: Sashin.Bhuta@bms.com. For initial orders, please note that both the SWOG study ID (**S0919**) **and** the BMS ID (CV123-285) will be required and must be recorded in the subject line of the e-mail request. This clarification will be incorporated into the protocol on Page 9, Section 3.3c under the "Supplier and Drug Ordering" sub-heading, with a forthcoming revision.

If you have questions regarding Pravastatin Drug Orders, please contact: Sashin Bhuta at 609/897-2828 .

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Hongli Li, M.S.
Louise Highleyman
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Barbara Skinn – B.M.S.

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Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
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503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: March 15, 2015
CTEP Submission Date: February 23, 2015

TO: ALL SWOG MEMBER, NCORP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Cara Laubach, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Chairs: Drs. A.S. Advani, and L.C. Michaelis.

REVISION #8

Study Chair: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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 #8

The protocol has been updated as follows:

1. The Version Date of the protocol and Model Consent Form have been updated.

2. Page, 1, Title Page: The participant list has been revised to be consistent with the new NCTN/CTSU guidelines.

3. Page 3, Table of Contents: This has been updated to reflect new page numbers for Sections 17.0, 18.0 and 18.1.

4. Page 9, Section 3.3c: The first paragraph in the "Drug Accountability" section has been revised as follows:

   "Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt*,* ~~and~~ disposition*, and disposal* of all drugs received from the supplier *using the NCI Oral Drug Accountability Record Form (NCI Oral DARF) available at: http://ctep.cancer.gov.*

5. Page 12, Section 5.1a: The MDS transformed to AML cohort is now clarified to be "Cohort 1" and the relapsed/refractory cohort is now clarified to be "Cohort 2" for clarity. This change also occurs in Section 5.1b (Page 12) and Section 11.6 (Page 27). To clarify eligibility of patients with prior CMML, MDS has been modified to read "MDS/CMML." This change has also been made in Section 5.1m (Page 14).

6. Page 26, Section 11.1: This paragraph has been revised to clarify the total sample size and now reads as follows:

   The primary objective of this study is to test whether the CR rate (CR+CRi) among ~~poor-risk~~ patients with AML is sufficient to warrant further investigation. *Originally, this regimen was investigated in relapsed patients with previous remission of longer than three months. Accrual to this cohort was closed on November 1, 2012 after meeting the protocol-defined criterion for efficacy. Thirty-six patients were enrolled to this cohort. The study was re-opened to investigate the regimen in poor-risk patients with AML. It will be* ~~The regimen will be~~ investigated independently in the two cohorts: (1) patients with MDS transformed to AML, and (2) refractory or relapsed patients. In each cohort, the regimen would be of no further interest if it yields a true CR rate of 20% (null), and would be of interest if it yields a true CR rate of 40% (alternative).

7. Page 26, Section 11.2: The third sentence of this paragraph has also been revised to clarify the total sample size and a fourth sentence has been inserted, so that it now reads as follows:

   Seventy-four ~~Thirty-seven~~ eligible patients will be accrued in ~~each cohort of~~ *the two poor-risk cohorts (thirty-seven in each cohort).The total accrual goal of the original cohort and two poor-risk cohorts is 110.*

8. Page 29, Section 13.3b: The words, "and the affirmation of eligibility on the Registration worksheet has been signed by the registering investigator or another investigator designate" have been added to the end of the first sentence (first bullet) of this section.

9. Page 34, Section 16.1b: This section has been revised to read as follows:

   This study requires that expedited adverse event reporting use the CTEP Adverse Event Reporting System (CTEP-AERS). ~~The NCI's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adeers_events.htm.~~
   CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

In the rare event when internet connectivity is disrupted an electronic report MUST be submitted immediately upon re-establishment of internet connection. ~~Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.~~

10. Page 35, Section 16.1e:

- The title of Table 16.1 has been revised to read as follows:

  Table 16.1. Expedited reporting requirements for adverse events experienced by patients ~~who have received commercial drug(s) on this study~~ *on either Induction or Consolidation Therapy within 30 days of the last administration of the commercial agents. All of the agents used in the study are commercial agents.*

- The following two bullets have been removed from the end of this section:

  "1) **Group-specific instructions.**
  The Operations Office will notify drug companies as required.
  3) For this study, the adverse events listed below do **not** require expedited reporting via CTEP-AERS:
  • Grade 4 myelosuppression"

11. Pages 35-36, Section 16.1f, "Reporting secondary AML/ALL/MDS" has been removed in its entirety and replaced with "Reporting Pregnancy, Fetal Death, and Death Neonatal." This updated section required a newly inserted Page 36. Subsequent pages have been renumbered accordingly.

Institutions should update their local consent forms to include the changes to the Model Consent Form within 90 days of distribution of this notice. SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk/benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes. Patients need not be informed of the following changes unless required by the local IRB.

12. The Model Consent Form, Page 4, "Before you begin the study…": "HIV test (for patients who are not known to have HIV)" has been removed from this section since the requirement for HIV testing of patients not known to be HIV-positive prior to registration was removed from the protocol with Revision #6.

13. The Model Consent Form, Page 9, "What are the costs of taking part in this study?": The website address listed in the second to last paragraph on this page has been revised to reflect the following updated website address: "http://cancer.gov/clinicaltrials/learningabout/payingfor/how-insurance-companies-decide"

14. The Model Consent Form, Page 11: "Where can I get more information?": The TTY number has been removed from the end of the first sentence of this section, so that it now reads: "You may call the National Cancer Institute's Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237)"

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Hongli Li, M.S.
Shannon McDonough, M.S.
Louise Highleyman
Laura Kingsbury, M.R.T.
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MC: L586
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503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: November 15, 2014
E-mailed Date: November 10, 2014

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Chairs: Drs. A.S. Advani, and L.C. Michaelis.

STATUS NOTICE

Study Chair: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

PARTIAL PERMANENT CLOSURE

Cohort 2 (the relapsed/refractory AML cohort) has met its accrual goal and will be **permanently closed to accrual effective November 24, 2014 at 11:59 p.m. Pacific**.

Cohort 1 (the MDS transformed to AML cohort) remains open to accrual.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Hongli Li, M.S.
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206-342-1616 FAX

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M3-C102
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206-667-4623
206-667-4408 FAX

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May 15, 2014

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Chairs: Drs. A.S. Advani, and L.C. Michaelis.

MEMORANDUM

Study Chair: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

The purpose of this memorandum is to inform sites of a change to the Master Forms Set for the above-mentioned study.

The Leukemia Follow-Up Form has been updated to remove "non-protocol" from the transplant question on Page 2.

The form date has been updated to 5/15/14. The form Version 1.1 has been added. The form number has not changed.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Jean Barce
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
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206-667-4408 FAX

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Distribution Date: March 1, 2014
CTEP Submission Date: February 13, 2014

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Chairs: Drs. A.S. Advani, and L.C. Michaelis.

REVISION #7

Study Chair: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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 #7

The protocol has been updated as follows:

1. The Version Date of the protocol and Model Consent Form have been updated.

2. Page 1, Title Page: The NCT number has been added below the title.

3. Pages 2-3, Table of Contents: The table of contents has been updated.

4. Page 4, Sections 1.2 and 1.3: A new Section 1.3 (Other Objectives) has been added to contain the objectives previously listed as Sections 1.2b and 1.2d (now Sections 1.3a and 1.3b, respectively). The remaining Section 1.2c has been renumbered to be Section 1.2a.

5. Page 12, Section 5.1b: The subsection 5.1b.4 has been moved to the beginning of Section 5.1b to clarify that the requirement for no previous stem cell transplant is applicable to both cohorts. The word "additional" has been added to the second paragraph for clarity.

6. Page 14, Section 5.1q: This section has been added to require history and physical examination within 28 days prior to registration.

7. Page 14, Section 5.1s: This section has been updated to the current OPEN registration system IRB approval language.

8. Pages 27-29, Sections 13.2-13.3: Registration information has been updated to change the registration system from the SWOG system to the CTSU's OPEN system. The updated information has caused information from Page 29 to be displaced to a newly inserted Page 30. Subsequent pages have been renumbered accordingly.

9. Page 31, Sections 14.4b and 14.4c: The Adverse Event Form will be submitted within 14 days after each cycle, so Section 14.4b has been deleted, subsequent sections have been renumbered and the Adverse Event Form has been placed under the new Section 14.4b.

10. Pages 31-32, Sections 14.4a-14.4g: Form numbers have been removed from these sections. Form numbers have also been removed from Section 5.0 (Pages 12 and 15), and 7.9 (Page 18).

Additionally, please note the following change to the Master Forms Set:

The **S0919** Registration Worksheet –Step 1 and the **S0919** Registration Worksheet – Step 2 have been updated to the OPEN registration system standards. The form dates have been updated to 3/1/14; the form numbers have not been changed.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Jean Barce
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Barbara Skinn – B.M.S.

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GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: February 1, 2014
CTEP Submission Date: January 10, 2014

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Chairs: Drs. A.S. Advani, and L.C. Michaelis.

REVISION #6

Study Chair: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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 #6

The protocol has been updated as follows:

1. The Version date of the protocol and Model Consent Form have been updated.

2. Pages 1-3, Title Pages: These pages have been updated to the current SWOG standard. The Study Chairs, Biostatisticians and Agents and Participants lists have been moved to Page 1 and the Table of Contents has been moved to Pages 2-3. Dr. Michaelis' contact information has been updated. The Version Date has been updated.

3. Page 5, Section 2.0: The reference to Section 5.1j has been corrected to 5.1l in the last sentence.

4. Page 5, Section 3.0: Pravastatin has been added to the list of commercially available drugs. The reference to the Physician's Desk Reference has been removed. The last paragraph stating that pravastatin is investigational and instructing to contact SWOG to request the Investigator's Brochure has been removed.

5. Pages 6 and 8, Sections 3.1c and 3.2d: The references to the Physician's Desk Reference have been removed.

6. Page 9, Section 3.3c: The fifth paragraph stating to return unused drug supply has been replaced with the statement that unused drug supplies should not be returned and should be destroyed per local institutional guidelines.

7. Page 13, Section 5.1l: This criterion has been updated to remove the requirement for HIV testing for patients not known to be HIV+ within 14 days prior to registration. The window for HIV+ patients to meet the additional HIV disease criteria has been updated from 14 days to 28 days.

8. Page 16, Section 7.0: Dr. Michaelis' telephone number has been updated. This change has also been made in Section 8.4 (Page 20).

9. Pages 21, 22 and 24, Sections 9.1 and 9.2: The HIV row and corresponding "§" footnote have been removed from Section 9.1, as the test is no longer required. The timeframe of "within 28 days prior to registration" has been added to the "#" footnotes of Sections 9.1 and 9.2, referencing history and physical exam.

10. Page 32, Section 16.0: SWOG's standard confidentiality clause has been added to the end of this section.

11. Page 33, Section 16.1b: The SAE reporting methods have been updated to the current standard. The link to CTEP-AERS has been updated. The requirement to submit SAEs via fax if internet connectivity is disrupted has been removed and a statement has been added advising that paper submissions will no longer be accepted.

12. Pages 33-34, Section 16.1: All instances of NCI's AdEERS system have been updated to the new CTEP Adverse Event Reporting System (CTEP-AERS).

13. Throughout the protocol, Study Coordinator has been updated to Study Chair. This change takes place on the Title Page (Page 1) and in Sections 7.1 (Page 16), 7.3 and 7.4 (Page 17), 8.2a (Page 19), 8.5 (Page 20), and 11.7 (Page 27).

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Jean Barce
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Barbara Skinn – B.M.S.

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GROUP CHAIR'S OFFICE
Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

October 1, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, and L.C. Michaelis.

MEMORANDUM

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

The purpose of this memorandum is to inform sites of an update to the Master Forms Set for the above-referenced study.

The Follow-Up Form (Form # 64587) has been replaced by the Leukemia Follow-Up Form (Form #31244).

The updated form can be accessed on the protocol abstract page of the SWOG website (www.swog.org).

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Jean Barce
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.

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GROUP CHAIR'S OFFICE
Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

September 1, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, and L.C. Michaelis.

MEMORANDUM

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

The purpose of this memorandum is to inform sites of an update to the Master Forms Set for the above-referenced study.

The Prestudy Form has been updated to include a note on the second page stating "if patient's disease status is MDS-related *and* relapsed, select 'Relapsed' and provide both MDS-related and Relapsed information below."

The form number and date have not changed.

The updated form can be accessed on the protocol abstract page of the SWOG website (www.swog.org).

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
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Tracy Maher, C.C.R.P.

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Laurence H. Baker, DO
CHAIR
24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106
734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

May 1, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, and L.C. Michaelis.

MEMORANDUM

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

The purpose of this memorandum is to inform sites of a change in the pravastatin drug return policy for this study.

Bristol-Myers Squibb (BMS), the manufacturer of pravastatin, will no longer require that unused study drug be returned to them upon conclusion of the study. Instead, all unused drug may be destroyed on-site in accordance with institutional policy. Prior authorization for local destruction is not required. Documentation of destruction does not need to be submitted to BMS.

This will be updated in the protocol with the next protocol revision.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Jean Barce
Tracy Maher, C.C.R.P.

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Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: April 1, 2013
CTEP Submission Date: February 25, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, and L.C. Michaelis.

RE-ACTIVATION REVISION

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

RE-ACTIVATION REVISION

Institutions must receive Institutional Review Board (IRB) approval of the Re-Activation Revision prior to enrolling new patients.

Institutions **must** update their local consent forms to include the changes to the Model Consent Form.

Patients currently receiving protocol therapy need not be informed of these changes unless required by the local IRB.

1. Title Page: The title has been updated to replace "relapsed" with "poor-risk". The Version Date has been updated.

2. Page 3, Study Coordinators/Biostatisticians: Dr. Edward Copelan has been replaced with Dr. Laura Michaelis as the secondary Study Coordinator. Corresponding contact information has been updated accordingly. These changes have also been made in Sections 7.0 (Page 16) and 8.4 (Page 20). Cheryl Willman has been removed from the list of Study Coordinators as banking/translational medicine is no longer part of this study. Holly Gundacker has been replaced with Shannon McDonough in the biostatistician's list. Corresponding contact information has been updated accordingly.

3. Page 4, Sections 1.1a and 1.2b-1.2d: Section 1.1a has been updated to include the patient population of "poor-risk patients" (previously relapsed patients). The second sentence has been added to state that CR will be tested independently in two groups of patients: (1) patients with MDS transformed to AML, and (2) refractory or relapsed patients with previous remission < 6 months. Sections 1.2b-1.2d have been updated to reflect that there are now two groups of patients.

4. Page 5, Section 2.0: Information regarding preliminary results has been added as a rationale for study expansion.

5. Pages 5-6, Section 3.0: Information regarding how to obtain Investigators Brochures has been added. The additional information caused information from Page 5 to be displaced to Page 6.

6. Page 10, Section 4.1c: The reference 16 has been corrected to 15.

7. Page 12, Section 5.1a: This section has been revised to include the eligibility requirement for previous MDS diagnosis with current AML diagnosis for patients in the MDS transformed to AML cohort. An allowance for prior non-intensive MDS therapy has been included.

8. Pages 12-14, Sections 5.1b and 5.1d: Section 5.1b has been updated as follows:

   - The section has been reformatted for clarity.
   - The section now indicates that it is only relevant to the relapsed/refractory AML cohort.
   - The allowance for hydroxyurea for high WBC has been added.
   - The requirement that patients not receive chemotherapy within 14 days prior to registration has been added.
   - The sentence regarding relapsed patients achieving remission has been removed and is now 5.1d. The length of remission has been updated from "at least three months" to "< 6 months".
   - The reorganization caused information from Pages 12-13 to be displaced to Pages 13-14.

9. Page 12, Section 5.1c: This section has been added to define requirements for primary refractory patients. Subsequent sections have been renumbered accordingly. Section references have been updated in Sections 2.0 (Page 5) and 9.0 (Page 24).

10. Page 13, Section 5.1e: The second sentence has been updated to require heart scans within 14 days prior to registration for patients that received anthracycline within the normal 28 day window.

11. Page 13, Section 5.1i: The reference to Section 10.8 has been corrected to 10.7.

12. Page 14, Section 5.1m: The prior malignancy exception has been updated to include AML "and MDS". The requirement for toxicity resolution has been updated to exclude MDS and AML treatments.

13. Page 14, Section 5.1: The section number of this heading has been corrected.

14. Page 15, Section 5.2: The section number of this heading has been corrected.

15. Page 15, Section 5.2a: The reference to Section 10.4 was corrected to 10.3.

16. Page 16, Section 6.0: Stratification factors have been added. This addition has caused information from Page 16 to be displaced to Page 17.

17. Page 26, Section 11.1: This section has been updated to include poor-risk patients (previously relapsed patients). The two stratification groups have been added and the statistical cut-points have been updated from CR rate of 30% being of no further interest and 50% being of further interest, to CR rate of 20% being of no further interest and 40% being of further interest.

18. Page 26, Section 11.2: Accrual information in this section has been updated to reflect the two individual cohorts.

19. Page 27, Section 11.3: The toxicity information has been updated to indicate that probability of observing a toxicity can be estimated at $\pm$ 16% (previously 14) and the probability of an occurrence rate of 5% or more has been updated to 85% (previously 92%).

20. Page 27, Section 11.6: The accrual rate has been updated from 2 patients per month over 25 months to 1.5-2 patients per month for MDS cohort and 1-2 patients per month for relapsed/refractory cohort over 25 months.

21. The protocol has been reformatted and repaginated to meet the current requirements for electronic protocol submission. This includes addition of second level headings in instances where they were previously absent, reformatting the title page to include all second level headings, reformatting the protocol calendars into MS Word and removal of the consent form as Section 18.0.

The following changes have been made to the Model Consent Form:

1. Page 3: The title has been updated to replace “relapsed” with “poor-risk”. The number of participants has been updated from 50 to 74.

2. Pages 3-4: The second paragraph on Page 3 has been updated to include refractory patients and patients in the MDS transformed to AML cohort. This addition caused information at the end of Page 3 to be displaced to Page 4.

Additionally, please note that the following forms changes have been made:

- In the Patient Disease and Description section of the Prestudy Form, a question has been added to differentiate between the two cohorts, a field for date of initial MDS diagnosis has been added, and previous response duration has been removed.
- Registration Worksheet – Step 1 has been updated to capture the patient cohort assignment.

The updated forms can be found in the forms packet which can be accessed via the protocol abstract page on the SWOG website (www.swog.org).

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Jean Barce
Tracy Maher, C.C.R.P.

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January 1, 2013

GROUP CHAIR'S OFFICE
Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

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TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL INVESTIGATORS AND CLINICAL RESEARCH ASSOCIATES

FROM: SWOG Operations Office

RE: Eligibility Affirmation

MEMORANDUM

By signing the FDA 1572, every SWOG investigator has agreed to conduct studies in compliance with the protocol, and to personally conduct or supervise the investigation. A critical step in this process is verification of patient eligibility.

Effective January 1st, 2013, every registering investigator or another SWOG investigator designate is required to sign a statement on the Registration Worksheet that the eligibility criteria have been confirmed. This worksheet will not be submitted to Data Operations Office but must be maintained at the local institution for review during audits.

As part of this transition, forms and the forms list (Section 18.2) are being removed from active studies and will be posted separately on the individual protocol abstract page for each study. Subsequent pages have been renumbered accordingly. No other form, protocol, or consent form changes have been made as part of the transition.

If you have any questions, please contact the SWOG Operations Office at 210/614-8808.

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GROUP CHAIR'S OFFICE
Laurence H. Baker, DO
CHAIR
24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106
734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

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Distribution Date: November 1, 2012
E-mailed Date: October 25, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

STATUS NOTICE

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

TEMPORARY CLOSURE

The previously distributed permanent closure was distributed in error. The study will be TEMPORARILY CLOSED during primary analysis **effective November 1, 2012 at 11:59 p.m. Pacific.**

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Jean Barce
Tracy Maher, C.C.R.P.

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October 15, 2012

GROUP CHAIR'S OFFICE
Laurence H. Baker, DO
CHAIR

24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106

734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-16[illegible] AX

1100 Fairview Ave N[illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

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TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

STATUS NOTICE

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.org

IRB Review Requirements

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- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√)Expedited review allowed

( ) No review required

PERMANENT CLOSURE

The above-referenced study has met the necessary accrual for primary analysis, therefore will be **permanently closed effective November 1, 2012 at 11:59 p.m. Pacific.**

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Jean Barce
Tracy Maher, C.C.R.P.

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Laurence H. Baker, DO
CHAIR
24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106
734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: August 1, 2012
E-mailed Date: July 24, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

MEMORANDUM

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.org

IRB Review Requirements

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(√) Expedited review allowed

( ) No review required

MEMORANDUM

The purpose of this memorandum is to inform investigators about a recall of the study drug cytarabine due to particles embedded in the glass at the neck of the vial.

There may be potential for product to come into contact with the embedded particles and the particles may become dislodged into the solution. In the event in which particulate matter could be injected into a patient, there may be the potential for patient injury where medical intervention may be required. Signs and symptoms might include bleeding, bruising, inflammation, itching, rash, chest pain and respiratory symptoms.

See the Press Release for a listing of affected product lot numbers and expiration dates.

BACKGROUND: These products were distributed nationwide to wholesalers and direct customers. Hospira completed an investigation and attributed the root cause to a supplier glass defect. Hospira is arranging for return/replacement etc. of all recalled products. Formal recall letters have been distributed within the US along with notification to safety organizations.

RECOMMENDATION: Anyone with an existing inventory in the United States should stop use and distribution, quarantine the product immediately, and call Stericycle at 1-888-628-0734 between the hours of 8am to 5pm EDT, Monday through Friday, to arrange for the return of the product.

Read the MedWatch safety alert, including a link to the Press Release, at:
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm312048.htm.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Jean Barce
Tracy Maher, C.C.R.P.

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Laurence H. Baker, DO
CHAIR
24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106
734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: May 1, 2012
CTEP Submission Date: March 30, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

REVISION #5

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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 #5

Institutions **must** update their local consent forms to include the changes to the Model Consent Form.

SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes.

Patients currently receiving pravastatin and patients who sign a consent form prior to Institutional Review Board (IRB) approval and local implementation of the consent form changes **must** be informed of these changes. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified at the next visit and this notification process must be documented in the patient chart.

The protocol has been updated as follows:

1. Title Page: The Version Date has been updated.

2. Page 7, Section 3.3b: Reversible cognitive side effects has been added to the first paragraph. Hyperglycemia and increased levels of glycosylated hemoglobin (HbA1c) have been added to the second paragraph.

3. Page 38, Model Consent Form: The following changes have been made:

   Less Likely

   The following have been added:

   - **Memory loss and confusion. This is generally not serious and generally goes away after stopping pravastatin.**
   - **Increased blood sugar**

   Updated in Rare but serious
   "Permanent liver damage" has been updated to "Permanent liver damage. You should tell your doctor if you have unusual fatigue or weakness, loss of appetite, upper belly pain, dark-colored urine or yellowing of the skin or whites of the eyes."

   These changes have been made in response to an FDA MedWatch drug safety communication and labeling change for statin drugs. The MedWatch safety alert, including links to the Recall Notice and Firm Correction Letter can be found at:

   http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm293670.htm

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher, C.C.R.P.

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Laurence H. Baker, DO
CHAIR
24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106
734-998-7130
734-998-7118 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

March 1, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

MEMORANDUM

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

The purpose of this memorandum is to inform investigators about a recall of the study drug cytosine arabinoside due to risk of lack of sterility.

Bedford Laboratories announced a nationwide recall of three lots of cytarabine for injection because vials have a potential risk of a lack of sterility. The risk was determined from a post-release investigation of the manufacturing area.

The affected lots are:

- 2066986
- 2111675
- 2131148

Sites should not use the product lots listed for patient care and should immediately quarantine any product for return. Should sites still have product which is being recalled, they should stop use and contact Bedford Laboratories Client Services at 800/562-4797.

- Complete and submit the report Online: www.fda.gov/MedWatch/report.htm
- Download form or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178

The MedWatch safety alert, including links to the press release can be found at:

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm293132.htm.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher, C.C.R.P.

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Laurence H. Baker, DO
CHAIR
24 Frank Lloyd Wright Dr
PO Box 483
Ann Arbor, MI 48106
734-998-7130
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OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, T X 78229
210-614-8808
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STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: December 1, 2011
CTEP Submission Date: November 8, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

REVISION #4

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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 #4

The protocol has been updated as follows:

1. Title Page: The Version Date has been updated. "Southwest Oncology Group" has been updated to "SWOG" above the title and on the participants list.

2. Pages 10, Section 5.1b: This section has been updated to allow patients achieving previous CRi to be eligible (previously required CR).

3. Master Forms Set: The **S0919** Prestudy Form has been updated to include the new CRi allowance. The form number has been updated from #5593 to #63222. The number has also been updated in Sections 5.0 (Page 10), 14.4 (Page 24) and 18.2c (Page 31).

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: September 1, 2010
CTEP Submission Date: August 30, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

REVISION #3

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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 has been updated as follows:

1. Title Page: The Version Date has been updated.

2. Pages 16-16a, Section 8.1: The criteria for reporting Adverse Events have been updated. **Effective October 1, 2010** CTCAE Version 4.0 will be utilized for SAE reporting. The CTCAE Version 3.0 will continue to be used for routine toxicity reporting. Page 16a was added to prevent extensive repagination.

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

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher
Camille White, C.C.R.P.

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: April 15, 2010
CTEP Submission Date: March 22, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

REVISION #2

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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 primary purpose of this revision is to remove the specimen submission requirements and instructions for **SWOG-9007**, "Cytogenetic Studies in Leukemia Patients" and **S9910**, "Leukemia Centralized Reference Laboratories and Tissue Repositories, Ancillary", as funding for specimen submission is no longer available for patients on **S0919**. The protocol has been updated as follows:

1. Title Page: The Version Date has been updated.

2. Pages 11-12, Sections 5.1m-5.1n: Section 5.1m, previously containing the requirement for registration to **SWOG-9007** has been updated to require submission of specimens obtained within 28 days prior to registration to the site's preferred cytogenetics lab. The note regarding submission of specimens at additional timepoints has been deleted. Section 5.1n, previously containing the requirement that patients be offered participation in **S9910**, has been deleted. Subsequent sections on Pages 11-12 have been renumbered accordingly. A reference to Section 5.1o has been updated to 5.1n in Section 9.1 (Page 18).

3. Page 14, Section 7.1: A sentence has been added advising that if an individual test is determined to be unnecessary, the rationale for not conducting the test must be documented in the medical record.

4. Page 16, Section 7.7: The last sentence of this section referencing central submission of specimens for cytogenetic studies has been deleted.

5. Pages 18-19, Sections 9.1-9.2: The "SPECIMEN SUBMISSION" and "BM Aspirate" rows and the "†" footnotes have been deleted from both Sections 9.1 and 9.2. The timing for performing serum creatinine, total bilirubin and SGOT and SGPT testing has been updated to Days 1 and 4-7 during Induction (Section 9.1) and to Days 1, 4 and 5 during Consolidation (Section 9.2). These changes have been made both in the calendars and in the "α" footnotes.

6. Page 22, Section 13.3: The SWOG Operations Office telephone number has been updated in this section. Similar changes have been made in Sections 14.3a (Page 24) and 16.1e (Page 28). The fax number has been updated in Table 16.1 (Page 29). The address has been updated in Section 16.1f (Page 29).

7. Page 24, Sections 14.4, 14.5 and 14.8: The heading of Section 14.4 has been updated to require submission of the outlined items within 7 days of registration (previously required within 14 days of registration). The requirement for submission of the pretreatment cytogenetics report has been added to Section 14.4. The references to Section 15.0 for specimen submission requirements have been deleted from Sections 14.5 and 14.8.

8. Pages 25-26, Sections 15.1-15.3: Information in Section 15.2, previously requiring specimen submission to **SWOG-9007** for cytogenetic studies, has been updated to instruct sites to submit specimens to their preferred cytogenetics laboratory at the outlined timepoints and submit reports of results as outlined in Section 14.0. Section 15.3, previously requesting submission of specimens to **S9910** has been deleted. As no central specimen submission will be taking place, Section 15.1, previously containing general instructions for central specimen submissions, has been deleted. Section 15.2 has been renumbered to Section 15.1.

9. Page 32, Model Consent Form: The note requiring sites to obtain approval from the Southwest Oncology Group Operations Office prior to making changes to questions related to banking of specimens for future research has been deleted, as it is no longer relevant.

10. Page 36, Model Consent Form: In the "During the study…" section, the information regarding additional samples submitted for molecular studies and banking has been removed.

11. Pages 42-46, Model Consent Form: Question #2 (*Future Use of Specimens*), the *Consent Form for Use of Specimens for Research*, and the *Specimen Consent Supplemental Sheets* have been removed. Pages 43-46 have been left blank to prevent extensive repagination.

12. Master Forms Set: The **S0919** Registration Worksheet has been updated to remove the questions regarding future use of specimens. The form number has been updated from #31039 to #57099. The form number has also been updated in Section 18.2 (Page 31).

Institutions **must** update their local consent forms to include the changes to the Model Consent Form.

The Southwest Oncology Group considers that the Model Consent Form changes **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes.

Patients currently on treatment **must** be informed of these changes. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified at the next visit and this notification process must be documented in the patient chart.

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

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher
Camille White, C.C.R.P.

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: January 15, 2010
CTEP Submission Date: January 6, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

REVISION #1

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

1. Ken Kopecky, Ph.D. has been replaced by Megan Othus, Ph.D. in the biostatisticians list. Corresponding contact information has been updated accordingly. The Version Date has been updated.

2. Page 7, Section 3.3c: The ordering instructions in this section have been updated so that initial drug supply may be ordered after local IRB approval of the protocol (previously after patient registration). Information advising that the SWOG patient ID would be required at the time of drug order has been replaced with information advising that the date of IRB approval will be required. A sentence has been added to the re-supply information indicating that the number of patients currently on study at the requesting institution will be required at the time of drug re-order.

3. Page 18, Section 9.1: The Weeks 2-7 columns of the "BM Aspirate" row have been merged and "Хд" has been added. The associated "д" footnote has been updated to state that the specimen must be obtained after completion of Induction therapy "at time of hematologic recovery or on Day 45, whichever comes first" (previously only stated "after completion of Induction therapy or by Day 45"). These changes have been made in order to clarify specimen submission requirements.

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

cc: PROTOCOL & INFORMATION OFFICE
Kenneth J. Kopecky, Ph.D.
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher
Camille White, C.C.R.P.

Southwest
Oncology Group
A National Clinical Research Group

January 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

MEMORANDUM

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

The purpose of this memorandum is to inform sites of updated protocol requirements necessary as a result of the memorandum regarding the change in reimbursements for leukemia specimen submissions, distributed 1/11/10.

Until further notice, institutions will not be required to register patients to **SWOG-9007**, "Cytogenetic Studies in Leukemia Patients" or to offer patients participation on study **S9910**, "Leukemia Centralized Reference Laboratories and Tissue Repositories, Ancillary" as part of the eligibility criteria for the study **S0919**.

The Southwest Oncology Group considers this change to be administrative, and therefore does not require that this information be IRB approved prior to institutional implementation.

It is requested that institutions perform local cytogenetic studies according to the schedule in Section 15.2 of protocol **S0919**, and that copies of the cytogenetics reports be obtained and kept in the patient's medical record.

A protocol revision to indicate this information, and to provide information about how to submit the cytogenetics reports, is forthcoming.

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

cc: PROTOCOL & INFORMATION OFFICE
Kenneth J. Kopecky, Ph.D.
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher
Camille White, C.C.R.P.

Southwest
Oncology Group
A National Clinical Research Group

December 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

MEMORANDUM

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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

The purpose of this memorandum is to inform sites of a change in drug ordering information for pravastatin. Pravastatin may now be ordered at the time of IRB approval prior to patient enrollment. This change is being made in order to ensure that drug will arrive in time for treatment. Please note that the date of IRB approval will be required at the time of the initial order. An updated drug order form is now available on the protocol abstract page of the Southwest Oncology Group website (swog.org). This change will be made in the protocol document with the first protocol revision/amendment.

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

cc: PROTOCOL & INFORMATION OFFICE
Kenneth J. Kopecky, Ph.D.
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher
Camille White, C.C.R.P.

Southwest
Oncology Group
A National Clinical Research Group

August 15, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0919**, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Relapsed Acute Myelogenous Leukemia." Study Coordinators: Drs. A.S. Advani, E.A. Copelan and C.L. Willman.

STATUS NOTICE

Study Coordinator: Anjali S. Advani, M.D.
Phone number: 216/445-9354
E-mail: advania@ccf.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.

Please submit this to your IRB.

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

cc: PROTOCOL & INFORMATION OFFICE
Kenneth J. Kopecky, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher
Camille White, C.C.R.P.

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activated August 15, 2009

SWOG

A PHASE II STUDY OF IDARUBICIN AND ARA-C IN COMBINATION WITH PRAVASTATIN FOR POOR-RISK ACUTE MYELOGENOUS LEUKEMIA (AML)

NCT #0084017

STUDY CHAIRS:

Anjali S. Advani, M.D. (Medical Oncology)
Cleveland Clinic Foundation
Hematologic Oncology and Blood Disorders
Desk R35, 9500 Euclid Avenue
Cleveland, OH 44195
Phone: 216/445-9354
FAX: 216/444-9464
E-mail: advania@ccf.org

Laura C. Michaelis, M.D. (Medical Oncology)
Medical College of Wisconsin
Froedtert Medical Center
9200 W. Wisconsin Avenue
Milwaukee, WI 53226
Phone: 414/805-1118
FAX: 414/805-4606
E-mail: lmichaelis@mcw.edu

ECOG-ACRIN CHAMPION:

Ehab Attallah, M.D.
Medical College of Wisconsin

AGENTS:

Cytosine Arabinoside (Ara-C)
(Cytarabine) (Cytosar U)
(NSC-63878)
Idarubicin HCL (Idamycin®)
(NSC-256439)
Pravastatin Sodium (NSC-740787)

BIOSTATISTICIANS:

Anna Moseley, M.S. (Biostatistics)
Megan Othus, Ph.D. (Biostatistics)
SWOG Statistical Center
At Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: amoseley@fredhutch.org
E-mail: mothus@fhcrc.org

PARTICIPANTS

ALLIANCE/Alliance for Clinical Trials in Oncology

ECOG-ACRIN/ECOG-ACRIN Cancer Research Group

SWOG/SWOG

TABLE OF CONTENTS

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section for instructions on using the OPEN system.	Online Data Submission: Institutions participating through the CTSU are required to submit and amend their data electronically via Online Data Submission. Access the SWOG Workbench using your CTSU user ID and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx. Exceptions: Data items that are not available for online submission (operative and pathology reports, scan reports, etc.) may be submitted by fax at 800-892-4007. Do not submit data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility questions contact the SWOG Data Operations Center by phone or email: 206-652-2267 leukemiaquestion@crab.org **For treatment or toxicity related questions** contact the Study Chairs at S0919@swog.org.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: 888-823-5923 ctsucontact@westat.com All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website: https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.org		

1.0 OBJECTIVES

1.1 Primary Objective

a. To test whether the complete remission (CR) rate (including CR with incomplete recovery [CRi]) in poor-risk patients with acute myeloid leukemia (AML) treated with a combination of chemotherapy and pravastatin is sufficiently high to warrant Phase III investigation. This will be tested independently in two groups of patients: (1) patients with MDS transformed to AML, and (2) refractory or relapsed patients with previous remission < 6 months.

1.2 Secondary Objectives

a. To estimate the frequency and severity of toxicities of this regimen in these two groups of patients.

1.3 Other Objectives

a. To estimate relapse-free survival and overall survival rates in these two groups of patients.

b. To evaluate in a preliminary manner whether prestudy cytogenetic features correlate with response in these two groups of patients.

2.0 BACKGROUND

Acute myelogenous leukemia (AML) is a difficult disease to treat. Although 65% of patients achieve CR with chemotherapy, only 15-30% of these patients remain free of disease for five years because of the high incidence of relapse. *(1)* Another 10-20% of patients have refractory AML and never achieve CR with induction chemotherapy. *(1)* Over the last several years, there has been excitement about the possibility of combining biologically targeted therapy in the treatment of various diseases including AML. Although AML is genetically heterogeneous, AML cells do share biologic characteristics that make molecular targeted therapies potentially effective. This study will evaluate chemotherapy in combination with pravastatin.

Cholesterol and AML

Cholesterol homeostasis is abnormal in AML cells, with cholesterol synthesis and LDL processing being hyperactive in cultured AML cells. *(2-5)* Cultured AML cells frequently overexpress the genes for low-density lipoprotein receptor (LDL), 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoAR), synthesize cholesterol at a higher level, and import more cholesterol. *(6)* Patients with AML often have hypercholesteremia at the time of diagnosis, but this typically resolves when patients achieve a complete remission. *(2,7)* This suggests that AML cells require high levels of cholesterol for their survival, and that abnormalities in cholesterol homestasis protect AML cells. *(2)* Therefore, the cholesterol pathway may be a valid target in the treatment of AML. In vitro, simvastatin, an HMG-CoA reductase inhibitor, inhibits AML cell growth. *(8)* HMG CoA reductase is the major regulatory enzyme of the mevalonate pathway. Mevalonate constitutes the precursor of isoprene units incorporated into sterol and non-sterol compounds such as cholesterol. Blocking protein geranylgeranylation appears to be essential for statin-induced apoptosis of human AML cells. *(9)*

Rationale for combining pravastatin with chemotherapy:

Cholesterol levels further increase in many AML cells treated with chemotherapy. *(6,10)* This occurs by chemotherapy increasing the level of LDL receptor and HMG-CoA reductase mRNA levels in AML cells. *(2)* Conversely, inhibiting cholesterol synthesis sensitizes AML cells to cytotoxic therapy. *(6,11,12)* This was the basis of a recently published Phase I study combining pravastatin with idarubicin and intermediate dose cytarabine. *(6)* This study demonstrated the safety of combining pravastatin with intermediate dose cytarabine and idarubicin. *(6)* Pravastatin

was chosen because of its high bioavailability, and because it is not substantially metabolized by the cytochrome p450 system. *(6)* Many other treatments and supportive care medications used in the treatment of AML patients (i.e. antifungals) are CYP substrates; therefore, choosing a statin that is not metabolized by the CYP system is important. A maximum tolerated dose (MTD) for pravastatin and idarubicin/intermediate dose cytarabine was not reached. However, pharmacokinetic studies demonstrated higher and more sustained serum pravastatin levels with pravastatin doses above 1,280 mg/day. *(6)* The CR and CRp rates were encouraging (including 8 of 10 with unfavorable cytogenetics and 9 of 22 salvage patients), suggesting that Phase II evaluation of this approach is warranted.

S0919 was initially designed for patients with relapsed AML, where the patient's preceding remission had lasted ≥ 3 months. The null response rate was 30%. The study closed to accrual on Nov 1, 2012 after meeting the defined criterion for a positive study; and the results are being submitted to the American Society of Clinical Oncology meeting. Based on the promising results from this trial, the trial has now been amended to evaluate this therapeutic regimen in poor-risk patients (patients with newly diagnosed AML arising out of myelodysplastic syndrome, primary refractory AML, and relapsed AML with the patient's preceding remission lasting < 6 months).

Inclusion of Women and Minorities

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

Since HIV-positive patients are immunocompromised and most are treated with already myelosuppressive antiretroviral regimens, they may not tolerate intensive chemotherapies. Therefore, patients with HIV infection will be excluded from this study, if they do not meet the parameters that are felt will allow safe participation in this study. HIV infected patients with no history of AIDS defining events, sufficient CD4 cell count, acceptable viral load and who are not receiving the myelosuppressive agents zidovudine or stavudine will be included in this study (see Section 5.1l).

3.0 DRUG INFORMATION

Investigator's Brochures

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this study, AraC, idarubicin and pravastatin are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the prescribing information and other resources.

3.1 Cytosine Arabinoside (Ara-C) (Cytarabine) (Cytosar U) (NSC-63878)

a. DESCRIPTION

AraC is chemically 4-amino-1-S-D-arabino-furanosyl-2(1H)-primidinone. AraC is metabolized to its active form, ara-CTP. The ara-CTP functions as an inhibitor of DNA polymerase. Ara-C exhibits cell phase specificity, killing cells undergoing DNA synthesis (S phase) and may also block cells from progressing to S phase from G1. Extensive chromosomal damage, including chromatid breaks, occurs. AraC appears to be most effective in tumors with high growth fraction.

b. TOXICOLOGY

Human Toxicology: Side effects of AraC include myelosuppression, nausea, vomiting, diarrhea, anorexia, anal ulceration, stomatitis, rash, headache, fever, myalgia, malaise, bone pain, chest pain, hepatic and renal dysfunction, and alopecia. Central nervous system toxicity, i.e., significant cerebral and cerebellar dysfunction, progression to coma, has been seen with high doses. Severe cardiomyopathy has been reported with high dose AraC in combination with cyclophosphamide. Progressive ascending paralysis has occurred in two patients receiving IV and intrathecal AraC. Marked keratoconjunctivitis has also occurred with high doses.

The most frequently reported reactions after intrathecal administration were nausea, vomiting and fever. Paraplegia and meningitis have been reported with intrathecal administration. AraC given intrathecally may cause systemic toxicity and careful monitoring of the hemopoietic system is indicated. If used intrathecally or if high dose therapy is used, do not use a diluent containing benzyl alcohol.

AraC can cause fetal harm when administered to a pregnant woman, however, there are no adequate and well controlled studies in pregnant women.

c. PHARMACOLOGY

Kinetics: AraC is metabolized by deoxycytidine kinase and related kinases to nucleotide triphosphate, which is an active inhibitor of DNA polymerase. Deoxycytidine prevents or delays cytotoxic activity. The active form is converted to nontoxic uracil derivatives by pyrimidine nucleoside deaminases. The balance of kinase and deaminase levels appears to be an important factor in sensitivity/resistance of the cell to AraC. After IV injection, plasma disappearance of ara-C is biphasic. Initial half-life is 10 minutes, delayed half-life is 1 - 3 hours. After 24 hours, 80% is excreted in the urine as its inactive metabolite, AraI. After a single IV administration of AraC, levels in CSF are low. With intrathecal administration, half-life is 2 hours. There is little conversion to AraU because of low CSF levels of deaminase. Drug interaction of AraC has been reported with digoxin, gentamycin and fluorocytocine.

Formulation: AraC is supplied as a sterile powder in 100 mg and 500 mg vials for injection. AraC is also available in 1 and 2 gram vials. The drug should be reconstituted with sterile water for injection.

Storage and Stability: The sterile powder should be stored at room temperature 15° - 30°C (59° - 86°). The resulting solution has a stability of 48 hours if stored at ROOM TEMPERATURE. Do not use if even a slight haze develops. The reconstituted solution may be further diluted in 5% Dextrose or sodium chloride injection.

Administration: AraC is usually administered by continuous IV infusion, but IV bolus and subcutaneous use have their place in treating certain leukemic responses (i.e., maintenance or remission). In this study, AraC will be administered by continuous infusion.

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

Please refer to the package insert for complete information.

3.2 Idarubicin HCL (Idamycin®) (NSC-256439)

a. DESCRIPTION

A sterile, synthetic antineoplastic anthracycline for intravenous use. Idarubicin is a DNA-intercalating analog of daunorubicin which has an inhibitory effect on nucleic acid synthesis and interacts with the enzyme topoisomerase II.

b. TOXICOLOGY

Idarubicin is a potent bone marrow suppressant. Idarubicin should not be given to patients with pre-existing bone marrow suppression induced by previous drug therapy. Deaths due to infection and/or bleeding have been reported during the period of severe myelosuppression. Other warnings include pre-existing heart disease, previous therapy with anthracyclines, previous radiation to the mediastinal-pericardial area, myocardial toxicity typically presenting as CHF, and arrhythmias or other cardiomyopathies. Other risks include bone marrow depression, infections, leukemic pericarditis and/or myocarditis, and renal or hepatic impairment. The most common side effects (90% to 100%): infection. Other common side effects include (20% to 90%): nausea, vomiting, hair loss, abdominal cramps, diarrhea, hemorrhage, mucositis, dermatologic, mental status, pulmonary-clinical, fever, headache. Other less common side effects include (10% to 20%): cardiac-clinical. Infrequent side effects include (1% to 10%): Neurologic-peripheral nerves, pulmonary allergy, seizure, cerebellar. Rare side effects include (less than 1%): None reported in this range.

c. PREGNANCY AND LACTATION

Pregnancy Category D- Idarubicin was embryotoxic and teratogenic in the rat. Idarubicin was embryotoxic but not teratogenic in the rabbit. There is no conclusive information about idarubicin adversely affecting human fertility or causing teratogenesis. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from idarubicin mothers should discontinue nursing prior to taking this drug. There has been one case reported of fetal fatality after maternal exposure to idarubicin during the 2nd trimester.

d. PHARMACOLOGY

Kinetics: The plasma concentrations follow a 2 or 3 compartment mode. Idarubicin has a rapid distribution phase with a high volume of distribution reflecting extensive tissue binding. Idarubicin undergoes extensive extrahepatic metabolism and a rapid distribution phase. Idarubicin has a very high volume of distribution. Elimination occurs predominantly by biliary and to a lesser extent by renal excretion. The mean terminal half-life is 22 hours when used as a single agent and 20 hours when used in combination. Elimination exceeds 45 hours.

Formulation: Idarubicin is a sterile, red-orange, isotonic parenteral preservative-free solution. It is available in 5mg/5ml, 10mg/10ml and 20mg/20ml single use only vials.

Storage and Stability: Idarubicin should be stored under refrigeration 2° - 8°C (36° to 46 °F), and protected from light. The vials are preservative-free and are for single use only.

Administration: Idarubicin should be administered over 10 - 15 minutes into a freely flowing line of NS or D5W. Unless there is specific data do not mix idarubicin with other drugs. Prolonged contact in an alkaline pH will degrade Idarubicin. Precipitation occurs with heparin. Extravasation can cause severe local tissue necrosis. Extravasation may occur with or without an accompanying burning sensation and even if blood returns well on aspiration of the infusion needle. If extravasation occurs terminate infusion immediately and restart in another vein. Treat extravasation with intermittent ice packs (Place ice pack on area of extravasation for 1/2 hour immediately, then for 1/2 hour four times a day for 3 days) and elevate the affected extremity. For more information see package insert and seek further medical treatment as deemed necessary.

Supplier: Idarubicin HCL is commercially available and therefore should be purchased by a third party. This drug will NOT be supplied by the NCI.

Please refer to the package insert for complete information.

3.3 Pravastatin Sodium (NSC-740787)

a. DESCRIPTION

Pravastatin sodium is a 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitor. HMG-CoA reductase catalyzes the early rate-limiting step of cholesterol biosynthesis, the conversion of HMG-CoA to mevalonate. The competitive inhibition of this enzyme results in reduced cholesterol biosynthesis.

b. TOXICOLOGY

Human toxicology: Side effects of pravastatin include chest pain, headache, fatigue, dizziness, rash, nausea, vomiting, diarrhea, heartburn, transaminase increase, myalgia, cough, and reversible cognitive side effects.

There have been case reports of hyperglycemia, increased levels of glycosylated hemoglobin (HbA1c), anaphylaxis, jaundice, cirrhosis, hepatitis, rhabdomyolysis, and Stevens-Johnson syndrome.

Safety in pregnant women has not been established. It is recommended that pravastatin be discontinued as soon as pregnancy is recognized.

c. PHARMACOLOGY

Kinetics: Pravastatin reduces the available intracellular amount of cholesterol after taken orally. This results in an increase in LDL-receptors and enhanced clearance of LDL from the serum. Pravastatin also inhibits LDL production by blocking the synthesis of VLDL, which is a building block for LDL. Pravastatin is rapidly absorbed producing peak levels 1 to 1.5 hours after taking the oral tablet. The half-life of the parent compound is 2-3 hours with 20% of the dose being excreted in the urine and 70% in the feces.

Formulation: Pravastatin is available as an oral tablet in 10 mg, 20 mg, 40 mg, and 80 mg tablets.

Storage and Stability: Pravastatin tablets should be stored at room temperature for distribution by Fisher-Acculogix (25ºC) with excursions allowed to 15-30ºC (59-8 ºF). Tablets should be protected from moisture and light.

Administration: For this study, pravastatin should be administered as a single dose (over up to 2 hours) once daily in the morning. It can be taken with or without food.

Supplier and Drug Ordering: For this study, pravastatin will be supplied free of charge by Bristol-Myers Squibb.

Initial Orders: Institutions may order pravastatin after local IRB approval of the protocol. The IRB approval date will be required at the time of drug order. Orders should be placed at the time of IRB approval. Do not wait until the time of patient registration as drug may not arrive in time to begin treatment. Participating institutions are instructed to order from Bristol-Myers Squibb via e-mail to bms.ist@acculogix-usa.com by submitting the Bristol-Myers Squibb order form (which is located on the protocol abstract page at www.swog.org). Please note: Both the SWOG study ID (**S0919**) and the BMS ID (CV123-285) will be required and must be recorded in the subject line of the e-mail request. Drug will be shipped within five days from receipt of Drug Order Form. Drug is shipped overnight Monday-Thursday for delivery on Tuesday-Friday. Drug will not be shipped on weekends or holidays. Only study drug ordered for this study may be used for protocol treatment.

Re-Supply: Send re-supply requests to Sashin.Bhuta@bms.com. Check "re-supply" on the drug supply form. The number of patients currently on study at the requesting institution will be required at the time of drug re-order. Re-supply requests should be submitted at least 5-7 business days prior to the expected delivery date. Deliveries will be made Tuesday-Friday. When assessing need for re-supply, institutions should keep in mind the number of pills used for treatment and that shipment may take 5 days from BMS receipt of request.

Drug Returns: Unused drug supplies should NOT be returned. Unused drug should be destroyed per local institutional guidelines.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and disposal of all drugs received from the supplier using the NCI Oral Drug Accountability Record Form (NCI Oral DARF) available at http://ctep.cancer.gov.

Question about drug orders, returns, or accountability should be addressed to the Fisher-Acculogix IS Coordinator. Contact information is provided on the drug order form.

Please refer to the product's package insert for full prescribing and toxicity information.

4.0 DIAGNOSTIC AND STAGING CRITERIA

4.1 Diagnostic Criteria *(13-15)*

a. Definitions:

1. Bone marrow cellularity: The volume of hematopoietic nucleated cells, expressed as a percentage of marrow volume less volume of fibrosis.

2. Blasts: For AML, the following cell types are considered equivalent to blasts and are included in the calculation of blast percentages. Note that erythroblasts are **not** counted as blasts in calculating blast percentages.

i. Myeloblasts include both agranular and granular variants.

ii. Neoplastic promyelocytes, for Acute Promyelocytic Leukemia. Neoplastic promyelocytes are defined as promyelocytes with heavy granulation and irregular nuclei and/or primitive promyelocytes with very large numerous Auer rods.

iii. Monoblasts and promonocytes for Acute Monoblastic and Monocytic Leukemia.

iv. Megakaryoblasts for Acute Megakaryoblastic Leukemia.

3. Bone Marrow Blast Percentage is calculated as the percent of blasts among all nucleated marrow cells.

b. Acute Myeloid Leukemia (AML) is a clonal expansion of myeloid blasts in bone marrow, blood or other tissue, ICD-O code 9861/3.

The most significant change from the FAB classification is that the requisite blast percentage for a diagnosis of acute myeloid leukemia be ≥ 20% myeloblasts in the blood or marrow.

There are two exceptions to this rule. Acute erythroleukemia (erythroid/myeloid subtype) is defined by the presence in the bone marrow of greater than or equal to 50% erythroid precursors in the entire nucleated cell population and greater than or equal to 20% myeloblasts in the non-erythroid cell population. Pure erythroid leukemia is defined as a neoplastic proliferation of immature cells committed exclusively to the erythroid lineage (> 80% of the marrow nucleated cells) with no evidence of a significant myeloblastic component.

c. Myelodysplastic Syndrome (MDS) is defined according to WHO criteria. *(15)*

d. WHO Classification of AML, with the following additions and clarifications. *(15)*

WHO histological classification of acute myeloid leukemias

	ICD-O Code	FAB Equivalent
Acute myeloid leukemia with recurrent genetic abnormalities		
Acute myeloid leukemia with t(8;21)(q22;q22); *(AML 1/ CBFa)/ETO)*	9896/3	
Acute myeloid leukemia with abnormal bone marrow eosinophils inv(16)(p13q22) or t(16;16)(p13;q22); *(CBFb/MYH11)*	9871/3	
Acute promyelocytic leukemia (AML with t(15;17)(q22;q12) *(PML/RARa)* and variants	9866/3	M3
Acute myeloid leukemia with 11q23 *(MLL)* abnormalities	9897/3	
Acute myeloid leukemia with multilineage dysplasia	9895/3	
Acute myeloid leukemia and myelodysplastic syndromes, therapy-related	9920/3	

Acute myeloid leukemia not otherwise categorized	9861/3	
Acute myeloid leukemia minimally differentiated	9872/3	M0
Acute myeloid leukemia without maturation	9873/3	M1
Acute myeloid leukemia with maturation	9874/3	M2
Acute myelomonocytic leukemia	9867/3	M4
Acute monoblastic and monocytic leukemia	9891/3	M5a, M5b
Acute erythroid leukemias	9840/3	M6a, M6b
Acute megakaryoblastic leukemia	9910/3	M7
Acute basophilic leukemia	9870/3	
Acute panmyelosis with myelofibrosis	9931/3	
Myeloid sarcoma	9930/3	
Acute leukemia of ambiguous lineage	9805/3	
Undifferentiated acute leukemia	9801/3	
Bilineal acute leukemia	9805/3	
Biphenotypic acute leukemia	9805/3	

4.2 Staging Criteria

Staging criteria are not applicable to this protocol.

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 criterion requiring test results and dates, please record this information on the Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 or leukemiaquestion@crab.org prior to registration.

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 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

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

5.1 Induction Registration (Step 1)

_____ a. For patients registered to the relapsed/refractory cohort (Cohort 2), patients must have a previous morphologically confirmed diagnosis of acute myeloid leukemia (AML).

For patients registered to the MDS transformed to AML cohort (Cohort 1), patients must have a previous morphologically confirmed diagnosis of MDS/CMML. Patients may have received previous non-intensive therapy (e.g. azacitadine, decitabine, low-dose cytarabine (LDAC), lenalidomide) given for treatment of MDS/CMML (with up to 20% blasts). At the time of registration they must have a morphologically confirmed diagnosis of AML.

Note: This protocol uses the WHO diagnostic criteria for AML (see Section 4.1). Patients with acute promyelocytic leukemia (APL, FAB, M3) or blastic transformation of chronic myelogenous leukemia are not eligible.

_____ b. Patients must NOT have received autologous or allogeneic stem cell transplantation.

Patients in the relapsed/refractory AML cohort (Cohort 2), must meet all of the following additional criteria:

1. Patient must have received at least one prior Induction chemotherapy regimen for their AML;
   - they may have received any type of chemotherapy
   - administration of hydroxyurea to control high WBC prior to, during, and after registration is permitted

2. Relapse or refractory disease must be documented by a bone marrow examination demonstrating > 5% blasts in the bone marrow not attributable to another cause;

3. Patient must NOT have received chemotherapy within 14 days prior to registration;

_____ d. Primary refractory patients will be eligible if, on Day 14 of their previous chemotherapy regimen, they have significant residual disease. Patients who received only hypomethylating agent or low dose therapy for Induction are not considered primary refractory for purposes of this study and are not eligible.

_____ e. Relapsed patients must have achieved a complete remission (CR) or CR with incomplete blood count recovery (CRi) lasting < 6 months with their last induction regimen.

SWOG Patient No. _____

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

5.1 Induction Registration (Step 1) (contd.):

_____ f. Patients must not have symptomatic congestive heart failure, coronary artery disease, cardiomyopathy, or uncontrolled arrhythmias. Either an echocardiogram or MUGA scan with an ejection fraction ≥ 45% must be obtained within 28 days prior to registration, or within 14 days prior to registration if the patient has received anthracycline in the 28 day window. (Either method for measuring cardiac function is acceptable; however, the same scan must be used throughout treatment and follow-up to monitor the patient for cardiac toxicity.) If the patient has symptoms suggestive of ischemia or congestive heart failure after that cardiac evaluation was done, a repeat study must be obtained prior to registration.

_____ f. Patients must have a serum creatinine < 2.0 mg/dl within 14 days prior to registration.

_____ g. Patients must have a total bilirubin ≤ 2.0 x Institutional Upper Limit of Normal (IULN) within 14 days prior to registration, unless the elevation is due primarily to elevated unconjugated hyperbilirubinemia secondary to Gilbert's syndrome or hemolysis and not to liver dysfunction.

_____ h. Patients must have SGOT (AST) ≤ 3.0 x IULN *and* SGPT (ALT) ≤ 3.0 x IULN within 14 days prior to registration. Treatment may begin with SGOT/SGPT above those limits, if the abnormalities are thought to be due to the patient's leukemia.

_____ i. Patients must have Zubrod performance status of 0-2 (see Section 10.7).

_____ j. Patients must be ≥ 18 years of age.

_____ k. Patients must not have clinical evidence of leptomeningeal disease (a spinal tap does not need to be performed).

_____ l. Patients who are known to be HIV+ may be eligible providing they meet all of the following additional criteria within 28 days prior to registration:

1. Patient must have no history of AIDS defining events.
2. CD4 cells ≥ 500/mm^3.
3. Viral load of < 50 copies HIV mRNA/mm^3 if on cART or < 25,000 copies HIV mRNA if not on cART.
4. No zidovudine or stavudine as part of cART.

Patients who are HIV+ and do not meet all of these criteria will not be eligible for this study.

SWOG Patient No. _____

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

5.1 Induction Registration (Step 1) (contd.):

_____ m. Patients with prior malignancy (other than AML and MDS/CMML) are eligible. However, the patient must be in remission from the prior malignancy and have completed all chemotherapy and radiotherapy at least 6 months prior to registration. Except for AML and MDS treatment, all treatment related toxicities must have been resolved.

NOTE: For patients with prior history of malignancy who have received anthracyclines or mediastinal/pericardial radiation in the past, the risk versus benefit of therapy should be weighed, particularly in the setting of receiving consolidation therapy.

_____ n. Patients must not have a systemic fungal, bacterial, viral or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).

_____ o. Pretreatment cytogenetics must be performed on all patients. Collection of pretreatment specimens must be completed within 28 days prior to registration to **S0919**. Specimens must be submitted to the site's preferred cytogenetics laboratory (see Section 15.1).

_____ p. Women of reproductive potential must have a negative pregnancy test within 14 days prior to registration. Patients must not be pregnant or nursing because of the teratogenic potential of the drugs used in this study. Women/men of reproductive potential must have agreed to use an effective contraceptive method.

_____ q. Patients must have complete history and physical examination within 28 days prior to registration.

_____ r. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ s. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

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 criterion requiring test results and dates, please record this information on the **S0919** Consolidation Eligibility Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 or leukemiaquestion@crab.org prior to registration.

SWOG Patient No. _____

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

5.2 Consolidation Registration (Step 2)

After completing Induction therapy, patients may be registered for Consolidation therapy **provided** that they were eligible for the initial registration and satisfy the following additional criteria at the time of Consolidation registration:

_____ a. Patients must have achieved CR as defined in Section 10.1c. Patients who achieved only CRi or PR, and patients who relapse from CR (Section 10.3) before this registration are not eligible.

_____ b. Patients must not have symptomatic congestive heart failure, coronary artery disease, cardiomyopathy, or uncontrolled arrhythmias. Either an echocardiogram or MUGA scan with an ejection fraction ≥ 45% must be obtained within 14 days prior to registration. (The same scan that was used during induction registration must be used for consolidation registration.) The ejection fraction must not have dropped ≥ 10% from the baseline ejection fraction. If patient has had symptoms suggestive of ischemia or congestive heart failure after that cardiac evaluation was done, a repeat study must be obtained prior to registration.

_____ c. Patients must have a serum creatinine < 2.0 mg/dl within 14 days prior to registration.

_____ d. Patients must have a total bilirubin ≤ 2.0 x Institutional Upper Limit of Normal (IULN) within 14 days prior to registration, unless the elevation is due primarily to elevated unconjugated hyperbilirubinemia secondary to Gilbert's syndrome or hemolysis and not to liver dysfunction.

_____ e. Patients must have SGOT (AST) ≤ 3.0 x IULN *and* SGPT (ALT) ≤ 3.0 x IULN within 14 days prior to registration.

_____ f. Patients must have Zubrod performance status of 0-2 (see **Section 10.8**).

_____ g. Patients must not have a systemic fungal, bacterial, viral or other infection that is not controlled (defined as exhibiting ongoing signs/symptoms related to the infection and without improvement, despite appropriate antibiotics or other treatment).

_____ h. Patients must have ANC ≥ 1,000/mcl and platelets ≥ 100,000/mcl within 7 days prior to registration.

_____ i. Patients must be registered to Consolidation therapy (Step 2) within 60 days of beginning Induction therapy (with Day 1 being the start of Induction).

6.0 STRATIFICATION FACTORS

Patients will be stratified according to disease status defined as follows:

(1) Patients with MDS transformed to AML

(2) Refractory or relapsed patients with previous remission < 6 months.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Anjali Advani at 216/445-9354, or if Dr. Advani is not available, Dr. Laura C. Michaelis at 414/805-1118. For dosing principles or questions, please consult the SWOG 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).

7.1 Good Medical Practice

The following pre-study tests should be obtained within 28 days prior to registration (both Induction and Consolidation) in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not affect patient safety in the clinical judgment of the treating physician. The Study Chair must be contacted if there are significant deviations in the values of these tests. If an individual test is considered to be unnecessary, the rationale for not conducting the test must be documented in the medical record.

a. Chest X-ray (posterior-anterior and lateral) and EKG.

b. PT, PTT

7.2 Pre-Medication

While the following pre-treatment medications are recommended, pre-treatment medication may be given at the discretion of the treating physician.

a. Granisetron, palonosetron or ondansetron prior to chemotherapy on Days 4-7.

b. Dexamethasone eye drops 0.1%: 2 drops to each eye every 6 hours on Days 3-8 for Induction therapy and Days 3-6 for Consolidation therapy (to prevent conjunctivitis associated with high dose AraC).

7.3 Induction Therapy

Patients should discontinue all other statin treatments while receiving protocol treatment.

A maximum of 1 cycle of Induction therapy will be allowed.

Agent	Dose	Route	Day
Pravastatin*	1,280 mg/day	PO	1-8
Idarubicin	12 mg/m^2/day	IV over 10-15 minutes	4-6
AraC	1.5 g/m^2/day	continuous IV	4-7

* Pravastatin will be provided in 80 mg tablets. Patients may receive 16 tablets/day of pravastatin over 2 hours to achieve total dose.

For patients with a high WBC count at the time of study enrollment, hydroxyurea can be used concurrently at the investigator's discretion, until Day 10 (with Day 1 being the start of pravastatin).

Pravastatin will be administered once daily in the morning on Days 1-8. Neurotoxicity exams should be performed prior to each dose of AraC. AraC should be held and no further doses administered if any signs of cerebellar neurotoxicity are found, and the Study Chair must be contacted.

7.4 Consolidation Therapy

Patients achieving complete remission (CR) as defined in Section 10.1 will be eligible to receive protocol Consolidation therapy, provided they meet the eligibility criteria outlined in Section 5.2, and are registered for Consolidation therapy before beginning Consolidation therapy.

A maximum of 2 cycles of Consolidation therapy will be allowed.

Consolidation Therapy must be initiated no sooner than 30 days and no later than 60 days after the start of Induction therapy (with Day 1 being the start of induction). The second cycle of Consolidation therapy must be initiated no sooner than 30 days and no later than 60 days after the start of the first cycle of Consolidation. Patients must remain in complete remission with an absolute neutrophil count ≥ 1,000/mcl and platelet count ≥ 100,000/mcl before beginning the second cycle of Consolidation therapy. A bone marrow examination to confirm CR is NOT required prior to initiating the second cycle of Consolidation therapy.

Agent	Dose	Route	Day
Pravastatin*	1,280 mg/day	PO	1-6
Idarubicin	12 mg/m^2	IV over 10-15 mins	4-5
AraC	1.5 g/m^2/day	Continuous IV	4-5

* Pravastatin will be provided in 80 mg tablets. Patients may receive 16 tablets/day of pravastatin over 2 hours to achieve total dose.

Pravastatin will be administered once daily in the morning on Days 1-6. Neurotoxicity exams should be performed prior to each dose of AraC. AraC should be held and no further doses administered if any signs of cerebellar neurotoxicity are found. AraC should be held, no further doses administered, and the Study Chair must be contacted.

ECHO or MUGA (whichever was performed at baseline) should be performed prior to each cycle of Consolidation therapy.

7.5 Follow-up

Patients will be followed for date of relapse and date of death. Follow-up will include complete physical examination and CBC with differential and platelets monthly for the first year, every three months for the second and third years, and every 6 months for the fourth and fifth years. Other tests will be performed at the discretion of the treating physician.

7.6 Growth Factors

G-CSF or GM-CSF therapy may be used at the discretion of the treating physician in patients who develop infections while neutropenic, but is discouraged for the sole purpose of accelerating count recovery. (Growth factors should be used in accordance with ASCO guidelines).

7.7 Assessment of Response

A bone marrow aspirate and biopsy will be obtained after completion of Induction therapy at the time of blood count recovery (ANC ≥ 1,000/mcl, platelets ≥ 100,000/mcl) or by Day 45, whichever comes first. This aspirate/biopsy, or an additional aspirate/biopsy showing a CR, must be obtained prior to the Consolidation registration (see Section 5.2a).

7.8 Criteria for Removal from Protocol Treatment

a. Progressive disease (as defined in Section 10.2).

b. Failure to achieve CR after one cycle of Induction therapy.

c. Ejection fraction drop of ≥ 10% from baseline before either cycle of Consolidation therapy.

d. Unacceptable toxicity.

e. Completion of all cycles of protocol therapy (one cycle of Induction and two cycles of Consolidation).

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

7.9 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.10 Follow-Up Period

All patients will be followed until death or 5 years after initial registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 will be utilized **for SAE reporting only**. The CTCAE Version 4.0 is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 3.0 for routine toxicity 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 Dose Modifications

a. AraC: There is no standard dose modification for AraC. Dose modification in the setting of renal or hepatic dysfunction will be left to the discretion of the treating physician, but the Study Chair should be notified of any modifications, and these changes should be captured on the data form (treatment forms). Any modifications should be made based on labs obtained the day of drug administration. If dose modifications are required and toxicities subsequently resolve, AraC may be re-introduced in full dose for the next cycle.

AraC should be held for creatinine ≥ 2 mg/dl at any time during treatment.

Neurotoxicity exams should be performed prior to each dose of AraC. AraC should be held and no further doses administered if any signs of cerebellar neurotoxicity are found, and the Study Chair must be contacted.

b. Idarubicin: Dosing of idarubicin will be based on the total bilirubin drawn the day of drug administration.

Bilirubin > 2.5 mg/dL but ≤ 5 mg/dL	50% reduction from full dose. Dose reductions will be based daily on bilirubin (and will be made based on full dose).
Bilirubin > 5 mg/dL	Hold idarubicin

Bilirubin should be checked the same day as the dose is due.

If dose modifications are required and toxicities subsequently resolve, idarubicin may be re-introduced in full dose for the next cycle.

c. Pravastatin:

Grade 1 – 2 myalgia (Secondary to pravastatin)	Supplement with ubiquinone Q10 60 mg 4 x/day
Grade 3 – 4 myalgia (Pravastatin – related)	Hold pravastatin

d. At each scheduled assessment during Consolidation Therapy, the following values must be met:

Serum creatinine < 2.0 mg/dl

Total bilirubin ≤ 2.0 x IULN

SGOT and SGPT ≤ 3.0 x IULN

If any of these values are elevated, treatment should be held until all values are within the allowable range.

8.3 Dose Delay

a. AraC and/or Idarubicin: If either drug is held, doses may be delayed and given if hepatic/renal function recovers to acceptable levels (see Sections 8.2a and 8.2b) within 8 days of the originally scheduled date. The Study Calendar will be stopped and Days will not be counted during the delay. If dose must be withheld > 8 days, patient will be removed from protocol treatment and proceed to follow-up.

b. Pravastatin: If pravastatin is held, doses may be given if myalgias resolve to Grade 2 or less. Doses must be given within 8 days of the originally scheduled date. The Study Calendar will be stopped and Days will not be counted during the delay. If dose must be withheld > 8 days, patient will be removed from protocol treatment and proceed to follow-up.

8.4 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Anjali Advani at 216/445-9354, or if Dr. Advani is not available, Dr. Laura C. Michaelis at 414/805-1118.

8.5 Adverse Event Reporting

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

9.0 STUDY CALENDARS

9.1 Remission Induction Therapy

¶

REQUIRED STUDIES	Pre	D	D	D	D	D	D	D	Wk	Wk	Wk	Wk	Wk	Wk	Relapse	Follow
	Study	1	2	3	4	5	6	7	2	3	4	5	6	7		Up
PHYSICAL																
History & Physical Exam #	X	1x/wk							X	X	X	X	X	X		X
Performance Status	X															
Toxicity Notation	X	1x/wk							X	X	X	X	X	X		X
Neurotoxicity evaluation ¥	X				X	X	X	X								
Leptomeningeal disease evaluation	X															
LABORATORY STUDIES																
CBC, Diff, Platelets Δ	X	2x/wk							2x/wk	2x/wk	2x/wk	X	X	X		X
PT, PTT √	X	1x/wk							X	X	X					
Serum creatinine α	X	X			X	X	X	X	2x/wk	2x/wk	2x/wk	X	X	X		
Total bilirubin α	X	X			X	X	X	X	2x/wk	2x/wk	2x/wk	X	X	X		
SGOT **and** SGPT α	X	X			X	X	X	X	2x/wk	2x/wk	2x/wk	X	X	X		
Disease Assessment/BM Asp/Bx	X								Xд						X	
Pregnancy test ß	X															
X-RAYS AND SCANS																
Chest X-Ray √	X															
EKG √	X															
MUGA **or** ECHO Ω	X															
TREATMENT (see Section 7.0)																
Pravastatin		X	X	X	X	X	X	X	Day 8							
Idarubicin					X	X	X									
AraC					X	X	X	X								

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Click here for Footnotes:

Footnotes for Calendar:

Complete history and physical exam should be performed within 28 days prior to registration and at least once a week until Day 45.

Δ CBC/diff/plts should be performed at least twice weekly until Day 28 and then at least once weekly until Day 45. Differential is not required if WBC < 0.5.

α To be performed daily prior to chemotherapy administration on Day 1 and 4-7, then at least twice weekly until Day 28 and then at least once weekly until Day 45.

√ To be performed as part of good medical practice. Results do not determine eligibility.

Ω Either MUGA or ECHO may be performed at baseline. The same test should be used throughout protocol therapy and follow-up.

¥ To be performed prior to each dose of AraC (see Section 7.3).
As determined by clinical evaluation. Spinal tap does not need to be performed (see Section 5.1k).

ß Women of reproductive potential must have a negative pregnancy test within 14 days prior to registration (see Section 5.1p).

¶ Follow up exams will be performed monthly for the first year, every three months for the second and third years, and every 6 months for the fourth and fifth years. Exams will include at a minimum history and physical, toxicity notation, and CBC, Diff, Plts, with additional testing at the discretion of the treating physician.

д To be obtained after completion of Induction therapy, at time of hematologic recovery or on Day 45, whichever comes first. This assessment must occur prior to Consolidation registration (see Sections 7.7 and 5.2a).

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines outlined in https://swog.org/Members/Download/QA/Best%20Practices%20update.pdf.

9.2 Consolidation Therapy

¶

REQUIRED STUDIES	Pre	D	D	D	D	D	D	D	Wk	Wk	Wk	Wk	Pre	D	D	D	D	D	D	D	Wk	Wk	Wk	Wk	Relapse	FU
	Cycle 1	1	2	3	4	5	6	7	2	3	4	5	Cycle 2	1	2	3	4	5	6	7	2	3	4	5		
PHYSICAL																										
History & Physical Exam # ∑	X	1x/wk							X	X	X	X	X	1x/wk							X	X	X	X		X
Performance Status #	X												X													
Toxicity Notation ∑		1x/wk							X	X	X	X	X	1x/wk							X	X	X	X		X
Neurotoxicity evaluation ¥					X	X											X	X								
LABORATORY STUDIES																										
CBC, Diff, Platelets Δ	X	2x/wk							2x/ wk	2x/ wk	2x/ wk	X	X	2x/wk							2x/ Wk	2x/ wk	2x/ wk	X		X
PT, PTT √	X																									
Serum creatinine α	X	X			X	X			2x/ wk	2x/ wk	2x/ wk	X	X			X			X		2x/ Wk	2x/ wk	2x/ wk	X		
Total bilirubin α	X	X			X	X			2x/ wk	2x/ wk	2x/ wk	X	X			X			X		2x/ Wk	2x/ wk	2x/ wk	X		
SGOT **and** SGPT α	X	X			X	X			2x/ wk	2x/ wk	2x/ wk	X	X			X			X		2x/ wk	2x/ wk	2x/ wk	X		
Disease Assessment/BM Asp/Bx	X£																								X	
X-RAYS AND SCANS																										
MUGA **or** ECHO Ω	X												X													
TREATMENT (see Section 7.0)																										
Pravastatin		X	X	X	X	X	X							X	X	X	X	X	X							
Idarubicin					X	X											X	X								
AraC					X	X											X	X								

Continued on next page.
Click here for Footnotes:

Footnotes for Calendar 9.2

To be performed within 28 days prior to registration and prior to each Consolidation Cycle.
∑ To be performed weekly until hematologic complete recovery.
Δ To be performed prior to Consolidation registration (see Section 5.2), at least twice weekly until Day 28 and then at least once weekly until Day 35 for each consolidation cycle. Differential is not required if WBC < 0.5.
α To be performed on Day 1, 4 and 5 then at least twice weekly until Day 28 of each Consolidation cycle, and then at least once weekly until Day 35 of each Consolidation cycle. Dosing may be administered based on the values collected at each scheduled assessment, providing the values are within those allowable in Sections 5.2 and 8.2d. If the values are elevated, therapy should be held/adjusted (see Sections 5.2 and 8.2d).
√ To be performed as part of good medical practice. Results do not determine eligibility
Ω To be performed prior to each Cycle of Consolidation therapy. The same test as used during baseline assessment must be used.
¥ To be performed prior to each dose of AraC (see Section 7.4).
¶ Follow up exams will be performed monthly for the first year, every three months for the second and third years, and every 6 months for the fourth and fifth years. Exams will include at minimum history and physical, toxicity notation, and CBC, Diff, Plts, with additional testing at the discretion of the treating physician.
£ Pre-Consolidation disease assessment is not required if post-Induction assessment showed CR (see Sections 5.2a and 7.7).

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines outlined in https://swog.org/Members/Download/QA/Best%20Practices%20update.pdf.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Remission Definitions: *(13)*

a. Morphologic complete remission (CR): ANC ≥ 1,000/mcl, platelet count ≥ 100,000/mcl, < 5% bone marrow blasts, no Auer rods, no evidence of extramedullary disease. (No requirements for marrow cellularity, hemoglobin concentration).

b. Morphologic complete remission with incomplete blood count recovery (CRi): Same as CR but ANC may be < 1,000/mcl and/or platelet count < 100,000/mcl.

c. Partial remission (PR): ANC ≥ 1,000/mcl, platelet count > 100,000/mcl, and at least a 50% decrease in the percentage of marrow aspirate blasts to 5-25%, or marrow blasts < 5% with persistent Auer rods.

10.2 Treatment Failures

Patients who fail to achieve CR, CRi or PR following Induction will be classified according to the type of failure:

a. Resistant Disease: Patient survives ≥ 7 days following completion of initial treatment course and has persistent leukemia in the peripheral blood smear or bone marrow after completion of therapy.

b. Aplasia: Patient survives ≥ 7 days following completion of initial treatment course then dies while cytopenic, with the last post-induction bone marrow aplastic to hypoplastic (i.e. < 20% cellularity) and without leukemic blasts.

c. Indeterminate:

1. Patient survives < 7 days after completion of initial treatment course.

2. Patient survives ≥ 7 days following completion of initial treatment course then dies with no persistent leukemia in the peripheral smear but no post-induction bone marrow examination.

10.3 Relapse from CR or CRi

Reappearance of leukemic blasts in the peripheral blood; or > 5% blasts in the bone marrow not attributable to another cause (e.g., recovery of normal cells following chemotherapy-induced aplasia); **or** appearance or reappearance of extramedullary disease. If there are no circulating blasts and no extramedullary disease and the bone marrow blast percentage is > 5% but ≤ 20%, then a repeat bone marrow performed at least 7 days after the first marrow examination and documenting bone marrow blast percentage is > 5% is necessary to establish relapse.

10.4 Relapse Free Survival (RFS)

RFS is calculated for patients who have achieved a CR or CRi. RFS will be measured from the date of CR or CRi until relapse from CR or CRi for death from any cause. Observation is censored at the date of last follow-up for patients last known to be alive without report of relapse.

10.5 Overall Survival (OS)

OS is calculated for all patients from the date of initial registration on study until death from any cause. Observation is censored at the date of last follow-up for patients last known to be alive.

10.6 Toxicity Criteria

The NCI Common Terminology Criteria for Adverse Events Version 3.0 will be used to determine severity of toxicity.

10.7 Performance Status

Patients will be graded according to the Zubrod performance status scale.

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

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Objective

The primary objective of this study is to test whether the CR rate (CR+CRi) among patients with AML is sufficient to warrant further investigation. Originally, this regimen was investigated in relapsed patients with previous remission of longer than three months. Accrual to this cohort was closed on November 1, 2012 after meeting the protocol-defined criterion for efficacy. Thirty-six patients were enrolled to this cohort. The study was re-opened to investigate the regimen in poor risk patients with AML. It will be investigated independently in the two cohorts: (1) patients with MDS transformed to AML, and (2) refractory or relapsed patients. In each cohort, the regimen would be of no further interest if it yields a true CR rate of 20% (null), and would be of interest if it yields a true CR rate of 40% (alternative).

11.2 Accrual and Power

Patients will be accrued to this study in a single step. Each of the cohorts will accrue independently which means that one cohort that has reached its accrual goal may be closed to further accrual while the other cohort remains open to accrual. Seventy-four eligible patients will be accrued in the two poor-risk cohorts (thirty-seven in each cohort). The total accrual goal of the original cohort and two poor-risk cohorts is 110. If 12 or more patients achieve CR or CRi then the regimen will be considered sufficiently effective to warrant further investigation, assuming toxicity findings and other pertinent results are favorable. This design has critical level (probability of erroneously concluding the regimen warrants further study) of 0.05 if the true CR rate 20%, and power (probability of correctly concluding the regimen warrants further study) of 0.87 if the true CR rate is 40%.

11.3 Toxicity

With 37 patients in each cohort, the probability of any particular toxicity of the double induction regimen can be estimated to within at most ±16% (95% confidence interval). Any toxicity having a true occurrence rate of 5% or more is very likely to be observed in at least one patient (probability ≥ 85%).

11.4 Overall Survival and Relapse-Free Survival

Distributions of overall survival and relapse-free survival will be estimated in each cohort using the method of Kaplan-Meier.

11.5 Cytogenetics

Prestudy cytogenetic features will be investigated for associations with treatment outcomes. These results along with other patient characteristics will be examined in descriptive analyses.

11.6 Expected Accrual

Based on **SWOG-9126**, **S0117**, **S9918** and **S9333**, the expected accrual rate for the MDS cohort (Cohort 1) is 1.5 - 2 patients per month. Based on **SWOG-9126** and **S0117**, the expected accrual rate for the relapsed/refractory cohort (Cohort 2) is 1 - 2 patients per month. Therefore, accrual to both cohorts of this study is estimated to be complete in approximately 25 months after study activation.

11.7 Data and Safety Monitoring Committee

There is no formal Data and Safety Monitoring Committee for Phase II studies. Toxicity and accrual monitoring are done routinely by the Study Chair, study Statistician, and the Disease Committee Chair. Response monitoring is done by the study Statistician and Study Chair. 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, and Executive Officer monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

Discipline review is not necessary for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment no more than seven working days prior to planned start of treatment.

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>.

For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

c. CTSU Registration Procedures

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

1. Downloading Site Registration Documents:

   Site registration forms may be downloaded from the S0919 protocol page located on the CTSU members' website. Add if a restricted access protocol: Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

   Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
   Click on the Protocols tab in the upper left of your screen
   Click on the SWOG link to expand, then select S0919. Click on the Site Registration Documents link.

2. Requirements for S0919 Site Registration:

   CTSU IRB Certification (for sites not participating via the NCI CIRB)
   CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

3. Submitting Regulatory Documents:

   Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

   CTSU Regulatory Office
   1818 Market Street, Suite 1100
   Philadelphia, PA 19103
   Phone: 1-866-651-2878
   Fax: 215-569-0206
   E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4. Checking Your Site's Registration Status:

   Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

   - Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
   - Click on the Regulatory tab at the top of your screen
   - Click on the Site Registration tab
   - Enter your 5-character CTEP Institution Code and click on Go

13.3 OPEN Registration Requirements

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>.

For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

c. CTSU Registration Procedures

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

1. Downloading Site Registration Documents:

Site registration forms may be downloaded from the **S0919** protocol page located on the CTSU members' website. ***Add if a restricted access protocol:*** Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the SWOG link to expand, then select **S0919**. Click on the Site Registration Documents link.

2. Requirements for **S0919** Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

3. Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval *and Model Informed Consent* to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4. Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

13.4 Registration procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

c. The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG 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 Submission Requirement

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

Master forms can be found on the protocol abstract page of the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) 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 SWOG 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 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

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

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF INITIAL REGISTRATION

Submit the following:

S0919 Prestudy Form

Pathology Report

Pretreatment Cytogenetics Report

b. WITHIN 14 DAYS AFTER EACH CYCLE (INDUCTION AND CONSOLIDATION):

Submit the following:

AML Disease Assessment Form

S0919 Treatment Form

S0919 Adverse Event Form

c. WITHIN 14 DAYS AFTER CONSOLIDATION REGISTRATION:

S0919 Consolidation Eligibility Form

d. WITHIN 14 DAYS AFTER KNOWLEDGE OF RESPONSE OR RELAPSE:

Submit a copy of the AML Disease Assessment Form documenting the date of and evidence for response or relapse.

e. AFTER THE PATIENT IS OFF TREATMENT, EVERY MONTH THE FIRST YEAR, EVERY 3 MONTHS FOR THE SECOND AND THIRD YEARS, AND EVERY 6 MONTHS FOR THE FOURTH AND FIFTH YEARS:

Submit Southwest Oncology Group Follow-up Form

f. WITHIN 14 DAYS AFTER GOING OFF PROTOCOL TREATMENT FOR STEP 1 OR STEP 2:

Submit the following for both Step 1 and Step 2:

Off Treatment Notice

AML Disease Assessment Form

g. WITHIN 4 WEEKS AFTER KNOWLEDGE OF DEATH:

Submit a final Southwest Oncology Group Follow-up Form (if death occurs after off treatment). Also submit a copy of the Notice of Death.

15.0 SPECIAL INSTRUCTIONS

15.1 Cytogenetic Studies

Effective with Revision #2, submission of specimens for cytogenetic studies through protocol **SWOG-9007** is no longer required. Cytogenetic studies must still be performed at each institution's preferred cytogenetics laboratory at the timepoints below:

a. Pretreatment (within 28 days of initial registration)

Reports of the results must be submitted as described in Section 14.0.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

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

Informed Consent

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

Institutional Review

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

Drug Accountability

For each drug supplied for a study, an accountability ledger containing current and accurate inventory records covering receipt, dispensing, and the return of study drug supplies must be maintained. Drug supplies must be kept in a secure, limited access storage area under the recommended storage conditions. During the course of the study, the following information must be noted on the accountability ledger; the identification code of the subject to whom drug is dispensed, the date(s) and quantity of drug dispensed to the subject, and the date(s) and quantity of drug returned by the subject; subjects should return empty containers to the investigator, with the return noted on the ledger. These Accountability Forms must be readily available for inspection and are open to FDA or NCI inspection at any time.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 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.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 18.1 for general and background information about expedited reporting.

b. Reporting method

This study requires that expedited adverse event reporting use the CTEP Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

In the rare event when internet connectivity is disrupted an electronic report MUST be submitted immediately upon re-establishment of internet connection.

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event.

d. Other recipients of adverse event reports

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

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

e. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 16.1. The commercial agent(s) used in both the Induction and Consolidation Therapy of this study are Cytosine Arabinoside (Ara-C) (Cytarabine) (Cytosar U) (NSC-63878), Idarubicin HCL (Idamycin®) (NSC-256439), and Pravastatin Sodium (NSC-740787). If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1. Expedited reporting requirements for adverse events experienced by patients on either Induction or Consolidation Therapy within 30 days of the last administration of the commercial agents. All of the agents used in the study are commercial agents.

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

[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.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent by fax to 210-614-0006.

f. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

   Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects/htm

17.0 BIBLIOGRAPHY

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Informed Consent Model for **S0919**

*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.

(Paragraph deleted 3/22/10)

Readability Statistics:	
Flesch Reading Ease	59.4 (targeted above 55)
Flesch-Kincaid Grade Level	8.9 (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) and SWOG. *(9-12-16)*

  "SWOG" 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 SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Operations Office, all intergroup studies for which the registration is being credited to SWOG (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 SWOG. *(9-12-16)*

- 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: *(section updated 9/12/16)*

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. 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/
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* 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.

S0919, "A Phase II Study of Idarubicin and Ara-C in Combination with Pravastatin for Poor-Risk Acute Myelogenous Leukemia (AML)"

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 one of two types of cancer: 1) relapsed or refractory acute myeloid leukemia (AML) (this means that you were treated before for this leukemia, but it has come back or has not responded to treatment) or 2) myelodysplastic syndrome (MDS) that has turned into AML. *(sentence updated 2/25/13)*

(Section deleted 9-12-16)

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, the combination of regular chemotherapy plus pravastatin has on you and your leukemia. The chemotherapy is made up of two drugs which are commonly used to treat your type of leukemia. These drugs are idarubicin and ara-c. Pravastatin is a drug that is usually used to treat high cholesterol. We would like to see whether adding pravastatin to the chemotherapy will have an effect on you and your leukemia. Since pravastatin is not usually used to treat leukemia, it will be considered investigational for this study.

How many people will take part in the study?

About 74 people will take part in this study.

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

Your treatment on this study will be separated into two parts. The first part is called induction treatment. Induction therapy uses drugs to kill your leukemia cells. The second part is called consolidation treatment. Consolidation treatment uses drugs to help keep your leukemia from coming back. In this study, induction and consolidation use the same drugs but at different times that are described below.

Induction treatment may last for up to seven weeks, but for most patients it will only last for 5-6 weeks. The amount of time induction treatment lasts will depend on your response to treatment. You will receive drugs for just over one week and then you will not receive drugs for the rest of induction. Induction treatment is described in the table below.

Drug	How often is it given?	How is it given?	What days is it given on?
Pravastatin	16 tablets given once in the morning	By mouth	1-8
Idarubicin	Once a day	Into a vein over 10-15 minutes	4-6
AraC	Once a day	Continuously for 4 days into a vein	4-7

Consolidation treatment will begin about two weeks after you finish the induction (about nine weeks after you started treatment). Consolidation treatment is divided into two cycles. Each cycle is 45 days long. The treatment for one consolidation cycle is described in the table below. After the first treatment cycle you will have a rest period that will last for up to fifteen days. It might be shorter if your doctor thinks that you are ready to continue earlier. After the rest period, you will have the second cycle. For each cycle you will receive drugs for about one week and then you will not receive drugs for the rest of the cycle.

Drug	How often is it given	How is it given	What days is it given on?
Pravastatin	16 tablets given once in the morning	By mouth	1-6
Idarubicin	Once a day	Into a vein over 10-15 minutes	4-5
AraC	Once a day	Continuously for 2 days into a vein	4-5

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 examination
- Blood tests including tests for your kidneys and liver
- A bone marrow aspirate and biopsy
- Tests/scans for your heart
- Chest x-ray
- *(deleted 2/23/15)*
- Pregnancy (test for women of child bearing potential)

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.

- A history and physical examination each week
- A neurotoxicity evaluation before every dose of AraC (to see how the drug affects your brain and nerves)

- Blood tests, including tests for your kidneys and liver once or twice a week
- Tests/Scans of your heart will be done during the study if your doctor thinks you need them
- A bone marrow aspirate and biopsy two to three times during treatment

(paragraph and bullet deleted 3/22/10)

When I am finished with the study treatment...

Your doctor will still check your disease status and how the study drugs have affected you and your leukemia. You will receive the following tests every month f or the first year, every three months for the second and third years and then every six months until five years from the time you began the study:

- History and physical examination
- Blood tests

How long will I be in the study?

You may remain on treatment as part of this study for up to about six months, or until you and/or your doctor feel the side effects of therapy are too great for you to remain on the study, or until your leukemia gets worse or comes back, if that happens.

After you are finished with consolidation treatment, the study doctor will ask you to visit the office for follow-up exams for about another four and a half years. You will be asked to come in monthly for the first year, every three months for the second and third years, and then every 6 months until five years after the time you began the study. At minimum, you will have a blood test and doctor exam at these visits. Your study doctor may decide to run more tests as needed.

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 treatment 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 you stop taking the study treatment. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

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

You may have the following risks and side effects at any time during this study:

Likely

- **Lower white blood cell count that may lead to infection**
- **Lower platelet count that may lead to bruising or bleeding**
- **Lower red blood cell count that may cause you to feel tired or have shortness of breath**
- **Headache**
- **Cough**
- **Fever**
- **Nausea**
- **Vomiting**
- **Diarrhea**
- **Rash**
- **Infection**
- **Bleeding**
- **Heartburn**
- **Loss of appetite**
- **Stomach cramps**
- **Fatigue**
- **General feeling of discomfort**
- **Hair loss**

Less Likely

- **Dizziness**
- **Anxiety**
- **Depression**
- **Changes in mood**
- **Memory loss and confusion. This is generally not serious and generally goes away after stopping pravastatin.** *(added 3/30/12)*
- **Eye problems including dryness, swelling and pinkeye**

- **Skin changes (itching, increased sweating)**
- **Muscle pain**
- **Bone pain**
- **Numbness or tingling in hands and feet**
- **Severe sores in the mouth, throat, esophagus or colon**
- **Lung problems, including difficulty breathing and scarring of the lungs**
- **Chest pain**
- **Yellowing of the skin or nails**
- **Liver problems (including changes in liver enzymes)**
- **Increased blood sugar** *(added 3/30/12)*
-

Rare but serious

- **Allergy-like symptoms (runny nose, sneezing)**
- **Kidney problems (including possible kidney failure)**
- **Permanent liver damage. You should tell your doctor if you have unusual fatigue or weakness, loss of appetite, upper belly pain, dark-colored urine or yellowing of the skin or whites of the eyes.** *(added 3/30/12)*
- **Seizure(s), tremor(s) and possibly coma**
- **Partial or complete paralysis**
- **Muscle loss**
- **Heart problems including reduced ability to pump blood and heart attack**
- **Rapid or slow heart beat**
- **Hepatitis**
- **Allergic reaction**
- **Severe skin and gut lining reaction that may include rash and sloughing or death of tissue**

Any of the side effects listed above may be made worse by the interaction of the drugs.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. 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.

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 that using pravastatin with chemotherapy will be more useful against cancer 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 use of pravastatin with chemotherapy as a treatment for cancer. 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**
- **Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.**

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:

- Qualified representatives of Bristol-Myers Squibb, the manufacturer of pravastatin
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- SWOG *(updated 9-12-16)*
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the NCI to provide greater access to clinical trials *(added 9-12-16)*

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

Bristol-Myers Squibb will provide you with the pravastatin at no cost to you. Pravastatin will be provided free of charge while you are participating in this study. However, if you should need to take the study agent much longer than is usual, it is possible that the free supply of study agent given through the study could run out. If this happens, your study doctor will discuss with you how to obtain additional drug from the manufacturer and you may be asked to pay for it.

Idarubicin and AraC are commercially available and will not be provided free of charge.

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/learningabout/payingfor/how-insurance-companies-decide. *(updated 2/23/15)* 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.]*

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Future Contact

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes No

(section deleted 3/22/10)

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) *(2/23/15)*

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 _____