

October 1, 2015

GROUP CHAIR'S OFFICE

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swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

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

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Chairs: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

MEMORANDUM

Study Chair: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@ Moffitt.usf.edu

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 clarify the intended timing of patient follow-up for **S0535**. All patients must be followed until death or a maximum of 3 years from time of initial patient registration (as indicated in Section 7.13 of the protocol).

There is a discrepancy in the follow-up language between the protocol (Section 7.13), which is correct, footnote (Θ) in Section 9.0, and the Model Consent Form language on Page 6, under "How long will I be in the study?." This discrepancy occurred due to a protocol change prior to the initial activation of the protocol. At that time, the update was inadvertently omitted from the footnote in Section 9.0 and the Model Consent Form (MCF).

The second sentence of footnote (Θ) in Section 9.0 indicates, that bone marrow aspirates should be obtained "Once maintenance is complete, every 3 months for the 1st year, then every 6 months for the 2nd year, then at the end of the 3rd year from registration." This was an oversight and the second word of this sentence should have been updated (at time of protocol activation) to reflect "treatment" in place of "maintenance", so that bone marrow aspirates should be obtained "Once treatment is complete, every 3 months for the 1st year, then every 6 months for the 2nd year, then at the end of the 3rd year from registration."

Similarly, the Model Consent Form indicates, "After you are finished with these courses of treatment, the study doctor will ask you to visit the office for follow-up exams every 3 months for the first year, every 6 months for the second year, then at 3 years from the time you finish treatment." Although there were subsequent changes to the MCF, unfortunately it was not previously noted that the "After you are finished with these courses of treatment" and the "then at 3 years from the time you finish treatment" qualifiers preceding and following the timing of follow-up visits were incorrect. Therefore, the Model Consent Form language does not reflect the intent of the protocol.

Patients still receiving treatment or who are still in follow-up may be notified, at the discretion of the treating physician and in a manner approved by the local IRB, that the follow-up period is 3 years from the time of initial patient registration.

The **S0535** study will be included on the no-follow list in June 2016, and is subject to SWOG-audit until that time. SWOG's Quality Assurance Department has made note of this discrepancy and sites will not be cited for differences in follow-up period resultant from this discrepancy.

This memorandum will serve as documentation for sites that may undergo audit by outside organizations or authorities.

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

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Anna Moseley, M.S.
Shannon McDonough, M.S.
Tracy Maher, C.C.R.P.
Louise Highleyman
Laura Kingsbury, M.R.T.
Samantha Sublett - Alliance
Laura Gagnon - ECOG-ACRIN
Daniel Matulich - Pfizer
Elliot Lee - Biologics

July 1, 2015

GROUP CHAIR'S OFFICE

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Updated Drug Order Form and Holiday Closure

MEMORANDUM

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 that Biologics, Inc has updated all SWOG Drug Order Forms to clarify that the prescriber's signature is required.

The updated Drug Order Form pertains to the following studies:

S1313 (Gastrointestinal)
S1406 (Gastrointestinal)
S1014 (Genitourinary)
S1216 (Genitourinary)

S0635 (Lung)
S1300 (Lung)
S1403 (Lung)
S1304 (Myeloma)

Please also note that Biologics, Inc will be closed Friday, July 3, 2015 in observance of Independence Day. Biologics, Inc. will resume regular business hours (M-F, 9-6 ET) on Monday July 6, 2015.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

<u>S1202</u> (Cancer Control – Symptomatic)	<u>S0635</u> (Lung)
<u>S1313</u> (Gastrointestinal)	<u>S0709</u> (Lung)
<u>S1406</u> (Gastrointestinal)	<u>S1300</u> (Lung)
<u>S1014</u> (Genitourinary)	<u>S1403</u> (Lung)
<u>S1216</u> (Genitourinary)	<u>S1304</u> (Myeloma)
<u>S0535</u> (Leukemia)	

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

cc: PROTOCOL & INFORMATION OFFICE Mary Alice Norrison - Boehringer Ingelheim
Laura Kingsbury, M.R.T. Linda Fischer - Bristol-Myers Squibb
Tracy Maher, C.C.R.P. Becky Fillingham – ECOG-ACRIN
Amy Johnson Laura Gagnon – ECOG-ACRIN
Austin Hamm. Mary Bonds – ECOG-ACRIN
Brian Zeller April Noska – Genentech
Christine McLeod NCI Coop Coverage - Genentech
Jean Barce Leta Truett, Ph.D., M.N. – Janssen Services, LLC
Jeri Jardine Mohan Chelladurai, Ph.D. M.S.A. –
Larry Kaye Janssen Services, LLC
Louise Highleyman Royce-Ann Adkins, Janssen Services, LLC
Monica Yee William Heckman - Lilly
Stephanie Edwards Theresa Bucher, R.N., Millennium
Vicki Green Mark Showers – Onyx
Guadalupe Aquino – Alliance Kellis Snodgrass – Pfizer
Samantha Sublett – Alliance Afrouz Bazmi – Quintiles, Inc.
Elliott Lee, Biologics, Inc. Steve Shuey – Halozyme Therapeutics

CLOSED EFFECTIVE 06/11/2013

Distribution Date: June 1, 2015
E-Mailed Date: May 19, 2015

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Holiday Closure for Monday, May 25, 2015 in Observance of Memorial Day

MEMORANDUM

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

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MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Monday, May 25, 2015 in observance of Memorial Day.

Regular business hours will resume on Tuesday, May 26, 2015. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

<u>S1202</u> (Cancer Control – Symptomatic)	<u>S0635</u> (Lung)
<u>S1313</u> (Gastrointestinal)	<u>S0709</u> (Lung)
<u>S1406</u> (Gastrointestinal)	<u>S1300</u> (Lung)
<u>S1014</u> (Genitourinary)	<u>S1403</u> (Lung)
<u>S1216</u> (Genitourinary)	<u>S1304</u> (Myeloma - Active)
<u>S0535</u> (Leukemia)	

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

cc: PROTOCOL & INFORMATION OFFICE
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Amy Johnson
Austin Hamm.
Brian Zeller
Christine McLeod
Jean Barce
Jeri Jardine
Larry Kaye
Louise Highleyman
Monica Yee
Stephanie Edwards
Vicki Green
Guadalupe Aquino – Alliance
Samantha Sublett – Alliance
Elliott Lee, Biologics, Inc.
Mary Alice Norrison - Boehringer Ingelheim
Linda Fischer - Bristol-Myers Squibb
Becky Fillingham – ECOG-ACRIN
Laura Gagnon – ECOG-ACRIN
Mary Bonds – ECOG-ACRIN
April Noska – Genentech
NCI Coop Coverage - Genentech
Leta Truett, Ph.D., M.N. – Janssen Services, LLC
Mohan Chelladurai, Ph.D. M.S.A. – Janssen Services, LLC
Royce-Ann Adkins, Janssen Services, LLC
William Heckman - Lilly
Theresa Bucher, R.N., Millennium
Mark Showers – Onyx
Kellis Snodgrass – Pfizer
Afrouz Bazmi – Quintiles, Inc.
Steve Shuey – Halozyme Therapeutics

CLOSED EFFECTIVE 06/01/2013

Distribution Date: January 15, 2015
CTEP Submission Date: December 26, 2014

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS
FROM: Sandi Jo Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Chairs: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

REVISION #14

Study Chair: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
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 - () Study closure due to new risk information
- () Expedited review allowed
- (☒) No review required

REVISION #14

The above-referenced protocol has been revised as follows:

1. Pages 1-2, Title Page: The Version Date of the protocol and Model Consent Form have been updated. The participant list has been moved from Page 1 to Page 2 and revised to be consistent with the new NCTN/CTSU guidelines. Page 2 has been added and subsequent pages have been repaginated.

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

cc: PROTOCOL & INFORMATION OFFICE Louise Highleyman
Megan Othus, Ph.D. Laura Kingsbury, M.R.T.
Hongli Li, M.S. Samantha Sublett - Alliance
Shannon McDonough, M.S. Laura Gagnon - ECOG-ACRIN
Tracy Maher, C.C.R.P. Kellis Snodgrass - Pfizer
Jean Barce Elliot Lee - Biologics

January 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Operations Office

RE: IND Safety Reports for Gemtuzumab Ozogamicin

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MEMORANDUM

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 - () Complete study redesign
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 - () Study closure due to new risk information
- (√) Expedited review allowed
- () No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug gemtuzumab ozogamicin. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (<https://swog.org/safetyreports/safetyreports.asp>).

These safety reports pertain to the following studies:

S0535 Leukemia
S0703 Leukemia

Reports:

Nov. 14, 2014 Mfr Rpt #2014169108 FU
Dec. 3, 2014 Mfr Rpt #FRWYEG01649708 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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

cc: PROTOCOL & INFORMATION OFFICE Samantha Sublett – Alliance
Megan Othus, Ph.D. Laura Gagnon – ECOG-ACRIN
Hongli Li, M.S. Becky Fillingham – ECOG-ACRIN
Shannon McDonough, M.S. Kellis Snodgrass – Pfizer
Tracy Maher, C.C.R.P. Elliot Lee – Biologics
Jean Barce
Laura Kingsbury, M.R.T.
Louise Highleyman

December 15, 2014

TO: ALL SWOG GROUP MEMBER, NCORP, AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

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

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

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MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@ Moffitt.usf.edu

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 - () Addition of tissue banking requirements
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- () Expedited review allowed
- (√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Wednesday, December 24, 2014, Thursday, December 25, 2014, and Thursday, January 1, 2015, in observance of the seasonal holidays.

Regular business hours will continue on December 26 and January 2 from 9:00 a.m. – 6:00 p.m. Eastern.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Research Services team at 800/693-4906 or via e-mail at clinicaltrials@biologicsinc.com.

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

cc:	PROTOCOL & INFORMATION OFFICE	Samantha Sublett - Alliance
	Megan Othus, Ph.D.	Mary Bonds – ECOG - ACRIN
	Shannon McDonough, M.S.	Kellis Snodgrass - Pfizer
	Hongli Li, M.S.	Elliott Lee - Biologics
	Tracy Maher, C.C.R.P.	
	Jean Barce	

November 15, 2014

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for Gemtuzumab Ozogamicin

GROUP CHAIR'S OFFICE

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 - () Study closure due to new risk information
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- () No review required

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug gemtuzumab ozogamicin. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (<https://swog.org/safetyreports/safetyreports.asp>).

This safety report pertains to the following studies:

S0535 Leukemia
S0703 Leukemia

Report:

Oct. 28, 2014 Mfr Rpt #2014169108 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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

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

Samantha Sublett – Alliance
Laura Gagnon – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Kellis Snodgrass – Pfizer
Elliot Lee – Biologics

November 1, 2014

TO: ALL SWOG GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

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

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

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MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@ Moffitt.usf.edu

IRB Review Requirements

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- (√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Thursday, November 27 and Friday, November 28, 2014 in observance of the Thanksgiving holiday.

Regular business hours will resume on Monday, December 1, 2014. Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Trial Project Manager at 800/693-4906 or via email at clinicaltrials@biologicsinc.com.

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

cc: PROTOCOL & INFORMATION OFFICE
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Tracy Maher, C.C.R.P.
Jean Barce
Samantha Sublett - Alliance
Mary Bonds – ECOG - ACRIN
Kellis Snodgrass - Pfizer
Elliott Lee - Biologics

October 1, 2014

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for Gemtuzumab Ozogamicin

GROUP CHAIR'S OFFICE

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MEMORANDUM

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This safety report pertains to the following studies:

S0535 Leukemia
S0703 Leukemia

Report:

Aug. 6, 2014 Mfr Rpt #2014211874

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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cc: PROTOCOL & INFORMATION OFFICE
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Samantha Sublett – Alliance
Laura Gagnon – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Kellis Snodgrass – Pfizer
Elliot Lee – Biologics

August 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

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

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Chairs: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

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MEMORANDUM

Study Chair: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@ Moffitt.usf.edu

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MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Monday, September 1, 2014, in observance of Labor Day.

Regular business hours will resume on Tuesday, September 2, 2014. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

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.
Tracy Maher, C.C.R.P.
Jean Barce
Laura Kingsbury, M.R.T.

Samantha Sublett - Alliance
Laura Gagnon – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Kellis Snodgrass - Pfizer
Elliot Lee - Biologics

swog.org

June 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

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

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Chairs: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

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Portland, OR 97239

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503-346-8038 FAX

MEMORANDUM

Study Chair: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moftitt.usf.edu

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

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MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Friday, July 4, 2014 in observance of Independence Day.

Regular business hours will resume on Monday, July 7, 2014. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

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

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

Samantha Sublett - Alliance
Laura Gagnon – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Alison Randall - Pfizer
Elliot Lee - Biologics

swog.org

May 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

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

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Chairs: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

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MEMORANDUM

Study Chair: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

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 - () 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 that Biologics, Inc. Clinical Trials Services will be closed Monday, May 26, 2014 in observance of Memorial Day.

Regular business hours will resume on Tuesday, May 27, 2014. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

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

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Hongli Li, M.S.
Shannon McDonough, M.S.
Tracy Maher, C.C.R.P.
Jean Barce
Laura Kingsbury, M.R.T.
Samantha Sublett - Alliance
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Becky Fillingham – ECOG-ACRIN
Alison Randall - Pfizer
Elliot Lee - Biologics

Distribution Date: May 1, 2014
CTEP Submission Date: April 16, 2014

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU
FROM: Sandi Jo Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Chairs: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

REVISION #13

Study Chair: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
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 - () 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 #13

1. The Version Date of the protocol and Model Consent Form have been updated.
2. Throughout the protocol, "Study Coordinator" has been updated to "Study Chair". This change takes place on the Title Page (Page 1) and in Sections 7.0 (Page 23), 7.2g and 7.3b (Page 24), 7.5d (Page 25), 7.6c (Page 26), 8.4a (Page 34), 8.4c (Page 35), 8.5 (Page 36), 8.7 (Page 37), 11.4 (Page 44) and 18.2 (Page 64).
3. Throughout the protocol, NCI's Adverse Event Expedited Reporting System (AdEERS) has been updated to CTEP's Adverse Event Reporting System (CTEP-AERS). This change takes place in Sections 3.2b (Page 8), 16.1 (Pages 55-58) and 18.4 (Page 69). Associated web links on these pages have also been updated.
4. Pages 1-3, Title Pages: The participant list, Study Chair, Biostatistician and Agent information have been moved to Page 1. The Table of Contents has been moved to Pages 2-3.

5. Page 37, Section 8.8: Information in this section has been reworded and reorganized for clarity.
6. Page 39, Section 9.0: The "Ø" footnote has been updated to clarify that marrows are obtained until the 3rd year "from registration".
7. Page 45, Section 13.3a: The SWOG phone number has been updated in the last paragraph.
8. Page 54, Section 16.0: The information in the Drug Accountability section has been updated to the current standard referencing the Code of Federal Regulations 21 CFR 312. The new standard confidentiality statement has been added.
9. Page 55, Section 16.1d: Information in this section has been reworded and reorganized for clarity.
10. Page 56, Table 16.1 and Section 16.1e: The table and related information below it have been updated to the current standard.
11. Pages 58-59, Sections 16.1h and 16.1i: The information for reporting secondary AML/ALL/MDS has been updated to the current standard in Section 16.1h. Section 16.1i has been add to include reporting requirements for pregnancy, fetal death and neonatal death. This addition has caused the addition of a new Page 59. Subsequent pages have been renumbered accordingly.

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

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Tracy Maher, C.C.R.P.
Jean Barce
Laura Kingsbury, M.R.T.
Samantha Sublett - Alliance
Laura Gagnon – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Alison Randall - Pfizer
Elliot Lee - Biologics

December 15, 2013

TO: ALL SWOG GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
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Portland, OR 97239

503-494-5586
503-346-8038 FAX

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Chairs: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

MEMORANDUM

Study Chair: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@ Moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
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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

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MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Tuesday, December 24, 2013, Wednesday, December 25, 2013, and Wednesday, January 1, 2014, in observance of the seasonal holidays.

Regular business hours will continue December 26-27 and December 30-31 from 9:00 a.m. – 6:00 p.m. Eastern.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Research Services team at 800/693-4906 or via e-mail at clinicaltrials@biologicsinc.com.

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

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

Samantha Sublett - CALGB
Laura Gagnon - ECOG/ACRIN
Becky Fillingham - ECOG/ACRIN
Alison Randall - Pfizer
Elliot Lee - Biologics

November 1, 2013

TO: ALL SWOG GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Chairs: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

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MEMORANDUM

Study Chair: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

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MEMORANDUM

The purpose of this memorandum is to inform sites of a holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trials Services is closed Thursday, November 28 and Friday, November 29, 2013 in observance of the Thanksgiving holiday.

Regular business hours will resume on Monday, December 2, 2013. Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE Jean Barce
Megan Othus, Ph.D. Samantha Sublett - Alliance
Shannon McDonough, M.S. Laura Gagnon - ECOG
Tracy Maher, C.C.R.P. Alison Randall - Pfizer
Laura Kingsbury, M.R.T. Elliott Lee - Biologics

swog.org

August 15, 2013

TO: ALL SWOG GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

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

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Chairs: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

MEMORANDUM

Study Chair: Jeffrey E. Lancet, M.D.

Phone number: 813/745-6841

E-mail: lancetje@moffitt.usf.edu

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swog.org

MEMORANDUM

The purpose of this memorandum is to inform sites of the Holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services is **closed Monday, September 2, 2013** in observance of the Labor Day holiday.

Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' new website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE Jean Barce
Megan Othus, Ph.D. Samantha Sublett - Alliance
Shannon McDonough, M.S. Laura Gagnon - ECOG
Tracy Maher, C.C.R.P. Alison Randall - Pfizer
Laura Kingsbury, M.R.T. Elliott Lee - Biologics

June 15, 2013

TO: ALL SWOG GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Chairs: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

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MEMORANDUM

Study Chair: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetj@usf.edu

IRB Review Requirements

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MEMORANDUM

The purpose of this memorandum is to inform sites of the Holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services is **closed Thursday, July 4, 2013** in observance of the Independence Day holiday.

Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' new website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE Samantha Sublett - Alliance
Megan Othus, Ph.D. Mary Bonds - ECOG
Shannon McDonough, M.S. Alison Randall - Pfizer
Tracy Maher, C.C.R.P. Elliott Lee - Biologics
Jean Barce

Distribution Date: June 1, 2013
E-mailed Date: May 21, 2013

TO: ALL SWOG GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
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FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@ Moffitt.usf.edu

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IRB Review Requirements

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MEMORANDUM

The purpose of this memorandum is to inform sites of the Holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services is **closed Monday, May 27, 2013** in observance of the Memorial Day holiday.

Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' new website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE Samantha Sublett - CALGB
Megan Othus, Ph.D. Mary Bonds - ECOG
Shannon McDonough, M.S. Alison Randall - Pfizer
Tracy Maher, C.C.R.P. Elliott Lee - Biologics
Jean Barce

swog.org

Distribution Date: June 1, 2013
E-mailed Date: May 21, 2013

TO: ALL SWOG GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

GROUP CHAIR'S OFFICE

Charles D. Blanke, MD

CHAIR

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MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@ Moffitt.usf.edu

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- () No review required

MEMORANDUM

The purpose of this memorandum is to inform investigators about a recall of the study drug methotrexate due to particulate matter in vials from two drug lots: CL0996 (expiration date 12/2013) and CJ4948 (expiration date 5/2013).

ISSUE: Sandoz is conducting a voluntary nationwide recall to the hospital/user level of two lots of its Methotrexate Sodium, USP, 25 mg/mL, 40 mL vial injectable product in the US, due to the discovery of particulate matter in vials during routine quality examination of retention samples at the manufacturer. Parenteral injection of drug from the affected lots can lead to microembolisation in areas where the particles lodge. Clinical symptoms are not to be expected from these microemboli and Sandoz is not aware of any reports of related adverse events.

BACKGROUND: Methotrexate is an antimetabolite used in the treatment of neoplastic diseases, severe psoriasis, and rheumatoid arthritis, including polyarticular juvenile rheumatoid arthritis. The lot numbers and expiration dates of the two recalled lots are: CL0996 (expiration date 12/2013) and CJ4948 (expiration date 05/2013). These lots were distributed nationally across the US and to a single foreign country (Poland).

RECOMMENDATION: In the event that a patient experiences an adverse reaction or quality problem involving this product, they should immediately contact their healthcare professional as well as Sandoz to report the finding. The Sandoz Drug Information Direct Line is open at 800-525-2492, 24 hours/day, seven days a week, or reports can be made via email at qa.druginfo@sandoz.com.

Read the MedWatch alert, including a link to the Recall Notice, at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicinalProducts/ucm353266.htm>

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

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Tracy Maher, C.C.R.P.
Jean Barce
Samantha Sublett - CALGB
Mary Bonds - ECOG
Alison Randall - Pfizer
Katie Reitzel - Biologics

CLOSED EFFECTIVE 06/01/2013

May 15, 2013

GROUP CHAIR'S OFFICE

Laurence H. Baker, DO
CHAIR

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swog.org

TO: ALL SWOG GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

STATUS NOTICE

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetj@moftt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
 - () Initial activation (should your institution choose to participate)
 - () Increased risk to patient
 - () Complete study redesign
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 - () Study closure due to new risk information
- (√) Expedited review allowed
- () No review required

PERMANENT CLOSURE

The above-referenced study has met its accrual goal and will permanently close to accrual **effective June 1, 2013 at 11:59 p.m. Pacific.**

Because the study is being permanently closed prior to local implementation of Revision #12, **sites do not need to update local consent forms per the requirement in the Revision #12 cover memorandum.**

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

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Tracy Maher, C.C.R.P.
Jean Barce
Samantha Sublett - CALGB
Mary Bonds - ECOG
Alison Randall - Pfizer
Katie Reitzel - Biologics

Distribution Date: May 15, 2013
CTEP Submission Date: April 25, 2013

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swog.org

TO: ALL SWOG GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, J. Radich, M. Fang, and D. Roulston.

REVISION #12

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 #12

The above-referenced study has been revised as follows:

1. 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.
2. Study Coordinators List, Page 3: Cheryl Willman has been replaced by Jerald Radich as the Surface Markers Studies Coordinator. Marilyn Slovak has been replaced by Min Fang and Diane Roulston as the Cytogenetics/FISH Coordinator. Corresponding contact information has been updated accordingly.

3. Biostatisticians List, Page 3: Holly Gundacker has been replaced by Shannon McDonough. Corresponding contact information has been updated accordingly.
4. Sections 14.4a, 14.4b, 14.4d, 14.4i and 14.4l, Pages 46-48: These sections have been updated to require that CALGB sites submit the RT-PCR report at the indicated timepoints.
5. Section 15.2, Page 49: A note has been added stating that no specimens will be banked for SWOG and other sites not affiliated with ECOG or CALGB.

The Model Consent Form has been updated as outlined below.

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 on protocol treatment and patients who sign a consent form prior to Institutional Review Board (IRB) approval and local implementation of the consent form changes need not be informed of these changes unless required by the local IRB.

1. Page 19: The website address for information on clinical trials and insurance coverage has been updated in the "What are the costs of taking part in this study?" section.
2. Page 25: The information stating that specimens will be kept at UNM Cancer Research Center for SWOG institutions and other institutions has been removed as banking for SWOG institutions is no longer part of this study.

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

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Tracy Maher
Jean Barce
Michele Seiler - CALGB
Mary Bonds - ECOG
Mary Voehl - Pfizer
Katie Reitzel - Biologics

January 1, 2013

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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

OPERATIONS OFFICE

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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.

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As part of this transition, forms 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.

December 15, 2012

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swog.org

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 the Holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services is **closed Monday, December 24, 2012, Tuesday, December 25, 2012 and Tuesday, January 1, 2013** in observance of the holidays.

Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' new website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE Mike Kelly – CALGB
Megan Othus, Ph.D. Morgen Alexander-Young - CALGB
Shannon McDonough, M.S. Mary Bonds - ECOG
Jean Barce Alison Randall - Pfizer
Tracy Maher, C.C.R.P. Elliott Lee - Biologics

November 15, 2012

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swog.org

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 the Holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services is **closed Thursday, November 22, 2012 and Friday, November 23, 2012** for the Thanksgiving holiday.

Regular business hours will resume on Monday, November 26, 2012. Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE Mike Kelly – CALGB
Megan Othus, Ph.D. Morgen Alexander-Young - CALGB
Shannon McDonough, M.S. Mary Bonds - ECOG
Jean Barce Alison Randall - Pfizer
Tracy Maher, C.C.R.P. Elliott Lee - Biologics

September 1, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS; CTSU

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swog.org

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
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 - () 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 updated expiration date for the study drug gemtuzumab ozogamicin (Mylotarg).

Pfizer, Inc., the drug's manufacturer, has extended the expiration date for lot # 10-084666 to November 30, 2013. Note that Pfizer does not require that drug be relabeled; sites are to follow their own local requirement for drug relabeling.

For questions, please contact Alison Randall (alison.randall@pfizer.com, 212/733-1765).

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

cc: PROTOCOL & INFORMATION OFFICE Mike Kelly – CALGB
Megan Othus, Ph.D. Morgen Alexander-Young - CALGB
Shannon McDonough, M.S. Mary Bonds - ECOG
Jean Barce Alison Randall - Pfizer
Tracy Maher, C.C.R.P. Elliott Lee - Biologics

Distribution Date: September 1, 2012
E-mail Date: August 30, 2012

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swog.org

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 that Biologics, Inc. will be closed on Monday, September 3, 2012 in observance of the Labor Day holiday.

If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc:	PROTOCOL & INFORMATION OFFICE	Mike Kelly – CALGB
	Megan Othus, Ph.D.	Morgen Alexander-Young - CALGB
	Shannon McDonough, M.S.	Mary Bonds - ECOG
	Jean Barce	Alison Randall - Pfizer
	Tracy Maher, C.C.R.P.	Elliott Lee - Biologics

August 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for Gemtuzumab Ozogamicin

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MEMORANDUM

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 following new safety report has been posted regarding an adverse event that occurred in association with the drug gemtuzumab ozogamicin. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (<https://swog.org/safetyreports/safetyreports.asp>).

This safety report pertains to the following studies:

S0106 Leukemia
S0535 Leukemia
S0703 Leukemia

Report:

Aug. 3, 2012 Mfr Rpt #2012117176

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

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

cc: PROTOCOL & INFORMATION OFFICE Morgen Alexander-Young – CALGB
Megan Othus, Ph.D. Michael Kelly – CALGB
Shannon McDonough, M.S. Camilla Byström – GTO/Karolinska, Sweden
Tracy Maher, C.C.R.P. Mary Bonds – ECOG
Jean Barce Andrea Hiltz – NCIC CTG
Alison Randall – Pfizer
Elliot Lee – Biologics

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

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swog.org

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 methotrexate 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.
Michele Seiler - CALGB
Mary Bonds - ECOG
Alison Randall - Pfizer
Elliott Lee - Biologics

CLOSED EFFECTIVE 06/01/2013

June 15, 2012

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swog.org

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 that Biologics, Inc. will be closed on Wednesday, July 4, 2012 in observance of the Independence Day holiday.

If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE
Kenneth J. Kopecky, Ph.D.
Megan Othus, Ph.D.
Shannon McDonough, M.S.
Jean Barce

Tracy Maher, C.C.R.P.
Michele Seiler - CALGB
Mary Bonds - ECOG
Mary Voehl - Pfizer
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May 1, 2012

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swog.org

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 - () Complete study redesign
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- () Expedited review allowed
- (☒) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. will be closed on Monday, May 28, 2012 in observance of the Memorial Day holiday.

If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE
Kenneth J. Kopecky, Ph.D.
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce

Tracy Maher
Michele Seiler - CALGB
Maury Bonds - ECOG
Mary Voehl - Pfizer
Katie Reitzel - Biologics

January 1, 2012

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swog.org

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetj@usf.edu

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 - () 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 Investigator Letter that was released by Pfizer on December 19, 2011 regarding the recommendation to visually inspect the study drug gemtuzumab ozogamicin after reconstitution and prior to use. The Investigator Letter is attached.

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

cc: PROTOCOL & INFORMATION OFFICE
Kenneth J. Kopecky, Ph.D.
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher
Michele Seiler - CALGB
Maury Bonds - ECOG
Mary Voehl - Pfizer
Katie Reitzel - Biologics



Pfizer, Inc.
235 East 42 Street
New York, NY 10017

Clinical Development & Medical Affairs

December 19, 2011

Pfizer recommends that investigators visually inspect MYLOTARG® (gentuzumab ozogamicin (GO)) vials after reconstitution with 5ml Sterile Water For Injection prior to administration to ensure the absence of particulate matter.

Dear Investigator:

This letter is to reinforce the importance of visually inspecting MYLOTARG vials after reconstitution with 5mls Sterile Water For Injection prior to mixing in the preparation of the intravenous solution. This communication has been triggered based on Good Manufacturing Practice (GMP) issues identified at the manufacturing site (Ben Venue Laboratories, BVL) where vials of MYLOTARG Powder for Solution for Injection have been produced. There is currently no evidence that the safety or efficacy of MYLOTARG is impacted by the issues identified at the BVL facility.

Recommendation to healthcare professionals

- **Healthcare professionals should visually inspect the MYLOTARG vials after reconstitution with 5mls Sterile Water For Injection in order to ensure the absence of particulate matter prior to administration of the reconstituted medicinal product, in order to minimize relevant risk.**
- *MYLOTARG is a Powder for Solution for Injection that is reconstituted with Sterile Water For Injection. **The reconstituted solution should be free from visible particulates.***
- ***Always carefully follow the administration instructions provided in the MYLOTARG dosage and administration instructions.***
- ***If you note particles in the vial after reconstitution please do not use the vial.*** Any evidence of particulate matter noted in Mylotarg vials after reconstitution should be reported. To report a product issue or speak to a member of Pfizer US Medical Information Team, please call 1-800-438-1985.

Further information

In November 2011, the European Medicines Agency carried out an inspection of a BVL site that manufactures products including Mylotarg. The inspection resulted in observations relating to the presence of particulate matter in certain products. No product-specific details have been provided relating to any Pfizer products.

There is currently no evidence that the safety or efficacy of MYLOTARG is impacted by the adverse inspection findings of the BVL facility.

Background information on MYLOTARG

MYLOTARG is a medicinal product containing Gentuzumab Ozogamicin. MYLOTARG has no Marketing Authorization in the EU and the marketing authorization in the USA (NDA) was withdrawn in 2010 when an important phase 3 study failed to confirm clinical benefit, but it is supplied for investigator-initiated studies and on a compassionate use basis for certain patients with Acute Myeloid Leukemia.

Reporting recommendations

Please report any adverse events associated with the use of MYLOTARG via the Pfizer Serious Adverse Event Reporting policy for Investigator Initiated Research studies. Additionally, this information may be reported to your local Health Authority and Institutional Review Board or Ethics Committee, as appropriate.

For further information or any questions on MYLOTARG, please contact Pfizer US Medical Information at 1-800-438-1985.

Sincerely,

A handwritten signature in black ink, appearing to read 'Mark Shapiro', with a stylized flourish at the end.

Mark Shapiro, MD, PhD
Global Medical Affairs
Pfizer Oncology

December 15, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS; CTSU

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

OPERATIONS OFFICE

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Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

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

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MEMORANDUM

The purpose of this memorandum is to inform sites of the New Year's holiday shipment schedule for Biologics, Inc. Biologics Inc. Clinical Trials Services will be open on January 2, 2012, but will **not** ship drug on that day. Normal shipments will resume on January 3, 2012. If you have questions or need to coordinate shipments in advance please don't hesitate to contact your Clinical Trials Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE
Kenneth J. Kopecky, Ph.D.
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher
Michele Seiler - CALGB
Maury Bonds - ECOG
Mary Voehl - Pfizer
Katie Reitzel - Biologics

swog.org

December 1, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS; CTSU

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swog.org

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

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 - () 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 the Holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services is **closed Friday, December 23, 2011 through Sunday December 25, 2011** for the holidays. Regular business hours will resume on Monday, December 26, 2011. If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE
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Megan Othus, Ph.D.
Holly Gundacker, M.S.
Jean Barce
Tracy Maher
Michele Seiler - CALGB
Maury Bonds - ECOG
Mary Voehl - Pfizer
Katie Reitzel - Biologics

Distribution Date: November 15, 2011
CTEP Submission Date: November 1, 2011

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swog.org

TO: ALL SWOG GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, C.L. Willman, and M.L. Slovak.

REVISION #11

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 #11

Institutions **should** 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 protocol therapy, and patients who have signed a consent form but not yet started treatment **need not** be informed of these changes unless required by the local Institutional Review Board (IRB).

The above-referenced study has been revised as follows:

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

2. Page 14, Section 5.1e: The window for ATRA allowance prior to registration has been updated from 3 days to 5 days.
3. Page 19, Section 7.3: The “ι” footnote reference has been added to ATRA in the treatment table with associated “ι” footnote indicating that Day 1 of treatment will be the first day the patient is treated with ATRA, regardless of patient's registration status. The π footnote below the treatment table has been updated to indicate that gemtuzumab ozogamicin may be delayed until Day 6 (previously Day 5).
4. Page 22, Section 7.8a: This section has been updated to clarify that subsequent bone marrow and biopsies will not be submitted centrally for cytogenetics and RT-PCR, but that these tests are still performed locally.
5. Page 28, Section 8.3b: A new bullet was added as follows:

Other Arsenic Trioxide-Related Toxicity: If grade ≥ 3 , then hold treatment until clear clinical evidence of resolution to \leq Grade 1 and then resume treatment with a 50% dose reduction (0.075 mg/kg/day). If toxicity persists for more than 14 days after holding treatment or recurrent toxicity occurs despite dose reduction, then discontinue As₂O₃.
6. Page 31, Section 8.5a: A new bullet was added as follows:

Other 6-MP or MTX-Related Toxicities: If grade ≥ 3 , then hold treatment. Treatment may resume after a 50% dose reduction when toxicity resolves to \leq Grade 1. If toxicity reoccurs after a first dose reduction, treatment may resume again after another 50% dose reduction (i.e., 25% of original dose) when toxicity resolves to \leq Grade 1. If toxicity reoccurs after a second dose reduction then discontinue drug(s).
7. Page 32, Section 9.0: The “f” footnote has been updated to be consistent with the updated 5 day ATRA allowance. The “ü” footnote has been updated to clarify the subsequent specimen submission requirements and to reference Section 7.8a.
8. Page 51a, Model Consent Form: The timeline for follow up visits has been updated to be consistent with the protocol, updating from every 3 months for 3 years to “every 3 months for the first year, every 6 months for the second year and at 3 years from the time you finish treatment”.

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

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Holly Gundacker, M.S.
Tracy Maher
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Katie Reitzel - Biologics

November 1, 2011

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swog.org

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 the Thanksgiving holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services will be **closed Thursday, November 24, 2011 and Friday, November 25, 2011** for the Thanksgiving holiday. Regular business hours will resume on Monday, November 28, 2011. If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE Michele Seiler - CALGB
Megan Othus, Ph.D. Mary Bonds - ECOG
Holly Gundacker, M.S. Mary Voehl - Pfizer
Tracy Maher Katie Reitzel - Biologics
Jean Barce

August 15, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS; CTSU

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FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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IRB Review Requirements

- () Full board review required. Reason:
 - () Initial activation (should your institution choose to participate)
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 - () Complete study redesign
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 - () Study closure due to new risk information
- () Expedited review allowed
- (√) No review required

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MEMORANDUM

The purpose of this memorandum is to inform sites of the Labor Day Holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services is **closed Monday, September 5, 2011** for the Labor Day holiday. Regular business hours will resume on Tuesday, September 6, 2011. If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906

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

cc: PROTOCOL & INFORMATION OFFICE
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Holly Gundacker, M.S.
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Camille White, C.C.R.P
Michele Seiler - CALGB
Hayley Dorfman - ECOG
Mary Voehl - Pfizer
Katie Reitzel - Biologics

swog.org

June 15, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS
AND PATHOLOGISTS; CTSU

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swog.org

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 the Independence Day Holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trial Services is **closed Monday, July 4, 2011** for the Independence Day holiday. Regular business hours will resume on Tuesday, July 5, 2011. If you have questions or need to coordinate shipments in advance, please don't hesitate to contact your Clinical Trial Project Manager at 800/693-4906

Additionally, please note that the gemtuzumab ozogamicin drug order form has been updated. The updated form can be downloaded from the protocol abstract page on the SWOG website (www.swog.org). Sites are instructed to begin using the updated order form immediately.

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

cc: PROTOCOL & INFORMATION OFFICE
Kenneth J. Kopecky, Ph.D.
Megan Othus, Ph.D.
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Jean Barce
Tracy Maher

Camille White, C.C.R.P
Michele Seiler - CALGB
Hayley Dorfman - ECOG
Mary Voehl - Pfizer
Katie Reitzel - Biologics

May 15, 2011

GROUP CHAIR'S OFFICE

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swog.org

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 that Biologics, Inc. Clinical Trial Services will be closed on Monday, May 30, for the Memorial Day holiday. Regular business hours will resume on Tuesday, May 31. Please plan drug orders accordingly. If you have questions or need to coordinate shipments in advance, please contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: PROTOCOL & INFORMATION OFFICE
Kenneth J. Kopecky, Ph.D.
Megan Othus, Ph.D.
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May 1, 2011

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swog.org

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R. Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

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MEMORANDUM

The purpose of this memorandum is to instruct sites on pre-ordering gemtuzumab ozogamicin. In order to avoid treatment delay, gemtuzumab ozogamicin may be pre-ordered **at the time a patient is being screened for study enrollment**. In the space for patient ID, sites should write "pre-order". If a drug is pre-ordered and the patient is not enrolled, the site is instructed NOT to return the pre-ordered supply, but instead to keep it on hand for the next potential patient. Section 3.5c will be updated to reflect this during the next protocol revision.

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

cc: PROTOCOL & INFORMATION OFFICE
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Hayley Dorfman - ECOG
Mary Voehl - Pfizer
Katie Reitzel - Biologics

Distribution Date: April 15, 2011
CTEP Submission Date: April 7, 2011

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

REVISION #10

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
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 - () Complete study redesign
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- (√) Expedited review allowed
- () No review required

REVISION #10

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

The 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 on treatment need not be informed of these changes unless required by the local Institutional Review Board (IRB).

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

2. Pages 11-11a, Section 3.4c: The supplier has been updated from Wyeth, Corp. to Pfizer, Inc. Drug ordering information has been updated to allow orders by the signature of the investigator or an authorized designate (previously required oncologist's signature). Information regarding use of commercial supplies to avoid treatment delays has been replaced by information allowing pre-orders for patients who are planned to be enrolled. Drug return and accountability information has been added. Information from Page 11 has been displaced to Page 11a.
3. Page 32, Section 9.0: The $\sqrt{\quad}$ footnote has been updated to require the indicated items after the patient is off treatment at the remaining of months 3, 6, 9, 12, 18, 24 and 36 from the time of initial registration (previously every 3 months until 3 years from initial registration).
4. Page 33, Section 10.1a: The requirement for > 20% marrow cellularity has been removed from the A1 bone marrow status in order to be consistent with current guidelines.
5. Page 39, Section 14.16: This section has been updated to require submission of the Follow Up Form after off treatment at the remaining of of months 3, 6, 9, 12, 18, 24 and 36 from the time of initial registration (previously every 3 months after off treatment for the first year, every 6 months for the second year, then at the end of the third year after patient entered the study).
6. Page 59, Model Consent Form: Wyeth Corp. has been updated to Pfizer Inc. in the list of organizations that may view patient medical records. The fourth paragraph in the "What are the costs of taking part in this study" section has been updated to state that gemtuzumab ozogamicin is investigational and will be provided by Pfizer, Inc. (previously stated that it was commercially available but provided by Wyeth, Corp.).

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

cc: PROTOCOL & INFORMATION OFFICE
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Holly Gundacker, M.S.
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Distribution Date: January 15, 2011
Effective Date: January 4, 2011
E-mailed Date: January 4, 2011

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swog.org

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

STATUS UPDATE

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
- () Initial activation
 - () Increased risk to patient
 - () Complete study redesign
 - () Addition of tissue banking requirements
 - () Study closure due to new risk information
- (√) Expedited review allowed
- () No review required

RE-ACTIVATION

Investigational gemtuzumab ozogamicin (Mylotarg) is now available for distribution to sites; therefore, the above-referenced study will re-open to accrual **effective 2:00 p.m. EST on January 4, 2011**. Note that prior to re-activation of this study, the local IRB must review and approve Revision #9, which changes gemtuzumab ozogamicin from commercial to investigational supply.

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

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Distribution Date: January 15, 2011
E-mailed Date: January 4, 2011
CTEP Submission Date: October 5, 2010

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swog.org

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

REVISION #9

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 #9

The above referenced protocol has been updated as follows:

1. Title Page: IND #66,366 has been added to gemtuzumab ozogamicin. This change has also been made in Section 3.4 (Page 9). The Version Date has been updated.
2. Page 11, Section 3.4d: Information has been updated in the "Supplier" section to state that gemtuzumab ozogamicin is considered investigational for this study (previously commercial).
3. Page 21, Section 7.7a: The ANC requirement of $1.5 \times 10^9/L$ has been updated to $1.0 \times 10^9/L$ to correct a typographical error.
4. Page 49, Model Consent Form: A sentence has been added to the end of the "Why is this study being done?" section to indicate that one of the chemotherapy drugs, gemtuzumab ozogamicin, is experimental.

5. Pages 42e-44b, Sections 16.0-16.1g: These sections have been updated/added to include adverse event reporting information for investigational drug in addition to the commercial drug reporting information. Pages 44a-b have been added to prevent extensive repagination.
6. Page 57, Model Consent Form: A note regarding the increased death rate and lack of efficacy of gemtuzumab ozogamicin based on a previous study has been added to the risks/side effects section. Institutions **must** update their local consent forms to include the changes to the Model Consent Form prior to enrolling new patients on this study.

This revision may undergo **expedited** review at the discretion of the local IRB chair.

Patients currently on treatment need not be informed of these changes unless required by the local Institutional Review Board (IRB).

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

cc: PROTOCOL & INFORMATION OFFICE
Kenneth J. Kopecky, Ph.D.
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Tracy Maher
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Jean Barce
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Mary Voehl - Pfizer
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Southwest Oncology Group

A National Clinical Research Group

November 1, 2010

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

FROM: Southwest Oncology Group Operations Office

RE: Biologics Inc. Holiday Schedule

MEMORANDUM

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 Biologics Inc. Clinical Trial Services will not be processing drug orders for shipment from November 25 to November 26, 2010 and Friday, December 24 and Friday, December 31, 2010 due to the holidays.

For the Thanksgiving holiday, the last shipment date will be Wednesday, November 24. Drug shipments will resume on Monday, November 29. For the Christmas holiday, the last shipment dates will be Thursday, December 23, with shipment resuming Monday, December 27. For the New Year's holiday, the last shipment date will be Thursday, December 30, 2010. Drug shipments will resume Monday, January 3, 2011.

This upcoming holiday closure schedule pertains to the following studies:

S0535 Leukemia
S0635 Lung
S0636 Lung
S0709 Lung
S0800 Breast
S0904 Gynecologic

Please append this notice to the front of your copy of the protocol.

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

cc: PROTOCOL & INFORMATION OFFICE	Camille White, C.C.R.P.	Larry Kaye
John Crowley, Ph.D.	Jean Barce	Janice Leaman
William Barlow, Ph.D.	Jennie Barrett	Arthur Cannon – Genentech
Mary Redman, Ph.D.	Iris Buchanan	Katie Reitzel – Biologics Inc.
Danika Lew, M.A.	Stephanie Edwards	
James Moon, M.S.	Jeri Jardine	

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Southwest Oncology Group

A National Clinical Research Group

Distribution Date: September 15, 2010

CTEP Submission Date: August 30, 2010

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

REVISION #8

Study Coordinator: Jeffrey E. Lancet, M.D.

Phone number: 813/745-6841

E-mail: lancetje@ Moffitt.usf.edu

IRB Review Requirements

- ☐ Full board review required. Reason:
 - ☐ Initial activation
 - ☐ Increased risk to patient
 - ☐ Complete study redesign
 - ☐ Addition of tissue banking requirements
 - ☐ Study closure due to new risk information
- ☒ Expedited review allowed
- ☐ No review required

REVISION #8

The above referenced protocol has been updated as follows:

1. Title Page: The Version Date has been updated. The contact information for Dr. Jeffrey Lancet and Dr. Rami Komrokji has been updated.
2. Pages 26-26a, 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 26a was added to prevent extensive repagination.

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.
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September 1, 2010

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
 - () Initial activation
 - () Increased risk to patient
 - () Complete study redesign
 - () Addition of tissue banking requirements
 - () Study closure due to new risk information
- () Expedited review allowed
- (☒) No review required

MEMORANDUM

The purpose of this memorandum is to clarify timing of doses for idarubicin used in place of daunorubicin during the national shortage. The memorandum dated January 15, 2010 instructed that idarubicin should be administered on Days 1-2. Since that time, the study team has determined that idarubicin should more correctly be given on Days 1-3, so during Revision #5 the protocol was updated to reflect this timing. Please note that the protocol is correct in instructing sites to administer idarubicin on Days 1-3.

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

cc: PROTOCOL & INFORMATION OFFICE
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Operations Office



Southwest Oncology Group

A National Clinical Research Group

Distribution Date: July 1, 2010
Effective Date: June 22, 2010
E-mailed Date: June 22, 2010

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

STATUS NOTICE

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
 - () Initial activation
 - () Increased risk to patient
 - () Complete study redesign
 - () Addition of tissue banking requirements
 - () Study closure due to new risk information
- (√) Expedited review allowed
- () No review required

TEMPORARY CLOSURE

Commercial gemtuzumab ozogamicin (Mylotarg) has been withdrawn from the market and will no longer be available to new patients. Therefore, this study will be temporarily closed **effective 5:00 p.m. EDT on June 22, 2010** while alternate drug supply is obtained.

The FDA press release can be accessed at
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm216448.htm>.

Sites **must** forward this information to their local IRB. With local IRB approval (and with implementation of any additional local IRB requirements), patients currently on treatment may continue treatment as planned with commercial drug supply. Documentation of this approval must be kept in the protocol file. Patients currently on treatment must be informed of the updated information. This information regarding drug availability and patient information may be located on the FDA press release noted above.

The study will be re-opened when the conversion to investigational drug supply for new patients has been completed. A Re-Activation memorandum will be distributed at that time.

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

cc: PROTOCOL & INFORMATION OFFICE
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Southwest Oncology Group

A National Clinical Research Group

Distribution Date: July 1, 2010
CTEP Submission Date: June 15, 2010

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

REVISION #7

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- ☐ Full board review required. Reason:
 - ☐ Initial activation
 - ☐ Increased risk to patient
 - ☐ Complete study redesign
 - ☐ Addition of tissue banking requirements
 - ☐ Study closure due to new risk information
- ☒ Expedited review allowed
- ☐ No review required

REVISION #7

The above referenced protocol has been updated as follows:

1. The Version Date has been updated.
2. Page 11, Section 3.4c: The drug ordering information for gemtuzumab ozogamicin has been updated to indicate that the drug order form may also be found on the protocol abstract page of the CTSU website (www.ctsu.org).
3. Page 15, Section 5.1g: The first bullet in this section has been updated to include the requirement that CALGB sites submit specimens to a CLIA-approved laboratory. A reference to Section 15.4 has been added. The third bullet has been updated to remove the requirement that CALGB sites be registered to **CALGB 9862** prior to registration (previously required for PCR specimen submission) and instead include the requirements that patients be offered participation on **CALGB 9862**, and that consenting patients be registered to **CALGB 9862** prior to registration.
4. Page 21, Section 7.5e: The "*" footnote reference has been added to "Daunomycin" in the treatment table. The associated "*" footnote has been added advising that idarubicin, 12mg/m²/day may be used in place of daunomycin only if daunomycin is unavailable due to the national shortage, and that this must be documented on the treatment summary form.

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5. Page 41, Section 5.2b: A sentence has been added indicating that CLIA certificates will be verified at the time of audit.
6. Pages 42c-42e, Section 15.4a: This section has been updated to include the specimen submission information for PCR testing (15.4a.1), **CALGB-9862** (15.4a.2) and the associated submission time points (15.4a.3). Page 42e has been added to prevent extensive repagination.
7. Master Forms Set: The **S0535** Consolidation Cycles 3 and 4 Treatment Summary Form has been updated to collect information regarding the usage of idarubicin. The form number has been updated from #19935 to #38269. The form number has also been updated in Section 14.8 (Page 39) and 18.2i (Page 46).
8. Master Forms Set: The **S0535** Adverse Event Summary Form has been updated to allow idarubicin as an option to be used during Consolidation Cycles 3 and 4. The form number and Version Date remain the same.
9. Pages 96, 98 and 99, Appendix 19.4: The CTSU website url has been updated to www.ctsu.org throughout this section.

Additionally, please note that this study has met the criteria to proceed to the second stage of accrual. The study will not be closed pending data analysis, but will continue to complete accrual.

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

cc: PROTOCOL & INFORMATION OFFICE
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Virginia Dixon-Lipscomb - Wyeth
Karl Buer - Biologics

Distribution Date: June 1, 2010
CTEP Submission Date: May 26, 2010

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

REVISION #6

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- ☐ Full board review required. Reason:
- ☐ Initial activation
 - ☐ Increased risk to patient
 - ☐ Complete study redesign
 - ☐ Addition of tissue banking requirements
 - ☐ Study closure due to new risk information
- ☒ Expedited review allowed
- ☐ No review required

REVISION #6

The above-referenced protocol has been revised as follows:

1. Title Page: The Version Date has been updated.
2. Pages 6-8b, Section 3.2b: The toxicity information for arsenic trioxide has been replaced by the CAEPR Version 2.0 (March 26, 2010).

CTEP has issued an updated CAEPR for arsenic trioxide. This study did not contain a CAEPR previously; therefore, a significant number of risks have been added. However, this information is considered to be similar to the risk information already communicated to patients in the Model Consent Form.

Pages 8a-8b have been added to prevent extensive repagination.

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3. Pages 52-54a, Model Consent Form: The following changes have been made to the Induction Therapy risks and side effects section of the Model Consent Form in order to be consistent with the updated arsenic trioxide CAEPR. Many omissions were noted in the previous version of the consent form. **Therefore, patients currently on treatment must be informed of the added information as outlined in bold below.**

In the Likely Section

- “Lower white blood count that may lead to infection, which could be life-threatening” has been updated to “Decreased number of a type of white blood cell (neutrophil/granulocyte)”
- “Lower platelets, which may lead to bruising or bleeding and which could be life-threatening. This side effect may require you to receive a transfer of blood platelets from a donor.” has been updated to “Decreased number of a type of blood cell that help to clot blood (platelet)”
- “Lower red blood counts, which may cause you to feel tired or have shortness of breath and require a transfer of red blood cells from a donor. Low red blood counts could be life-threatening.” has been updated to “Lack of enough red blood cells (anemia)”
- “Fever, chills, headache” has been updated to “Fever”, “Chills” and “Headache or head pain”
- “Nausea, vomiting, diarrhea” has been updated to “Nausea or the urge to vomit”, “Vomiting” and “Diarrhea”
- “Loss of appetite, abdominal pain” has been updated to “Loss of appetite” and “Belly pain”
- “Sores in the mouth” has been updated to “Irritation or sores in the lining of the mouth”
- “Pain at the site of injection/local reaction” has been updated to “Inflammation (swelling and redness) or damage to the tissue surrounding where a drug was injected”
- “Weakness” has been updated to “Muscle weakness”
- “Difficulty breathing, shortness of breath” has been updated to “Shortness of breath”
- “Fatigue” has been updated to “Fatigue or tiredness”
- “Difficulty sleeping” has been updated to “Difficulty sleeping or falling asleep”
- “Rash” has been updated to “Skin rash with the presence of macules (flat discolored area) and papules (raised bump)”
- “Changes in blood pressure” has been updated to “High blood pressure” and “Low blood pressure”
- “Dizziness” has been updated to “Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)”
- “High blood sugar” has been updated to “Increased blood sugar level”
- “Headache” has been deleted to correct a duplication
- “Low levels of potassium in the blood, which may cause: an irregular heartbeat; muscle weakness, cramping, or flaccid paralysis (limpness); leg discomfort; extreme thirst; frequent urination; confusion” has been updated to “Decreased blood level of potassium”
- “Chest pain” has been updated to “Chest pain not heart related”
- “Dryness of the skin and lips” has been updated to “Dryness of the lips” and “Dry skin”
- “Damage to the kidneys, which could result in the need for dialysis” has been updated to “Sudden or traumatic injury to the kidney”
- **“Infection” has been added**
- **“Itching” has been added** (moved from Less Likely; previously “Itchy skin”)

In the Less Likely Section

- “Dry nose and mouth” has been updated to “Dry nose” and “Dry mouth”
- “Fever associated with dangerously low levels of a type of white blood cell (neutrophils)” has been added
- “Decreased number of all blood cell types” has been added”
- “Unpleasant sensation of irregular and/or forceful beating of the heart” has been added
- “Fast heartbeat; regular rhythm” has been added
- “Irregular heartbeat resulting from an abnormality in one of the lower chambers of the heart (ventricle)” has been added
- “Noise in the ears, such as ringing, buzzing, roaring, clicking” has been added
- “Swelling or feeling of fullness and tightness in the abdomen (belly)” has been added
- “Irritation or sores in the lining of the anus” has been added
- “Heartburn ” has been added
- “Inflammation (swelling and redness) of the pancreas” has been added
- “Irritation or sores in the lining of the rectum” has been added
- “Irritation or sores in the lining of the small bowel” has been added
- “Swelling of the face” has been added
- “Swelling of the extremities (arms and/or legs)” has been added
- “Pain” has been added
- “Infection associated with a decrease in a type of white blood cell (lymphocyte)” has been added
- “Bruising” has been added
- “Increased blood level of a liver enzyme (ALT/SGPT)” has been added
- “Increased blood level of a liver enzyme (AST/SGOT)” has been added
- “Increased blood level of a liver pigment (bilirubin) often a sign of liver problems” has been added
- “Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)” has been added
- “Abnormal electrical conduction within the heart” has been added
- “Increased blood level of a liver enzyme (GGT)” has been added
- “Increased blood level of a fat-digesting enzyme (lipase)” has been added
- “Increased blood level of a digestive enzyme (amylase)” has been added
- “Weight loss” has been added
- “Decrease in the total number of white blood cells (leukocytes)” has been added
- “More acid than normal in the blood” has been added
- “Increased blood level of potassium” has been added
- “Decreased blood level of magnesium” has been added
- “Joint pain” has been added
- “Bone pain” has been added
- “Shrinking of the muscles” has been added
- “Muscle pain” has been added
- “Commonly known as “pins and needles”, where part of the body (typically a foot or hand) begins to tingle and becomes numb, or “falls asleep” ” has been added
- “Weakness or paralysis (loss of muscle function) caused by damage to peripheral nerves (those nerves outside of brain and spinal cord)” has been added
- “Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning” has been added
- “Anxiety, feelings of dread or danger” has been added
- “More protein in the urine than usual, often a sign of kidney disease” has been added

- “Stuffy or runny nose, sneezing” has been added
- “Sudden constriction of the muscles in the walls of the bronchioles (small airways of the lung)” has been added
- “Cough” has been added
- “Irritation or sores in the lining of the voice box” has been added
- “Irritation or sores in the lining of the throat” has been added
- “Build up of a large amount of fluid between the layers of tissue that line the lungs and chest cavity” has been added
- “A collection of symptoms including fever, difficulty breathing, chest pain, fluid in the lungs (seen on chest X-ray), fluid around the lungs and heart, and lack of oxygen first seen in patients receiving the drug retinoic acid” has been added
- “Sore throat” has been added
- “Irritation or sores in the lining of the windpipe” has been added
- “Hair loss” has been added
- “Excess sweating” has been added
- “Area of bleeding within the skin causing a reddish purple discoloration” has been added
- “Inflammation (swelling and redness) of the skin” has been added
- “Thickening of the skin” has been added
- “Darkening of the skin” has been added
- “Hives” has been added
- “Increase in the number and size of the pores in the capillaries (small blood vessels) which causes leakage of fluid from the blood to the tissue spaces resulting in dangerously low blood pressure, swelling and multiple organ failure” has been added
- “Sudden reddening of the face and/or neck” has been added

Page 54a has been added to prevent extensive repagination.

4. Pages 54a-54e, Model Consent Form: The following changes have been made to the Consolidation #1 and #2 Therapy risks and side effects section of the Model Consent Form in order to be consistent with the updated arsenic trioxide CAEPR. Many omissions were noted in the previous version of the consent form. **Therefore, patients currently on treatment must be informed of the added information as outlined in bold below.**

In the Likely Section

- “Fatigue” has been updated to “Fatigue or tiredness”
- “Nausea” has been updated to “Nausea or the urge to vomit”
- “Headache” has been updated to “Headache or head pain”
- “Lower white blood count that may lead to infection, which could be life-threatening” has been updated to “Decreased number of a type of white blood cell (neutrophil/granulocyte)”
- “Lower platelets, which may lead to bruising or bleeding and which could be life-threatening. This side effect may require you to receive a transfer of blood platelets from a donor.” has been updated to “Decreased number of a type of blood cell that help to clot blood (platelet)”
- “Low blood oxygen levels” has been removed
- **“Vomiting” has been added**
- **“Fever” has been added** (moved from Less Likely)
- **“Infection” has been added**
- **“Itching” has been added** (moved from Less Likely)
- **“Skin rash with the presence of macules (flat discolored area) and papules (raised bump)” has been added**

In the Less Likely Section

- “Fluid retention” has been removed
- “Upper respiratory infection” has been removed
- “Damage to the liver, which could cause yellowing of the skin and/or eyes” has been removed
- “Heart problems (Abnormal electrical conduction within the heart and irregular heartbeat)” has been updated to “Abnormal electrical conduction within the heart”
- “Increased blood sugar level” has been added (moved from Likely; previously “High blood sugar”)
- “Lack of enough red blood cells (anemia)” has been added (moved from Likely; previously Lower red blood counts that may cause you to feel tired or have shortness of breath and require a transfer of red blood cells from a donor. Low red blood counts could be life-threatening.)
- “Belly pain” has been added (moved from Likely; previously “Abdominal pain”)
- “Chest pain not heart-related” has been added (moved from Likely; previously “Chest pain”)
- “Dry skin” and “Dry mouth” have been added (moved from Likely; previously “Dryness in the skin and lips”)
- “Build up of a large amount of fluid between the layers of tissue that line the lungs and chest cavity” has been added (moved from Likely; previously “Fluid collection in the lungs”)
- “Sudden or traumatic injury to the kidney” has been added (moved from Likely; previously “Damage to the kidneys, which could result in the need for dialysis”)
- “Toothache” has been added (moved from Likely)
- “Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)” has been added (moved from Likely; previously “Dizziness”)
- **“Fever associated with dangerously low levels of a type of white blood cell (neutrophils)” has been added**
- **“Decreased number of all blood cell types” has been added**
- **“Unpleasant sensation of irregular and/or forceful beating of the heart” has been added**
- **“Fast heartbeat; regular rhythm” has been added**
- **“Irregular heartbeat resulting from an abnormality in one of the lower chambers of the heart (ventricle)” has been added**
- **“Noise in the ears, such as ringing, buzzing, roaring, clicking” has been added**
- **“Swelling or feeling of fullness and tightness in the abdomen (belly)” has been added**
- **“Irritation or sores in the lining of the anus” has been added**
- **“Constipation” has been added**
- **“Heartburn” has been added**
- **“Irritation or sores in the lining of the mouth” has been added**
- **“Inflammation (swelling and redness) of the pancreas” has been added**
- **“Irritation or sores in the lining of the rectum” has been added**
- **“Irritation or sores in the lining of the small bowel” has been added**
- **“Swelling of the face” has been added**
- **“Swelling of the extremities (arms and/or legs)” has been added**
- **“Inflammation (swelling and redness) or damage to the tissue surrounding where a drug was injected” has been added**
- **“Pain” has been added**
- **“Infection associated with a decrease in a type of white blood cell (lymphocyte)” has been added**
- **“Bruising” has been added**
- **“Increased blood level of a liver enzyme (ALT/SGPT)” has been added**
- **“Increased blood level of a liver enzyme (AST/SGOT)” has been added**

- “Increased blood level of a liver pigment (bilirubin) often a sign of liver problems” has been added
- “Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)” has been added
- “Increased blood level of a liver enzyme (GGT)” has been added
- “Increased blood level of a fat-digesting enzyme (lipase)” has been added
- “Increased blood level of a digestive enzyme (amylase)” has been added
- “Weight loss” has been added
- “Decrease in the total number of white blood cells (leukocytes)” has been added
- “More acid than normal in the blood” has been added
- “Loss of appetite” has been added
- “Increased blood level of potassium” has been added
- “Decreased blood level of potassium” has been added
- “Decreased blood level of magnesium” has been added
- “Joint pain” has been added
- “Bone pain” has been added
- “Muscle weakness of the whole body” has been added
- “Shrinking of muscles” has been added
- “Muscle pain” has been added
- “Commonly known as “pins and needles”, where part of the body (typically a foot or hand) begins to tingle and becomes numb, or “falls asleep” ” has been added
- “Weakness or paralysis (loss of muscle function) caused by damage to peripheral nerves (those nerves outside of brain and spinal cord)” has been added
- “Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning” has been added
- “Anxiety, feelings of dread or danger” has been added
- “Difficulty sleeping or falling asleep” has been added
- “More protein in the urine than usual, often a sign of kidney disease” has been added
- “Stuffy or runny nose, sneezing” has been added
- “Sudden constriction of the muscles in the walls of the bronchioles (small airways of the lung)” has been added
- “Cough” has been added
- “Irritation or sores in the lining of the voice box” has been added
- “Irritation or sores in the lining of the throat” has been added
- “A collection of symptoms including fever, difficulty breathing, chest pain, fluid in the lungs (seen on chest X-ray), fluid around the lungs and heart, and lack of oxygen first seen in patients receiving the drug retinoic acid” has been added
- “Sore throat” has been added
- “Irritation or sores in the lining of the windpipe” has been added
- “Hair loss” has been added
- “Excess sweating” has been added
- “Area of bleeding within the skin causing a reddish purple discoloration” has been added
- “Inflammation (swelling and redness) of the skin” has been added
- “Thickening of the skin” has been added
- “Darkening of the skin” has been added
- “Hives” has been added
- “Increase in the number and size of the pores in the capillaries (small blood vessels) which causes leakage of fluid from the blood to the tissue spaces resulting in dangerously low blood pressure, swelling and multiple organ failure” has been added
- “Sudden reddening of the face and/or neck” has been added

- “High blood pressure” has been added
- “Low blood pressure” has been added

Pages 54b-54e have been added to prevent extensive repagination.

Institutions **must** update their local consent forms to include the additions 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 (and those who have already signed a consent form but have not yet started treatment) **must** be informed of these additions. 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 amendment is being submitted in response to an RA from Dr. Naoko Takebe (takeben@mail.nih.gov; 301/496-1196).

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

cc: PROTOCOL & INFORMATION OFFICE
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Southwest Oncology Group

A National Clinical Research Group

May 15, 2010

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
 - () Initial activation
 - () Increased risk to patient
 - () Complete study redesign
 - () Addition of tissue banking requirements
 - () Study closure due to new risk information
- (√) Expedited review allowed (for CALGB institutions)
- (√) No review required (for SWOG and ECOG institutions)

MEMORANDUM

The purpose of this memorandum is to inform CALGB institutions of updated RT-PCR specimen submission requirements. CALGB institutions must submit specimens to a CLIA-approved laboratory for RT-PCR testing. Results of the RT-PCR testing will be reported by the CLIA-approved laboratory directly back to the site.

Patients who are enrolled in **CALGB-9862** must also continue to have specimens submitted for that correlative study as outlined in Section 15.4a.

A protocol revision to update the information in the protocol document is forthcoming.

Southwest Oncology Group and Eastern Oncology Group institutions will continue to submit specimens as outlined in the protocol.

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

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Southwest Oncology Group

A National Clinical Research Group

April 15, 2010

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
 - () Initial activation
 - () Increased risk to patient
 - () Complete study redesign
 - () Addition of tissue banking requirements
 - () Study closure due to new risk information
- (√) Expedited review allowed
- () No review required

MEMORANDUM

Due to the national shortage of daunorubicin, institutions without appropriate daunorubicin supply to treat patients according to the protocol schedule may substitute idarubicin for daunorubicin as follows:

During Consolidation Cycles #3 and #4:

Idarubicin 12 mg/m² Days 1-2

If Idarubicin is given, it must be documented on the **S0535** Consolidation Cycles 3 and 4 Treatment Summary Form in the "Other therapy" section as follows: (1) idarubicin must be written in "Specify agent(s)", and (2) the start and end treatment dates and the total idarubicin dose given for the reporting period must be recorded in the Comments section.

The protocol and forms will be revised soon. Until that revision is made, the use of idarubicin should be documented as described above according to the schedules in protocol Section 14.8.

This allowance is being made only for instances when daunorubicin is not available due to the national drug shortage. Any questions regarding this temporary allowance should be directed to the Study Coordinator.

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

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Southwest Oncology Group

A National Clinical Research Group

Distribution Date: April 1, 2010
CTEP Submission Date: March 25, 2010

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

REVISION #5

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- ☐ Full board review required. Reason:
 - ☐ Initial activation
 - ☐ Increased risk to patient
 - ☐ Complete study redesign
 - ☐ Addition of tissue banking requirements
 - ☐ Study closure due to new risk information
- ☒ Expedited review allowed
- ☐ No review required

REVISION #5

The primary purpose of this revision is to remove specimen submission requirements for **SWOG-9007**, "Cytogenetic Studies in Leukemia Patients" and **S9910**, "Leukemia Centralized Reference Laboratories and Tissue Repositories, Ancillary" from the above referenced study. For Southwest Oncology Group sites and other sites NOT affiliated with ECOG or CALGB, registration and submission of specimens to these ancillary studies will no longer be required. For these sites, RT-PCR testing according to the protocol schedule is still mandatory, but this testing may be done at any CLIA-approved laboratory. Similarly, for these sites, cytogenetic studies should be performed according to the protocol schedule, but at the site's preferred cytogenetics laboratory. Results of these RT-PCR and cytogenetics studies will be submitted as part of the protocol data as described in protocol Section 14.0. No changes are being implemented for CALGB or ECOG affiliated patients at this time.

1. The Version Date has been updated.
2. Page 14, Section 5.1b: This section has been revised to remove the mention of a central lab, since that no longer applies to SWOG sites and other sites NOT affiliated with ECOG or CALGB. Similar changes have been made in Sections 7.8a, 7.8b, 7.8c and 7.8d (Page 22), 7.8e (Page 23), and 15.1 (Page 40).
3. Page 14, Section 5.1f: This section has been updated to indicate that participation in SWOG cytogenetics study **SWOG-9007** is no longer required for patients at SWOG sites or other sites NOT affiliated with ECOG or CALGB, but that submission of specimens to each site's preferred cytogenetics laboratory is now required instead. Participation in cytogenetics studies remains mandatory for patients affiliated with CALGB or ECOG. Similar changes have been made in Sections 5.2b (Page 16) and 19.4 (Page 98).

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4. Page 15, Section 5.1g: This section has been updated to indicate that participation in SWOG ancillary study **S9910** is no longer required for patients at SWOG sites or other sites NOT affiliated with ECOG or CALGB, although pretreatment RT-PCR assay for PML-RAR α is still required. The first sentence has been revised to emphasize that the pretreatment RT-PCR assay is still required for all patients. The third sentence has been updated to state that specimen submissions must be via the “mechanisms” indicated, since the mechanism for SWOG and other non-ECOG/CALGB patients does not involve an ancillary protocol. The last sentence has been updated to indicate that repository aspects of the ancillary protocols “for CALGB and ECOG” are optional. The first bullet regarding specimen submission for SWOG patients has been updated to remove the references to **S9910** and the Southwest Oncology Group Leukemia Repository and to instead instruct that specimens must be submitted to a CLIA-approved laboratory. Similar changes have been made in Sections 5.2c (Page 16) and 5.3b (Page 17).
5. Page 16, Section 5.2c: The reference to Section 15.3 has been updated to 15.2 in this section. This change has also been made in Section 5.3b (Page 17).
6. Page 22, Sections 7.8a and 7.8b: The second sentence has been updated to indicate that specimens must be submitted for cytogenetics for patients affiliated with CALGB or ECOG and that specimens must be submitted for PCR for all patients. The fourth sentence has been revised to clarify that neither cytogenetic nor RT-PCR testing is required for repeat marrow aspiration and biopsy. Similar changes have been made in Sections 7.8e (Page 23) and 15.1 (Page 40). The word “ONLY” has been removed from the last sentence for clarity.
7. Page 10, Section 9.0: The “Specimen Submission” row has been replaced by rows entitled “Cytogenetics” and “RT-PCR for PML-RAR α ”. The “Σ” footnote has been included in both rows. In the “Cytogenetics” row, Xs have been added to the Pre-study and Induction columns. In the “RT-PCR for PML-RAR α ” row, Xs have been added to the Pre-study, Induction and Consolidation #1 through 2 columns. An “X¶” has been added to the Consolidation #3 through 4 (Prior) column, with associated “¶” footnote indicating that RT-PCR is required prior to Consolidation #3, but not #4. An “X $\dot{\iota}$ ” has been added to each of the new rows in the “Follow-Up” columns, with associated “ $\dot{\iota}$ ” footnotes indicating that follow-up cytogenetics and RT-PCR are required at relapse only. The “Ø” footnote has been updated to state that the marrow documenting CR may serve as the prior to Consolidation #1 marrow, providing it was performed within 8 weeks prior to Consolidation registration. A reference to Section 5.2 has also been included. An “X” has been added to the “Maintenance” column of the “RT-PCR for PML-RAR α ” row, as this test is required prior to maintenance.
8. Pages 38-39, Sections 14.4, 14.5, 14.7, 14.12, and 14.15: Submission of RT-PCR reports for SWOG sites and sites NOT affiliated with ECOG or CALGB has been added to each of these sections. The requirement for submission of the cytogenetics results has been added to Sections 14.4 and 14.15.
9. Page 40, Section 15.1: This section has been updated as follows to reflect the changes in specimen submission requirements for SWOG patients and other patients not affiliated with CALGB or ECOG:
 - The first sentence has been updated to remove the wording “regardless of Group affiliation”.
 - Information has been added indicating that RT-PCR and pretreatment cytogenetic requirements are applicable to all patients, regardless of group affiliation; associated times have been outlined.
 - The sentence referencing “additional details regarding specimen submission” has been updated to “additional details regarding mechanisms for obtaining these studies”.

- The “b” footnote reference has been added to the “Cytogenetics” column of the “At the time of neutrophil recovery or on Day 42” row. The associated “b” footnote has been added to state that these specimens are not required for SWOG sites and other sites not affiliated with ECOG or CALGB.
 - The “*” footnote has been updated to replace a reference to the “central” laboratory with references to the “testing” laboratory. The sentence indicating that the lab “will” contact the site for collection and submission of an additional specimen if the analysis is indeterminate has been updated to state that the lab “may” contact the site.
 - The “a” footnote, previously stating that the RT-PCR result will be reported back to the submitting institution, has been updated to emphasize that the pretreatment RT-PCR determines whether the patient is eligible or should continue on protocol treatment, and that if the pretreatment RT-PCR result is indeterminate, additional specimens should be submitted for RT-PCR testing to avoid indeterminate pretreatment results whenever possible.
10. Pages 40-41, Section 15.2a: This section, regarding patients at SWOG sites and other sites NOT affiliated with ECOG or CALGB, has been updated to replace specimen submission instructions for **SWOG-9007** with instructions to perform required cytogenetic studies at each institution’s preferred cytogenetics laboratory. A similar change has been made in Section 19.4 (Pages 96 and 98). The section heading has been revised accordingly.
 11. Page 41, Section 15.2b: This section, regarding patients at SWOG sites and other sites NOT affiliated with ECOG or CALGB, has been updated to remove specimen submission instructions for **S9910**. The section heading and Section 15.2b.1 have been revised accordingly. Section 15.2b.2 has been deleted and subsequent sections have been renumbered accordingly. The new Section 15.2b.2 (previously Section 15.2b.3) has been revised to clarify that RT-PCR testing must be performed at CLIA-approved laboratories. A similar change has been made in Section 19.4 (Pages 96 and 98).
 12. Pages 42-42a, Sections 15.2c, 15.2d and 15.2e have been deleted, since they are no longer applicable. Page 42 has intentionally been left blank.
 13. Page 50, Model Consent Form: In the “During the study...” section, the note to investigators after the last bullet on this page has been updated to indicate that this refers to the mandatory cytogenetic studies and RT-PCR testing (previously “submission of specimens to **SWOG-9007** and **S9910**”).
 14. Page 61, Model Consent Form: A note to investigators has been added after question #2 (regarding banking of specimens for future research) indicating that this section is applicable only to CALGB and ECOG institutions.
 15. Page 63, Model Consent Form: The instruction “[For patients participating through SWOG or any other institution not affiliated with ECOG or CALGB, use the following]” and the text immediately following have both been deleted.
 16. Page 96, Section 19.4: The last bullet under “Pre-study requirements for patient enrollment on **S0535**” has been revised to delete mention of **SWOG-9007** and **S9910**. The fourth bullet regarding CALGB sites has been updated to include requirement of registration to **CALGB8461** and **CALGB9862** prior to registration to **S0535**.
 17. Page 98, Section 19.4: The “Special materials or Substudies” section has been updated to delete mention of studies **SWOG-9007** and **S9910**. All information regarding the SWOG Specimen Tracking System has also been deleted. The information for CALGB sites has been updated to cite Section 15.4.

Southwest Oncology Group institutions (and other institutions NOT affiliated with ECOG or CALGB) **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 those changes.

Patients currently on treatment need not be informed of these changes unless required by the local Institutional Review Board (IRB).

ECOG and CALGB institutions need not update their local consents.

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

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CLOSED EFFECTIVE 06/01/2013



Southwest Oncology Group

A National Clinical Research Group

January 15, 2010

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- ☐ Full board review required. Reason:
 - ☐ Initial activation
 - ☐ Increased risk to patient
 - ☐ Complete study redesign
 - ☐ Addition of tissue banking requirements
 - ☐ Study closure due to new risk information
- ☐ Expedited review allowed
- ☒ No review required

MEMORANDUM

The purpose of this memorandum is to provide further information about requirements for SWOG patients on study **S0535**, following the change in reimbursements for leukemia specimen submissions as explained in the Memorandum distributed 1/11/10. A protocol revision that includes the following information, and that provides information about how to submit cytogenetics and PCR reports, is forthcoming.

PCR studies. SWOG institutions are no longer required to register patients on study **SWOG-9910**, "Leukemia Centralized Reference Laboratories and Tissue Repositories, Ancillary", as stated in Sections 5.1g, 5.2c and 5.3b of protocol **S0535**. However pretreatment PCR studies are still required to determine patient eligibility. These studies must be done at CLIA-approved laboratories. Patients must have a report documenting the PCR result as positive or indeterminate in order to be eligible; if PCR is negative or not done, the patient will be considered ineligible.

Institutions should also attempt to complete the subsequent PCR studies according to the current protocol schedule (see Section 15.1 of protocol **S0535**). Copies of all PCR reports should be obtained and kept in the patient's medical record.

The procedure for submitting PCR reports will be described in the forthcoming revision of protocol **S0535**.

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Cytogenetic studies. SWOG institutions are no longer required to register patients on study **S9007** "Cytogenetic Studies in Leukemia Patients", as stated in Sections 5.1f and 5.2b of protocol **S0535**. However it is requested that SWOG institutions perform local cytogenetic studies according to the protocol schedule (see Section 15.1 of protocol **S0535**), and that copies of the cytogenetics reports be obtained. The procedure for submitting cytogenetics reports will be described in the forthcoming revision of protocol **S0535**.

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.

This memorandum is applicable to SWOG sites and other sites not affiliated with CALGB or ECOG only. CALGB and ECOG specimen submission requirements will remain unchanged.

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

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CLOSED EFFECTIVE 06/01/2013



Southwest Oncology Group

A National Clinical Research Group

Distribution Date: December 1, 2009

CTEP Submission Date: October 29, 2009

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

REVISION #4

Study Coordinator: Jeffrey E. Lancet, M.D.

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E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
- () Initial activation
 - () Increased risk to patient
 - () Complete study redesign
 - () Addition of tissue banking requirements
 - () Study closure due to new risk information
- (√) Expedited review allowed
- () No review required

REVISION #4

1. Title page: The version date has been updated.
2. Pages 14-15, Sections 5.1f and 5.1g: Information regarding specimen submission for cytogenetics and PCR testing for CALGB institutions has been added to Sections 5.1f and 5.1g, respectively.
3. Page 16, Section 5.2b: This criterion requiring MUGA/ECHO evaluation and ejection fraction $\geq 50\%$ has been deleted as it is not necessary prior to consolidation Cycle #1. Subsequent sections have been renumbered accordingly.
4. Pages 16-17, Sections 5.2b, 5.2c and 5.3b: In the CALGB bullet in each of these sections, the note advising that details will be inserted as they become available has been replaced by a reference to Section 15.4 for specimen submission requirements.
5. Page 20, Sections 7.4d and 7.5c: Section 7.4d has been added and Section 7.5c has been updated to advise that MUGA or echocardiogram must be performed prior to initiation of Consolidation Cycle 3, and that if it was performed at baseline or any time prior to Cycle 3, it does not need to be repeated immediately prior to Cycle 3.

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6. Page 32, Section 9.0: The "X" and corresponding "Ω" footnote have been removed from the "Consolidation #1 through 2" column of the "MUGA/ECHO" row as the test is no longer required at this time point.
7. Pages 42c-42d, Section 15.4: This section has been updated to include specimen submission instructions for CALGB institutions for both PCR and cytogenetics testing.
8. Master Forms Set: The Induction Treatment Summary Form (Form #25817) has been updated to increase the number of spaces available for arsenic dose. The form # has been updated from #25817 to #55067 in Sections 14.5 (Page 38) and 18.2f (Page 46).
9. Master Forms Set: The **S0535** Consolidation Eligibility Form (Form #46528) has been removed from the master forms set as it is no longer relevant. As a result of this change, the requirement for submission of the Consolidation Eligibility Form has been deleted from above Section 5.2 (Page 16). Section 14.6 on Page 38 (previously requiring submission of the Consolidation Eligibility Form) has been deleted and subsequent sections on Pages 38-40 have been renumbered accordingly. Section 18.2h on Page 46 (previously listing the Consolidation Eligibility Form) has been deleted and subsequent sections on that page have been renumbered accordingly.
10. Master Forms Set: The **S0535** Consolidation Cycles 1 and 2 Treatment Summary Form has been updated to collect MUGA/ECHO results. The form # has been updated from #9341 to #25052 in Sections 14.6 (Page 38) and 18.2h (Page 46).

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.
Tracy Maher
Camille White
Jean Barce
Michael Kelly - CALGB
Ryan Palmer - ECOG
Virginia Dixon-Lipscomb – Wyeth
Karl Buer - Biologics



Southwest Oncology Group

A National Clinical Research Group

Distribution Date: December 1, 2009
E-mailed Date: November 20, 2009

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

IRB Review Requirements

- () Full board review required. Reason:
- () Initial activation
 - () Increased risk to patient
 - () Complete study redesign
 - () Addition of tissue banking requirements
 - () Study closure due to new risk information
- () Expedited review allowed
- (√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites of the Thanksgiving holiday closure for Biologics Clinical Trial Services (BCTS), the distributor of gemtuzumab ozogamicin for this study. BCTS will be closed on Thursday, November 26 and Friday, November 27, 2009. Regular business hours will be resumed on Monday, November 30, 2009.

Please plan shipment needs for gemtuzumab ozogamicin accordingly.

If you have questions or need to coordinate shipments in advance, please contact the **S0535** Biologics Clinical Trial Project Manager, Karl Buer, at 800/693-4906 ext. 4991.

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

cc:	PROTOCOL & INFORMATION OFFICE	Camille White
	Kenneth J. Kopecky, Ph.D.	Jean Barce
	Megan Othus, Ph.D.	Michael Kelly – CALGB
	Holly Gundacker, M.S.	Ryan Palmer - ECOG
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Distribution Date: February 15, 2009
CTEP Submission Date: January 28, 2009

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

REVISION #3

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
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IRB Review Requirements

- () Full board review required. Reason:
- () Initial activation
 - () Increased risk to patient
 - () Complete study redesign
 - () Addition of tissue banking requirements
 - () Study closure due to new risk information
- (√) Expedited review allowed
- () No review required

REVISION #3

1. Title page: The version date has been updated.
2. Pages 11-11a, Section 3.4c: Wyeth, Corp. will now supply the drug gemtuzumab ozogamicin for this study. The supplier information in Section 3.4c has been updated to indicate this, and drug ordering information has been added. Page 11a has been added to prevent extensive repagination.
3. Page 57, Model Consent Form: ATRA Syndrome has been moved from "Less Likely" to "Rare but Serious" in the risks and side effects related to maintenance therapy. This side effect was incorrectly added to the "less likely" section during a previous revision.
4. Page 59, Model Consent Form: Wyeth Corp. has been added to the list of organizations that may access medical records of patients taking part in this study. Gemtuzumab ozogamicin has been removed from the list of commercially available drugs in the "what are the costs of taking part in this study?" section. A sentence has been added indicating that the drug is commercially available but it will be provided free of charge by Wyeth, Corp. for this study.

Operations Office

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

The Southwest Oncology Group considers that the changes in the Model Consent Form that are associated with this Revision are solely administrative and editorial in nature, and do not impact the risk/benefit ratio for participants on this study. Local accrual to the study does not have to be suspended pending implementation of these changes.

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.
Tracy Maher
Camille White
Jean Barce
Michael Kelly – CALGB
Ryan Palmer - ECOG

CLOSED EFFECTIVE 06/01/2013

December 1, 2008

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

MEMORANDUM

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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 (**for institution already participating**)
- (√) No review required

MEMORANDUM

Please note that Revision #2 contains the following error: The cover memorandum states that "ATRA syndrome" has been added to the "Rare but Serious" side effects category for Maintenance therapy, but it was incorrectly added to the "Less Likely" category in the consent form. ATRA syndrome is a "Rare but Serious" side effect, and the cover memorandum was correct in stating it should have been added to that category. This correction will be made during the next revision/amendment, and institutions may make this correction to local consent forms in the meantime.

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.
Tracy Maher
Michael Kelly – CALGB
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Operations Office



Southwest Oncology Group

A National Clinical Research Group

Distribution Date: November 15, 2008

CTEP Submission Date: November 12, 2008

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

FROM: Sandi Jo McMillan, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

REVISION #2

Study Coordinator: Jeffrey E. Lancet, M.D.

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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 (**for institution already participating**)
- () No review required

REVISION #2

1. Title page: The version date has been updated.
2. Page 14, Section 5.1e: This eligibility criterion has been revised to allow prior therapy with ATRA administered for up to 3 days prior to registration. It is not felt that this ATRA exposure will affect the outcome of the trial, and is more feasible for enrollment as immediate start of ATRA is standard care for this disease. The "f" footnote has been added to the Study Calendar (Section 9.0, Page 32) explaining this as well. Because of this change, Section 7.8a (Page 22) has been reworded to clarify that the marrow exam is performed on Day 42 after beginning protocol ATRA, and does not include any ATRA administration that may have occurred prior to starting protocol therapy. This change has also been made in Section 15.2a.1b (Page 41).
3. Pages 14-17, Sections 5.1f-5.1g, 5.2c-5.2d, and 5.3b: These sections have been updated to indicate that SWOG patients and any patients not affiliated with ECOG or CALGB must submit specimens as outlined for each section (previously said any Southwest Oncology Group patients). The reference to Section 15.2 in Section 5.3b has been changed to 15.3 for accuracy.

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4. Page 18, Section 7.1e: This section has been added to indicate that patients who become pregnant after registration must be removed from protocol therapy. Similar changes have been made in Section 7.11f (Page 26) and the Model Consent Form (Pages 51a and 58). The sentence in Sections 3.1b (Page 5) stating that ATRA use in pregnant women is not prohibited on this protocol has been deleted.
5. Page 18, Section 7.2c: Serial coagulation studies outlined in this section have been changed from twice weekly during induction and then as clinically indicated thereafter to twice weekly during induction until normal and then as clinically indicated thereafter, as it is not necessary for this testing to be performed so often once numbers have stabilized. The "Δ" footnote has been updated in the Study Calendar (Section 9.0, Page 32) indicating this as well.
6. Page 32, Section 9.0: The "√" footnote has been updated to indicate that the marked tests are performed every 3 months until 3 years from initial registration (previously said for 3 years after off treatment).
7. Page 55, Model Consent Form: Increased blood level of a fat called triglyceride has been added to the risks/side effects (likely section) for Consolidation #3 and 4. This change was previously made to the Induction risks/side effects but the cover memorandum incorrectly stated that it had been changed in the Consolidation #3 and 4 section instead of the Induction section. The added risk is necessary for both sections, so will remain in the Induction section as well.
8. Page 57, Model Consent Form: ATRA syndrome has been added to the rare but serious risks/side effects for maintenance therapy, along with a brief explanation of related symptoms.
9. Page 96, Section 19.4: The italicized words "protocol number" have been replaced by the study number "**S0535**".

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

The Southwest Oncology Group considers that the changes in the Model Consent Form that are associated with this Revision are solely administrative and editorial in nature, and do not impact the risk/benefit ratio for participants on this study. Local accrual to the study does not have to be suspended pending implementation of these changes.

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.
Tracy Maher
Amy Edwards
Michael Kelly – CALGB
Ryan Palmer - ECOG



Southwest Oncology Group

A National Clinical Research Group

Distribution Date: June 15, 2008

CTEP Submission Date: May 30, 2008

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

REVISION #1

Study Coordinator: Jeffrey E. Lancet, M.D.

Phone number: 813/745-6841

E-mail: lancetje@moffitt.usf.edu

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 (**for institution already participating**)
- () No review required

REVISION #1

1. Title page: The version date has been updated. The page number for Section 16.0 has been updated. The spelling of the drug Tretinoin has been corrected (previously written as Trentinoin). This change has also been made in Section 3.1 (Page 4). CTSU has been added to the participants list.
2. Pages 2-2a: The Study Coordinator information for the cooperative groups ECOG and CALGB have been added. CTSU participation information and CTSU address and contact information text boxes have been added. Page 2a has been added to prevent extensive repagination.
3. Pages 14-15, Sections 5.1f-5.1g: These sections have been updated to include specimen submission requirements for the cooperative group ECOG as part of the eligibility criteria. These sections have also been structured to allow for the addition of CALGB requirements which are still pending. Similar changes have been made in Sections 5.2c and 5.2d (Page 16) and 5.3b (Page 17).
4. Page 20, Section 7.5c: The phrase "if performed" has been added to the requirement to use the same test (MUGA or echocardiogram) that was used during Consolidation Cycle 1 for clarity.

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5. Page 32, Section 9.0: A "Ω" footnote has been added to the "MUGA/ECHO" row in the prior to Consolidation #1 through 2 column. This footnote states that this test is only to be performed for patients who experienced signs or symptoms of clinically significant cardiac toxicity during or after Induction therapy, and references Section 5.2b. A "≠" footnote has been added to the "MUGA/ECHO" row in the prior to Consolidation #3 through 4 column. This footnote states that if MUGA/ECHO was performed prior to Consolidation #1, the same test should be used prior to Consolidation #3, and references Section 7.5c. A "†" footnote has been added to the "Height, Weight and BSA" row in the during Consolidation #1 through 2, # 3 through 4 and #5 through 6 columns. This footnote states that these are required prior to each cycle of consolidation.
6. Page 36, Section 13.0: A note has been added directing non-SWOG participants to Appendix 19.4 for CTSU participation procedures.
7. Pages 40-42d, Sections 15.1-15.4: Sections 15.1-15.4 have been restructured to allow for the addition of ECOG and CALGB participation information. Section 15.1 now contains the specimen submission summary for all groups, Section 15.2 contains information for SWOG (and other institutions not associated with ECOG or CALGB), and Section 15.3 contains information for ECOG. Section 15.4 has been kept as a placeholder for the CALGB specimen submission information which is still pending. Pages 42a-42d were added to prevent extensive repagination.
8. Page 44, Section 16.1: Footnote "b" in Table 16.1 has been updated to reflect changes in Southwest Oncology Group Policy No. 23. It now states that following an AdeERS report, supporting data does not need to be submitted unless specifically requested by SWOG. In addition, the requirement to submit evidence of IRB notification to SWOG has been rescinded (although the requirement to notify IRBs of all SAEs has not).
9. Pages 50-51a, Model Consent Form: Treatment tables have been added for each of the treatment cycles in order to provide a treatment summary for patients as requested by several local IRBs. Page 51a has been added to prevent extensive repagination.
10. Page 53-55, Model Consent Form: Several items have been moved in the risks and side effects sections in order to more closely coincide with the associated probability of each risk as listed in the drug information sections of the protocol. In the Induction Therapy section, "Nosebleed" has been moved from "Less Likely" to "Likely" and "Severe injury to liver (veno-occlusive disease)" has been moved from "Rare, but Serious" to "Less Likely". In the Consolidation #3 and #4 section, "Eye problems, visual disturbances" has been moved from "Less Likely" to "Likely". "Increased blood level of a form of fat called triglyceride" had been added to the "Likely" section to coincide with the drug toxicology in Section 3.1b.
11. Pages 57-58, Model Consent Form: The section for Risks and side effects related to Maintenance Therapy with gemtuzumab ozogamicin has been removed. Gemtuzumab ozogamicin is not used during Maintenance therapy, and therefore this section is not pertinent to this protocol.
12. Page 59, Model Consent Form: CTSU has been added to the list of organizations that might have access to patient information under the "will my medical information be kept private" section.
13. Pages 63, Model Consent Form and 65, Specimen Consent Supplemental Sheets: The existing specimen and repository information and address have been updated to indicate that they are relevant for patients participating through SWOG or other institutions not affiliated with ECOG or CALGB. Information for the ECOG specimen repository has been added to each page as well.

14. Page 91, Section 19.0: "19.4 Cancer Trials Support Unit (CTSU) Participation Procedures" was added to the Appendix list.
15. Pages 96-100, Appendix 19.4: "Cancer Trials Support Unit (CTSU) Participation Procedures" was added as Appendix 19.4. Pages 96-100 were added to the protocol.

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

The Southwest Oncology Group considers that the changes in the Model Consent Form that are associated with this Revision are solely administrative and editorial in nature, and do not impact the risk/benefit ratio for participants on this study. Local accrual to the study does not have to be suspended pending implementation of these changes.

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.
Tracy Maher
Amy Edwards
Michael Kelly – CALGB
Ryan Palmer - ECOG

CLOSED EFFECTIVE 06/01/2013



Southwest Oncology Group

A National Clinical Research Group

November 15, 2007

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

FROM: Southwest Oncology Group Operations Office

RE: **S0535**, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab
Ozogamicin in Patients with Previously Untreated High-Risk Acute
Promyelocytic Leukemia" Study Coordinators: Drs. J.E. Lancet, R.
Komrokji, C.L. Willman, and M.L. Slovak.

STATUS NOTICE

Study Coordinator: Jeffrey E. Lancet, M.D.
Phone number: 813/745-6841
E-mail: lancetje@moffitt.usf.edu

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. The entire protocol is attached for your use.

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.
Tracy Maher
Amy Edwards
Michael Kelly – CALGB
Ryan Palmer - ECOG

Operations Office

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SOUTHWEST ONCOLOGY GROUP

PROTOCOL FAST FACT SHEET

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

S0535

A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients with Previously Untreated High-Risk Acute Promyelocytic Leukemia

Drugs provided: **Gemtuzumab Ozogamicin**

Induction ATRA 45mg/m ² /day(in 2 doses, 22.5 mg/m ² every 12 hours PO, Day 1 to CR Gemtuzumab Ozogamicin 9 mg/m ² IV infusion over 2h, Day 1 only Arsenic Trioxide 0.15 mg/kg/d IV infusion over 2 hours 5 days/wk beginning on Day 10 and continuing until CR	
Consolidation Cycles 1 and 2 Arsenic Trioxide 0.15 mg/kg/day IV over 2 hours 5 days/week x 5 weeks, repeat after 2 weeks rest	
Consolidation Cycles 3 and 4 ATRA 45mg/m ² /day(in 2 doses, 22.5 mg/m ² every 12 hours PO, Days 1-7 Daunomycin 50 mg/m ² /day IV bolus or 1 hour infusion Days 1-3	
Consolidation Cycles 5 and 6 Gemtuzumab Ozogamicin 9 mg/m ² IV infusion over 2 hours Day 1 only	
Maintenance Chemotherapy ATRA 45/m ² /day(in 2 doses, 22.5 mg/m ² every 12 hours PO, Days 1-7 every 14 days 6MP 60mg/m ² /day PO daily for 1 year Methotrexate 20mg/m ² PO once per week for 1 year	
Eligibility	Ineligibility
Morphologically confirmed diagnosis of high risk acute promyelocytic leukemia (APL). Based on bone marrow examination performed within 14 days before registration. The WBC confirming high risk must be obtained within 14 days prior to registration.	Known PML-RARα-negative by the RT-PCR assay.
Patient must have reached their 18 th birthday	Prior systemic therapy for acute leukemia (except ATRA for up to 3 days prior to registration). Administration of hydroxyurea, corticosteroids, and leukapheresis to control high cell counts prior to registration is permitted.
Participation in cytogenetic studies is mandatory. Collection of pretreatment specimens must be completed within 14 days prior to registration.	Patients must not be pregnant or nursing because ATRA as well as other drugs used in this protocol may cause fetal harm and because of the potential for serious adverse reactions in nursing infants from the drug. Women of child bearing potential must have a negative pregnancy test performed within 14 days prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method.
Pretreatment specimens for baseline RT-PCR assays for PML-RARα must be collected and submitted within 14 days prior to registration	No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.
Patient must not have prolonged QTc > 0.47 seconds	

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

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activated November 15, 2007

SWOG

A PHASE II STUDY OF ATRA, ARSENIC TRIOXIDE AND GEMTUZUMAB OZOGAMICIN IN PATIENTS WITH PREVIOUSLY UNTREATED HIGH-RISK ACUTE PROMYELOCYTIC LEUKEMIA

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AGENTS:

All Trans Retinoic Acid (Tretinoin) (NSC-122758)
Arsenic Trioxide (Trisenox[®]) (NSC-706363)
Daunomycin (Cerubidine)
(daunorubicin hydrochloride) (NSC-82151)
Gemtuzumab Ozogamicin (Mylotarg[®])
(NSC-720568)
6-Mercaptopurine (NSC-755)
Methotrexate (NSC-740)

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ALLIANCE/Alliance for Clinical Trials in Oncology

ECOG-ACRIN/ECOG-ACRIN Cancer Research Group

SWOG/SWOG

CLOSED EFFECTIVE 06/01/2013

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with **SWOG** will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- 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://members.ctsu.org>
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the Southwest Oncology Group. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to SWOG *unless* otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the Southwest Oncology Group. Please send query responses and delinquent data to the Southwest Oncology Group Data Operations Center and do not copy the CTSU Data Operations.
- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the SWOG data center.

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, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays) [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 am and 5:30 pm.]	Preferred method: Fax: 800/892-4007 Mailing address: Southwest Oncology Group Data Operations Center Cancer Research and Biostatistics 1730 Minor Ave, STE 1900 Seattle, WA 98101-1468 Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For patient eligibility or treatment-related questions contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctscontact@westat.com . All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Public Web site is located at: www.ctsu.org The CTSU Registered Member Web site is located at https://members.ctsu.org		

CTSU logistical information is located in Appendix [18.4](#)

1.0 OBJECTIVES

1.1 Primary Objective

To assess the event-free survival and death during the first six weeks in patients with previously untreated high-risk acute promyelocytic leukemia treated with a combined regimen of all trans retinoic acid (ATRA), arsenic trioxide, and gemtuzumab ozogamicin.

1.2 Secondary Objective

To estimate the frequency and severity of toxicities of this regimen in this group of patients.

1.3 Translational Medicine Objective

To investigate the molecular response rate utilizing this regimen in high-risk patients.

2.0 BACKGROUND

The outlook for patients with APL has improved markedly over the past decade, mostly because of the development of all trans retinoic acid and an increased appreciation for the importance of anthracycline dose in therapy. Nonetheless, at least 20% of patients presenting with APL still die of the disease or a complication of its treatment. The Spanish (PETHEMA) and Italian (GIMEMA) cooperative groups have identified risk factors for treatment failure based on presenting white blood cell (WBC) and platelet counts. (1) Low risk patients are those presenting with a WBC $\leq 10,000$ and a platelet count $> 40,000$, intermediate risk patients also have a WBC $\leq 10,000$ but have a platelet count $\leq 40,000$, while high risk patients have a presenting WBC $> 10,000$. Other groups, including the British (MRC) and French, have reported similar findings. (2,3) Using modern therapies, both low and intermediate risk patients can be expected to enter complete remission in at least 95% of cases, and have a risk of relapse during the first year of therapy of less than 5%. (4) These outstanding results raise the question of whether these patients may be receiving more therapy than necessary, a question that will be addressed in the North American Leukemia Intergroup study for low- and intermediate-risk APL, study **S0521**. For patients with high-risk disease, as defined by the PETHEMA and GIMEMA groups, the outcomes of treatment have been less favorable, with early death seen in at least 20% of patients, most often due to hemorrhage, usually of the CNS or lungs, and/or infection, and a substantial risk for relapse, estimated to be at least 25%. For example, in the MRC trial, among patients presenting with a WBC of over 10,000, the risk of early death in patients treated with ATRA until CR was 24% and the risk of relapse was 47%. In the recently reported PETHEMA LPA99 trial, although outstanding results were reported in the low- and intermediate-risk groups, early deaths were seen in at least 20% of high-risk patients, and the recurrence rate was 24% for this group. (5) Thus, for patients with high-risk disease, improved therapies are needed.

The last North American Intergroup study, **CALGB 9710**, included induction therapy with ATRA, an anthracycline and cytarabine, and consolidation with an anthracycline and ATRA. In addition, the study asked two questions, both in a randomized fashion. First, the study asked whether additional consolidation with arsenic trioxide impacted outcome. And second, the study asked whether the addition of methotrexate and 6-mercaptopurine to ATRA maintenance improved disease-free and overall survival. The study has completed its accrual goal of 500 patients, but additional follow-up will be needed to determine the answers to the randomized questions. While data from the study according to specific treatment arm are not available, the Data and Safety Monitoring Board has released sufficient information to at least confirm the general conclusions of the PETHEMA and GIMEMA groups. These data both confirm the PETHEMA/GIMEMA risk stratification, and emphasize the need to find better therapy for high-risk patients.

There have been various attempts to improve therapy in this high-risk group. One approach has been to add additional supportive care measures. For example, the PETHEMA group has reported on the use of prophylactic prednisone and prophylactic tranexamic acid, and concluded that neither was effective in reducing the incidence of early deaths in newly diagnosed APL. (6)

Encouraging results have been reported with the combination of ATRA plus arsenic trioxide, but these studies have not been confined to high-risk patients. (7,8) Gemtuzumab ozogamicin (G.O.) is composed of a humanized anti-CD33 monoclonal antibody conjugated to calicheamicin, a potent antitumor antibiotic. Because CD33 is brightly expressed by APL blasts in virtually all cases of APL, the conjugate has been studied as therapy for patients with recurrent disease. Initial results appeared promising and led Estey et al. to combine gemtuzumab with ATRA as initial therapy for APL. (9,10) This regimen was found to have a high rate of CR, including a 43% rate of PCR negativity at the conclusion of induction therapy. (11) Most recently, Estey et al. have conducted a pilot study of the combination of ATRA, arsenic trioxide and gemtuzumab ozogamicin as initial therapy for 18 patients with high-risk APL, i.e. those with a WBC > 10,000. (12) They report a CR rate of 86% in this high-risk group, a figure superior to what they have achieved with any other regimen they have tested. In addition, all evaluable patients became PCR negative at 3 and 6 months from the date of initial CR.

Given the clinical problem posed by the patients with high-risk APL and the encouraging results so far utilizing the combinations described above, the Southwest Oncology Group has proposed the Phase II study described herein, utilizing a novel treatment regimen including induction therapy with ATRA, arsenic and gemtuzumab ozogamicin, in order to explore both its impact on disease-free survival and toxicity.

Inclusion of Women and Minorities

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

3.0 DRUG INFORMATION

3.1 All Trans Retinoic Acid (Tretinoin) (NSC-122758)

a. DESCRIPTION:

Chemistry: All trans retinoic acid (tRA) is a natural retinol metabolite formed from the intestinal oxidation of B-carotene and from tissue anabolism of retinaldehyde. Both retinol and tRA circulate in the blood in tight association with serum proteins, retinol binding protein for retinol and albumin for tRA. tRA is a major endogenous metabolite of Vitamin A (retinol). tRA induces differentiation and/or growth-inhibition in many tumorigenic cell lines and demonstrates therapeutic efficacy in the treatment of certain leukemias particularly promyelocytic leukemia. It also acts to stimulate clonal proliferation of hematopoietic cells and augments, either directly or indirectly, a variety of immune functions.

b. TOXICOLOGY:

Human Toxicology: The toxicities of tRA closely resemble those of hypervitaminosis A. Cheilitis (80% of patients) and headache (77%) are the most common toxicities of tRA usage. Other toxicities include visual disturbances, dryness of mucous membranes, pruritis, dry skin, peeling, fatigue and epistaxis in 10 - 50% of patients. 10% or less of patients develop musculoskeletal pain, conjunctivitis and psychological changes. The CNS toxicity appears dose-related, occurring in 4% or less when tRA is administered at 30 mg/day, but occurring in 50% when tRA is administered at 70 - 100 mg/day. Increases in SGOT/SGPT/bilirubin, triglycerides, cholesterol and fibrinogen have also been seen. All trans retinoic acid has been associated with cases of pseudotumor cerebri.

Skeletal changes have been reported in adults receiving prolonged treatment with cis retinoic acid (cRA). Whether these effects accompany tRA administration of long term is not well defined. In APL patients treated with tRA, 55% developed hypertriglyceridemia and 40% manifested increased liver transaminases. Patients with APL have also experienced hyperleukocytosis and a cardio-pulmonary syndrome.

Like cRA, tRA must be considered a teratogen, and may potentially cause craniofacial abnormalities, CNS abnormalities, thymic aplasia and cardiac abnormalities. It is considered a class C FDA pregnancy risk since animal studies have shown adverse effects and toxicities on the fetus. No adequate or well-controlled studies have been done on pregnant women.

It is strongly recommended that women of childbearing potential have a pregnancy test performed within two weeks prior to all trans retinoic acid therapy. Females should be fully counseled regarding the risk to the fetus of using ATRA.

Females should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment. An effective form of contraception should be used for at least one month before and also throughout all trans retinoic acid therapy, and two months after. If pregnancy does occur during treatment, the physician and patient should discuss the desirability of continuing the pregnancy.

c. PHARMACOLOGY

Pharmacokinetics: Unlike cRA, little published data exists regarding the pharmacokinetics of tRA. However, the pharmacologic transformations of tRA may resemble cRA. Under ambient light, cRA in solution equilibrates with tRA in 2 hours in a ratio of 3:1, cis:trans. In vivo conversion occurs to a variable extent, tRA representing 0 - 30% of cRA plasma concentration in patients taking oral cRA. cRA is conjugated to glucuronic acid and is excreted via the biliary tract into the enterohepatic circulation. cRA achieves peak plasma concentration after oral dosing in 1.5 - 3.0 hours. An 80 mg dosage of cRA produces peak plasma levels approaching 1 μ M; doses of 4 mg/kg produce peak plasma concentrations of 4 μ M. cRA shows a biphasic elimination profile with a $t_{1/2\beta}$ of 2 - 4 hours and $t_{1/2\alpha}$ of 10 - 77 hours. cRA oxidizes to 13-cis-4-ketoretinoic acid, the major serum metabolite which accumulates with chronic cRA oral therapy to produce an AUC 5-fold greater than the parent compound.

Formulation: 10 mg capsules of the active ingredient formulated with butylated hydroxyanisole, disodium edate, refined soybean oil, BHA, and a wax mixture consisting of purified beeswax, hydrogenated soybean oil flakes and hydrogenated vegetable oil. The capsules should be stored at room temperature protected from light.

Administration: PO.

Supplier: All Trans Retinoic Acid 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 product's package insert for full prescribing and toxicity information.

3.2 Arsenic Trioxide (Trisenox[®]) (NSC-706363)

a. Description

Arsenic trioxide is a trivalent inorganic arsenical. The molecular formula is As₂O₃.

b. Toxicology

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Arsenic trioxide (Trisenox, NSC 706363)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements'

http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf further clarification. *Frequency is provided based on 680 patients.* Below is the CAEPR for Arsenic trioxide (Trisenox).

Version 2.0, March 26, 2010¹

Adverse Events with Possible Relationship to Arsenic trioxide (Trisenox) (CTCAE 4.0 Term) [n= 680]			EXPECTED AEs FOR CTEP-AERS REPORTING Agent Specific Adverse Event List (ASAEL)
Likely (> 20%)	Less Likely (<=20%)	Rare but Serious (<3%)	Expected
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		Anemia
	Febrile neutropenia		Febrile neutropenia
	Blood and lymphatic system disorders - Other (pancytopenia)		
CARDIAC DISORDERS			
	Conduction disorder		Conduction disorder
	Palpitations		Palpitations
	Sinus tachycardia		Sinus tachycardia
	Ventricular arrhythmia		Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS			
	Tinnitus		Tinnitus
GASTROINTESTINAL DISORDERS			
	Abdominal distension		Abdominal distension
	Abdominal pain		Abdominal pain
	Anal mucositis		Anal mucositis
	Constipation		Constipation
Diarrhea			Diarrhea
	Dry mouth		Dry mouth
	Dyspepsia		Dyspepsia
	Mucositis oral		Mucositis oral
Nausea			Nausea
	Pancreatitis		Pancreatitis
	Rectal mucositis		Rectal mucositis
	Small intestinal mucositis		Small intestinal mucositis
	Toothache		Toothache
Vomiting			Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		Chills
	Edema face		Edema face
	Edema limbs		Edema limbs
Fatigue			Fatigue
Fever			Fever
	Injection site reaction		Injection site reaction
	Non-cardiac chest pain		
	Pain		Pain
INFECTIONS AND INFESTATIONS			
Infection ²			Infection²
	Infections and Infestations - Other (opportunistic infection associated with \geq Grade 2 lymphopenia)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		Bruising
INVESTIGATIONS			
	Alanine aminotransferase increased		Alanine aminotransferase increased
	Aspartate aminotransferase increased		Aspartate aminotransferase increased
	Blood bilirubin increased		Blood bilirubin increased
	Creatinine increased		Creatinine increased
	Electrocardiogram QT corrected interval prolonged		Electrocardiogram QT corrected interval prolonged
	GGT increased		GGT increased
	Lipase increased		Lipase increased
Neutrophil count decreased			Neutrophil count decreased
Platelet count decreased			Platelet count decreased
	Serum amylase increased		Serum amylase increased
	Weight gain		Weight gain
	Weight loss		Weight loss
	White blood cell decreased		White blood cell decreased
METABOLISM AND NUTRITION DISORDERS			
	Acidosis		Acidosis
	Anorexia		Anorexia
	Hyperglycemia		Hyperglycemia
	Hyperkalemia		
	Hypokalemia		Hypokalemia
	Hypomagnesemia		Hypomagnesemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		<i>Arthralgia</i>
	Bone pain		<i>Bone pain</i>
	Generalized muscle weakness		<i>Generalized muscle weakness</i>
	Musculoskeletal and connective tissue disorder - Other (muscle atrophy)		<i>Musculoskeletal and connective tissue disorder - Other (muscle atrophy)</i>
	Myalgia		<i>Myalgia</i>
NERVOUS SYSTEM DISORDERS			
	Dizziness		<i>Dizziness</i>
Headache			<i>Headache</i>
	Paresthesia		
	Peripheral motor neuropathy		<i>Peripheral motor neuropathy</i>
	Peripheral sensory neuropathy		<i>Peripheral sensory neuropathy</i>
PSYCHIATRIC DISORDERS			
	Anxiety		
	Insomnia		<i>Insomnia</i>
RENAL AND URINARY DISORDERS			
	Acute kidney injury		<i>Acute kidney injury</i>
	Proteinuria		<i>Proteinuria</i>
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		<i>Allergic rhinitis</i>
	Bronchospasm		<i>Bronchospasm</i>
	Cough		<i>Cough</i>
Dyspnea			<i>Dyspnea</i>
	Epistaxis		
	Laryngeal mucositis		<i>Laryngeal mucositis</i>
	Pharyngeal mucositis		<i>Pharyngeal mucositis</i>
	Pleural effusion		<i>Pleural effusion</i>
	Retinoic acid syndrome		<i>Retinoic acid syndrome</i>
	Sore throat		
	Tracheal mucositis		<i>Tracheal mucositis</i>
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		<i>Alopecia</i>
	Dry skin		<i>Dry skin</i>
	Hyperhidrosis		<i>Hyperhidrosis</i>
Pruritus			<i>Pruritus</i>
	Purpura		<i>Purpura</i>
Rash maculo-papular			<i>Rash maculo-papular</i>
	Skin and subcutaneous tissue disorders - Other (dermatitis)		
	Skin and subcutaneous tissue disorders - Other (hyperkeratosis)		<i>Skin and subcutaneous tissue disorders - Other (hyperkeratosis)</i>

SKIN AND SUBCUTANEOUS TISSUE DISORDERS (contd.)			
	Skin hyperpigmentation		<i>Skin hyperpigmentation</i>
	Urticaria		<i>Urticaria</i>
VASCULAR DISORDERS			
	Capillary leak syndrome		<i>Capillary leak syndrome</i>
	Flushing		<i>Flushing</i>
	Hypertension		<i>Hypertension</i>
	Hypotension		<i>Hypotension</i>

¹ This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

² Infection includes all 75 sites of infection under the INFECTIONS and INFESTATIONS SOC.

³ Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

Also reported on Arsenic trioxide (Trisenox) trials but with the relationship to Arsenic trioxide (Trisenox) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy); Disseminated intravascular coagulation; Leukocytosis

CARDIAC DISORDERS - Heart failure; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - External ear pain; Vertigo

EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Eye pain; Watering eyes

GASTROINTESTINAL DISORDERS - Dysphagia; Fecal incontinence; Flatulence; Gastrointestinal hemorrhage³; Ileus

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Gait disturbance; Malaise

HEPATOBIILIARY DISORDERS - Hepatobiliary disorders - Other (cytolytic hepatitis)

IMMUNE SYSTEM DISORDERS - Allergic reaction

INVESTIGATIONS - Alkaline phosphatase increased; INR increased; Investigations - Other (blood lactate dehydrogenase); Investigations - Other (electrocardiogram T wave abnormal); Investigations - Other (inverted T wave)

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypermagnesemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hyponatremia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (joint swelling); Musculoskeletal and connective tissue disorder - Other (muscle cramps); Neck pain; Pain in extremity

NERVOUS SYSTEM DISORDERS - Depressed level of consciousness; Dysgeusia; Lethargy; Nervous system disorders - Other (hypoesthesia); Nervous system disorders - Other (restless leg syndrome); Neuralgia; Seizure; Tremor

PSYCHIATRIC DISORDERS - Agitation; Confusion; Depression
RENAL AND URINARY DISORDERS - Renal and urinary disorders - Other (renal insufficiency); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Bronchopulmonary hemorrhage; Hypoxia; Nasal congestion; Pharyngolaryngeal pain; Pneumonitis; Pulmonary edema; Respiratory, thoracic and mediastinal disorders - Other (bronchitis); Respiratory, thoracic and mediastinal disorders - Other (crepitations); Respiratory, thoracic and mediastinal disorders - Other (rales); Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Palmar-plantar erythrodysesthesia syndrome; Periorbital edema; Skin and subcutaneous tissue disorders - Other (folliculitis); Skin hypopigmentation
VASCULAR DISORDERS - Thromboembolic event; Vasculitis

Note: Arsenic trioxide (Trisenox) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

c. Pharmacology

Formulation: Each ampule contains 10 mg of arsenic trioxide (1 mg/mL) in a sterile, nonpyrogenic, preservative-free clear solution in water for injection using NaOH and HCl to adjust to pH 7-9. The drug should be diluted in 100 mL to 500 mL of 5% Dextrose in Water Injection, USP or 0.9% Sodium Chloride Injection, USP prior to infusion.

Storage and Stability: Intact ampules should be stored at room temperature. The solution as diluted above is chemically and physically stable at room temperature for 24 hours.

Administration: The route of administration is intravenous.

Supplier: Arsenic trioxide 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 product's package insert for full prescribing and toxicity information.

3.3 Daunomycin (Cerubidine) (daunorubicin hydrochloride) (NSC-82151)

a. DESCRIPTION

Daunomycin (Cerubidine) is the hydrochloride salt of an anthracycline antibiotic produced by a strain of *Streptomyces oeruleorubidus*. It inhibits synthesis of nucleic acids, exhibiting antimitotic and cytotoxic activity.

b. TOXICITY

Human Toxicity: Dose-limiting toxicity includes myelosuppression and cardiotoxicity. Cumulative dose beyond 550 mg/M² results in increased risk for CHF. Radiation therapy involving the heart and previous adriamycin administration increases the risk for cardiomyopathy. Hepatic and renal dysfunction may occur. Other reactions include reversible alopecia, nausea and vomiting, anorexia, diarrhea and mucositis. If extravasation occurs during administration, tissue necrosis can result. Rarely, chills, fever, skin rash and anaphylactoid reactions can occur. Because of its teratogenic properties, women

of childbearing potential should be advised to avoid pregnancy. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Following IV injection, plasma levels rapidly decline. Subsequently, levels decline slowly with half-life of 18.5 hours. There is no evidence of the drug crossing the blood-brain barrier. Active metabolites are present in the plasma one hour after injection. Twenty-five percent of administered dose is eliminated by the kidney and 40% by biliary excretion.

Formulation: The drug is supplied in vials containing 20 mg of daunomycin as a reddish lyophilized powder. The daunomycin should be reconstituted with 4 mL of Sterile Water for Injection, USP, or PF 0.9% Sodium Chloride for Injection, USP, to give a final concentration of 5 mg/mL.

Storage and Stability: The drug is stored at room temperature (15° - 25°C). The reconstituted solution is stable for 24 hours at room temperature and 48 hours under refrigeration. Protect from sunlight.

Administration: When reconstituted with 4 mL of sterile water for injection, USP, each mL contains 5 mg of daunomycin activity for intravenous administration only.

Supplier: Daunomycin 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 product's package insert for full prescribing and toxicity information.

3.4 Gemtuzumab ozogamicin (Mylotarg®) (NSC-720568) (IND-66,366)

a. DESCRIPTION

Antineoplastic Agent, Monoclonal Antibody.

Mechanism of Action: Antibody to CD33 antigen, which is expressed on leukemic blasts in 80% of patients with acute myeloid leukemia (AML), as well as normal myeloid cells. Binding results in internalization of the antibody-antigen complex. Following internalization, the calicheamicin derivative is released inside the myeloid cell. The calicheamicin derivative binds to DNA resulting in double strand breaks and cell death. Pluripotent stem cells and nonhematopoietic cells are not affected.

b. TOXICOLOGY

Human Toxicology: The following toxicities occurred in adults > 60 years of age. It is anticipated that these same toxicities are likely to occur (less frequently or to a lesser degree) in younger patients. Percentages estimated in adults > 60 years of age. > 10%: Cardiovascular: Peripheral edema (21%), hypertension (20%), hypotension (16%). Central nervous system: Chills (66%), fever (80%), headache (26%), pain (25%), dizziness (11%), insomnia (18%). Dermatologic: Rash (23%), petechiae (21%), ecchymosis (15%). Endocrine and metabolic: Hypokalemia (30%), hypokalemia. Gastrointestinal: Nausea (64%), vomiting (55%), diarrhea (38%), anorexia (31%), abdominal pain (29%), constipation (28%), stomatitis/mucositis (25%), abdominal distention (11%), dyspepsia (11%). Hematologic: Neutropenia (98%; median recovery 40.5 days), thrombocytopenia (99%; median

recovery 39 days); anemia (47%), bleeding (15%), lymphopenia. Hepatic: Hyperbilirubinemia (23%) increased LDH (18%), increased transaminases (9% to 17%). Local: Local reaction (25%). Neuromuscular & skeletal: Weakness (45%), back pain (18%). Respiratory: Dyspnea (36%), epistaxis (29%; severe 3%), cough (19%), pharyngitis (14%). Miscellaneous: Infection (28%), sepsis (24%), neutropenic fever (20%).

Percentages estimated in adults > 60 years of age. 1% to 10%: Cardiovascular: Tachycardia (10%). Central nervous system: Depression (10%), cerebral hemorrhage (2%), intracranial hemorrhage (2%). Endocrine and metabolic: Hypomagnesemia (4%), hyperglycemia (2%). Genitourinary: Hematuria (10%; severe 1%), vaginal hemorrhage (7%). Hematologic: Hemorrhage (8%), disseminated intravascular coagulation (DIC) (2%). Hepatic: Elevated PT. Respiratory: Rhinitis (10%), hypoxia (6%), pneumonia (10%), rhinitis (10%). Neuromuscular & skeletal: Arthralgia (10%).

Percentages estimated in adults > 60 years of age. < 1% (limited to significant and/or life threatening): Hepatic failure, jaundice, hepatosplenomegaly, veno-occlusive disease.

Hypersensitivity: Gemtuzumab ozogamicin administration can result in severe hypersensitivity reactions (including anaphylaxis), and other infusion-related reactions which may include severe pulmonary events. Infrequently, hypersensitivity reactions and pulmonary events have been fatal. In most cases, infusion-related symptoms occurred during the infusion or within 24 hours of administration of gemtuzumab ozogamicin and resolved. Gemtuzumab ozogamicin infusion should be interrupted for patients experiencing dyspnea or clinically significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinuation of gemtuzumab ozogamicin treatment should be strongly considered for patients who develop anaphylaxis, pulmonary edema, or acute respiratory distress syndrome. Physicians should consider leukoreduction with hydroxyurea or leukapheresis to reduce the peripheral white count below 30,000 prior to administration of gemtuzumab ozogamicin.

Overdosage/Toxicology: Symptoms are unknown. General supportive measures should be instituted. Gemtuzumab ozogamicin is not dialyzable.

Drug Interactions: No formal drug interaction studies have been conducted.

Pregnancy/Breast-Feeding Implications: May cause fetal harm when administered to a pregnant woman. Women of childbearing potential should avoid becoming pregnant while receiving treatment. If used in pregnancy, or if patient becomes pregnant during treatment, the patients should be apprised of potential hazard to the fetus. Excretion in breast milk unknown, breast feeding is not recommended.

c. PHARMACOLOGY

Kinetics: Half-life: Total calicheamicin: 45 hours (initial dose); 60 hours on repeat dosing. Unconjugated calicheamicin: 100 hours (no change noted in repeat dosing).

Formulation: Powder for injection: 5 mg.

Storage and Stability: Light sensitive; protect from light. Store vials under refrigeration 2° to 8°C or 36° to 46°F. Reconstituted vials may be stored under refrigeration for up to 8 hours.

Reconstitution: Prepare in biologic safety hood with the fluorescent light turned off. Allow to warm to room temperature prior to reconstitution. Reconstitute vial with 5 mL sterile water for injection, USP. Final concentration in vial is 1 mg/mL. Dilute desired dose in 100 mL of 0.9% sodium chloride injection. The resulting I.V. bag should be placed in a UV protectant bag and infused immediately.

If not used immediately, the reconstituted admixture may be placed in the refrigerator (at 2° to 8°C) until 30 minutes before time of use. Before administration, take the IV bag from the refrigerator and warm it to room temperature in the UV light protectant bag. The infusion must be completed within 18 hours of initial infusion of the drug.

Compatibility: No information (infuse via separate line)

Administration: Administer as infusion only, over at least 2 hours. Do not administer I.V. push (bolus). Infuse through a separate line equipped with a low protein-binding 0.2-1.2 micron PES (polyether sulfone), 0.8-1.2 micron cellulose acetate/cellulose nitrate (mixed ester), or 1.2 micron acrylic copolymer terminal filter. May be infused peripherally or through a central line. Pre-medication with acetaminophen and diphenhydramine and/or corticosteroids should be administered prior to each infusion.

Supplier: Gemtuzumab ozogamicin is considered investigational for this study and will be supplied free of charge by Pfizer, Inc. to each site for distribution by Biologics', Inc. to patients on this study. Participating institutions are instructed to order as outlined below.

Drug Ordering: Orders need to be submitted by faxing the Clinical Drug Request Form to Biologics' Clinical Trial Division at 919/256-0794. The form can be found on the protocol abstract page of the Southwest Oncology Group website (www.swog.org) or on the protocol abstract page of the CTSU website (www.ctsu.org). Patient initials, SWOG patient ID, dose, and signature of the investigator or an authorized designate will all be required at the time of drug order. Biologics will ship drug on the same day for orders received before 4:00 p.m. E.S.T. Monday through Thursday. Orders received after 4:00 p.m. E.S.T. Monday through Thursday or any time on Friday will be processed and shipped the next business morning. Drug will be ordered and shipped in 1 cycle increments. To avoid treatment delays, drug may be pre-ordered for patients who are planned to be enrolled. The SWOG patient ID will not be required for pre-orders. Subsequent drug requests can be directly faxed to 919/256-0794. Unused drug should be destroyed according to local policies and procedures.

Drug Returns: Unused drug supplies should NOT be returned. Unused drug should be disposed of 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 by the supplier using the NCI Drug Accountability Record Form (DARF) available at <http://ctep.cancer.gov>.

Questions regarding drug ordering/shipping should be directed to the Biologics Clinical Trial Department at 800/850-4306.

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

3.5 6-Mercaptopurine (NSC-755)

a. DESCRIPTION

6-Mercaptopurine (6MP) is an antimetabolite chemically known as 1,7-dihydro-6H-purine-6-thione monohydrate, an analogue of the purine bases, adenine and hypoxanthine. 6MP competes with hypoxanthine and guanine for the enzyme, HGPRTase. The conversion to TIMP inhibits IMP conversion to xanthylic A and adenylic acid. TIMP also inhibits glutamine-5-phosphoribosylpyrophosphate amidotransferase, the first enzyme unique to the de novo pathway for purine ribonucleotide synthesis.

b. TOXICOLOGY

The dose limiting toxicity is myelosuppression. Hyperuricemia may occur as a result of rapid cell lysis. Tumor lysis syndrome with hyperuricemia can be minimized with increased hydration, urine alkalinization and xanthine oxidase inhibitors. Since xanthine oxidase catabolizes 6MP, the simultaneous administration of allopurinol (a xanthine oxidase inhibitor) should alert the investigator to reduce the dose of 6MP by 25 - 30% of the usual dose. In addition, enhanced marrow suppression has occurred in patients receiving trimethoprim-sulfamethoxazole. Other reactions include mucositis; skin rash; intestinal, rectal and genital ulcerations; nausea and vomiting; anorexia, and diarrhea. Progressive liver damage, increases in LFTs, jaundice with intrahepatic cholestasis and parenchymal cell necrosis occur and may progress to encephalopathy. Drug fever, pulmonary infiltrates, electrolyte imbalances, alopecia and fatigue have been reported. Oligospermia has been observed with oral administration.

c. PHARMACOLOGY

Kinetics: Absorption of the oral dose of 6MP is incomplete and variable, averaging 50% of administered dose. After intravenous administration, half life is 21 minutes in children and 47 minutes in adults. 46% of an oral dose is excreted in the urine in 24 hours. The blood-brain transport is negligible. Monitoring plasma levels of 6MP is of questionable value.

Formulation: The drug is available in 50 mg tablets in bottles of 25 and 250.

Storage and Stability: The tablets should be stored at 15° - 25°C (59-77°F) in a dry place.

Administration: PO.

Supplier: 6-Mercaptopurine 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 product's package insert for full prescribing and toxicity information.

3.6 Methotrexate (NSC-740)

a. DESCRIPTION

Methotrexate is an antimetabolite and has as its principle mechanism of action the competitive inhibition of dihydrofolate reductase.

b. TOXICOLOGY

Human Toxicology: Adverse reactions include mucositis (gingivitis, pharyngitis, stomatitis, enteritis, hematemesis, melena and ulceration), nausea, vomiting, diarrhea, anorexia, myelosuppression, skin rashes, itching, hives, photosensitivity, pigmentation changes, alopecia, ecchymosis, acne, telangiectasia, furunculosis, malaise, fatigue, chills, fever, dizziness, headache, blurred vision, decreased resistance to infection, impaired renal function (including cystitis, azotemia, hematuria and acute renal failure), hepatotoxicity (including elevated transaminase, fibrosis and cirrhosis), and pulmonary toxicity (including death from interstitial pneumonitis and chronic interstitial obstructive pulmonary disease). Pulmonary symptoms (especially a dry, nonproductive cough) may require interruption of treatment and special investigation. Central nervous system toxicities have included headache, drowsiness, blurred vision, aphasia, hemiparesis, paresis, convulsions, transient subtle cognitive dysfunction, mood alteration and unusual cranial sensations. Leukoencephalopathy may occur in patients who have had cranial irradiation. Toxicity is directly related to duration of blood levels. Because the drug is excreted in the urine, impaired renal function is usually a contraindication to its use. Calcium leucovorin must be administered after high-dose methotrexate to prevent life threatening toxicity. Other potential toxicities include reproductive dysfunctions (defective oogenesis or spermatogenesis, transient oligospermia, menstrual dysfunction, vaginal discharge, infertility), opportunistic infection, loss of libido, myalgia, arthralgia, diabetes, osteoporosis, tinnitus, eye discomfort, epistaxis, sweating and sudden death. A few cases of anaphylactoid reactions have been reported. Patients with a known hypersensitivity to methotrexate should not receive the drug. Fetal death and/or congenital anomalies have been reported. Women of childbearing potential should be cautioned. Unexpectedly severe (sometimes fatal) marrow suppression and gastrointestinal toxicity have been reported with concomitant administration of methotrexate (usually in high doses) along with some non-steroidal anti-inflammatory drugs. METHOTREXATE FORMULATIONS AND DILUENTS CONTAINING PRESERVATIVES MUST NOT BE USED FOR INTRATHECAL OR HIGH-DOSE METHOTREXATE THERAPY.

c. PHARMACOLOGY

Kinetics: Oral absorption appears to be dose dependent. The absorption of doses greater than 80 mg/m² is significantly less than lower doses. Methotrexate in serum is approximately fifty percent protein-bound. It does not penetrate the blood-brain barrier. Terminal half-life is 3 - 10 hours for doses less than 30 mg/m² and 8 - 15 hours with higher doses. With intravenous administration, 80 - 90% of unchanged methotrexate is excreted in the urine within 24 hours. Ten percent or less is excreted in the bile.

Formulation: Methotrexate is available as tablets for oral administration.

Storage and Stability: The tablets should be stored at 15° - 25°C (59 - 77°F) in a dry place.

Administration: PO.

Supplier: Methotrexate 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 product's package insert for full prescribing and toxicity information.

4.0 DIAGNOSTIC AND STAGING CRITERIA

4.1 Diagnostic Criteria

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: Neoplastic promyelocytes defined as promyelocytes with heavy granulation and irregular nuclei and/or primitive promyelocytes with very large, numerous Auer rods.
3. Bone Marrow Blast Percentage is calculated as the percent of blasts among all nucleated marrow cells.

- b. Acute Promyelocytic Leukemia (APL, FAB M3, ICD-O code 9866/3) is defined by ≥ 20% neoplastic promyelocytes, and the presence of t(15;17), PML-RARα, or RARα-PML.

The variant form of APL (FAB M3V) is defined morphologically by the presence of cells with reniform, bi- or multilobed, or convoluted nuclei, and either sparse fine granules or agranular cytoplasm.

4.2 Risk Categories

Risk categories are defined for APL on the basis of pretreatment WBC and platelet count as follows within 14 days of registration: (1)

- a. Low risk: WBC ≤ 10,000/mcl (10 X 10⁹/L) and platelets > 40,000/mcl (40 x 10⁹/L)
- b. Intermediate risk: WBC ≤ 10,000/mcl (10 X 10⁹/L) and platelets ≤ 40,000/mcl (40 x 10⁹/L)
- c. High risk: WBC > 10,000/mcl (10 X 10⁹/L)

4.3 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 **S0535** 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 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 four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 14 or 28 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 Initial Registration

- _____ a. Patients must have a morphologically confirmed diagnosis of high risk (see Section [4.2c](#)) acute promyelocytic leukemia (APL), based on bone marrow examination performed within 14 days before registration. The WBC confirming high risk must be obtained within 14 days prior to registration.
- _____ b. Patients who are known to be PML- RAR α negative by the RT-PCR assay required in Section [5.1g](#) below are not eligible. (NOTE: If the RT-PCR result is indeterminate, additional blood specimens should be submitted for RT-PCR testing to avoid indeterminate pretreatment results whenever possible; if the RT-PCR result remains indeterminate after the initial and any additional specimens are assayed, the patient will be eligible provided all other eligibility criteria are met. Patients may be registered before the RT-PCR assay result is known, but if the result is negative they must be removed from protocol treatment and treated at the physician's discretion; see Section [7.3d](#).)
- _____ c. Patients must have reached their 18th birthday.
- _____ d. Patients must not have prolonged QTc > 0.47 seconds.
- _____ e. Patients must not have received prior systemic chemotherapy for acute leukemia, with the exception of the ATRA, which may be administered for up to 5 days prior to registration. Administration of hydroxyurea, corticosteroids, or leukapheresis to control high cell counts prior to registration is permitted.
- _____ f. Pretreatment cytogenetics must be performed on all patients. Participation in cytogenetic studies is mandatory for patients affiliated with CALGB or ECOG. Collection of pretreatment specimens must be completed within 14 days prior to registration to **S0535**. Note that there are also additional time points at which specimens are required to be submitted for cytogenetics (see Section [15.2](#)). Collection and submission of required materials must be by one of the following mechanisms:
 - SWOG Sites and Other Sites not Affiliated with ECOG or CALGB: Specimens must be submitted to each institution's preferred cytogenetics laboratory (see Section [15.2](#)).
 - ECOG Sites: Baseline karyotypes must be submitted via **E3903**. Register patient to **E3903** PRIOR to registration to **S0535**. The ECOG patient number will be required at the time of **S0535** registration (see Section [15.3](#)).
 - CALGB Sites: CALGB patients must be registered on **CALGB 8461** PRIOR to registration to **S0535**. The CALGB patient number will be required by CTSU at the time of **S0535** registration (see Section [15.4](#)).

SWOG Patient No. _____

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

- _____ g. For all patients, pretreatment specimens for baseline RT-PCR assays for PML-RAR α must be collected and submitted within 14 days prior to registration to **S0535**. Note that there are also additional time points at which specimens are required to be submitted for RT-PCR assays (see Section [15.0](#)). Specimen submissions must be via the mechanisms indicated below. Repository aspects of the ancillary protocols for CALGB and ECOG are optional as outlined in the informed consent documents.
- SWOG and CALGB Sites and other sites not affiliated with ECOG: Specimens must be submitted to a CLIA-approved laboratory. See Sections [15.2](#) and [15.4](#).
 - ECOG Sites: Pretreatment specimens of marrow and/or peripheral blood must be submitted to the Leukemia Translational Studies Laboratory (LTSL) at Our Lady of Mercy Cancer Center, New York via **E3903**, "Ancillary laboratory protocol for collecting diagnostic material on patients considered for ECOG treatment trials for Leukemia or related hematologic disorders". Register patient to **E3903** PRIOR to registration to **S0535**. The ECOG patient number will be required at the time of **S0535** registration. See Section [15.3](#).
 - CALGB Sites: CALGB patients must be offered participation on **CALGB 9862**. Consenting patients must be registered to **CALGB 9862** PRIOR to registration to **S0535** (see Section [15.4](#)).
- _____ h. Patients must not be pregnant or nursing because ATRA as well as other drugs used in this protocol may cause fetal harm and because of the potential for serious adverse reactions in nursing infants from the drug. Women of childbearing potential must have a negative pregnancy test performed within 14 days prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method.
- _____ i. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.
- _____ j. 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.
- _____ k. At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

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. Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

SWOG Patient No. _____

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

5.2 Consolidation Therapy Registration

After completing induction therapy, patients will be registered for consolidation treatment provided that they were eligible for the initial registration and satisfy the following additional criteria.

- _____ a. Patients must have achieved A1 marrow status, B1 peripheral blood status and C1 extramedullary disease status (see Section [10.1](#)). Patients must have maintained a B1 peripheral blood status for at least 7 days prior to registration for this protocol step.
- _____ b. For patients affiliated with CALGB or ECOG, collection of cytogenetic specimens must be completed within 8 weeks (preferably within 4 weeks) prior to this registration. Collection and submission of required materials must be by one of the following mechanisms:
 - ECOG Sites: See Section [15.3](#).
 - CALGB Sites: See Section [15.4](#).
- _____ c. For all patients, specimens for RT-PCR assays for PML-RAR α must be collected and submitted within 8 weeks (preferably within 4 weeks) prior to this registration. Note that submission of specimens for RT-PCR assays is also required prior to Consolidation Cycle 3. Specimen submissions must be via the mechanisms indicated below.
 - SWOG Sites and other sites not affiliated with ECOG or CALGB: Specimens must be submitted to a CLIA-approved laboratory. See Section [15.2](#).
 - ECOG Sites: See Section [15.3](#).
 - CALGB Sites: See Section [15.4](#).

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 APL Disease Assessment 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 prior to registration.

SWOG Patient No. _____

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

5.3 Maintenance Therapy Registration

After completing consolidation therapy, patients will be registered for maintenance treatment provided that they were eligible for the consolidation registration and satisfy the following additional criterion:

- _____ a. Patients must remain in A1 marrow status, B1 peripheral blood status and C1 extramedullary disease status (see Section [10.1](#)). Patients must have maintained a B1 peripheral blood status for at least 7 days prior to registration for this protocol step.
- _____ b. For all patients, specimens for RT-PCR assays for PML-RAR α must be collected and submitted within 8 weeks (preferably within 4 weeks) prior to this registration. Specimen submissions must be via the mechanisms indicated below.
 - SWOG Sites and other sites not affiliated with ECOG or CALGB: Specimens must be submitted to a CLIA-approved laboratory. See Section [15.2](#).
 - ECOG Sites: See Section [15.3](#).
 - CALGB Sites: See Section [15.4](#).

6.0 STRATIFICATION FACTORS

There are no stratification factors in this study.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact the Study Chair, Dr. Lancet at 813/745-6841, or if Dr. Lancet is not available, Dr. Komrokji at 513/584-6915. For dosing principles or questions, please consult the Southwest Oncology Group Policy #38 "Dosing Principles for Patients on Clinical Trials" at <http://swog.org> (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy #38).

7.1 Good Medical Practice

This clinical trial can fulfill its objectives only if patients appropriate for the trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. To maximize patient safety, patients should be treated on this protocol only at centers having ready access to blood product support and adequate staff to care for the severely neutropenic patient with multiple-therapy induced toxicities. Physicians should consider the risks and benefits of any therapy, and, therefore, only enroll patients for whom the agents administered are appropriate. Although they will not be considered as formal eligibility criteria, as part of this decision-making process, physicians should recognize that the following problems may increase the risk to the patient entering this protocol. These are guidelines, not strict eligibility criteria. See Section 5.0 for strict eligibility criteria. These guidelines apply to all registration steps (Initial Registration, Consolidation Therapy Registration, and Maintenance Therapy Registration).

- a. Patient should not have other serious illnesses that would limit survival to < 2 years.
- b. Patient should not have psychiatric conditions that would prevent compliance with treatment or informed consent.
- c. Patient should not have uncontrolled or severe cardiovascular or pulmonary disease. This would include history of a recent acute myocardial infarction, congestive heart failure, or active angina.
- d. Abnormalities in measured parameters of hepatic and renal function must be considered as potentially serious obstacles for safe tolerance of the therapy prescribed in this protocol. The degree to which such perturbations are attributable to comorbid disease or are leukemia-related should be considered in the decision to enroll a patient on this protocol.
- e. Patients who become pregnant after registration must be removed from protocol therapy.

7.2 General Considerations

- a. Immediate measures to diagnose and begin treatment of infections should be instituted prior to induction therapy.
- b. A lumbar puncture is recommended following completion of induction, but not required. Prophylactic intrathecal chemotherapy may be given at the treating physician's discretion.
- c. All patients should be carefully followed serially with coagulation studies (PTT, PT, fibrinogen, FDP, and D-dimer). These tests should be done pretreatment, twice weekly during induction until normal and as clinically indicated thereafter. Optimal management of coagulopathy is controversial. Heparin usage is discouraged since all patients will be receiving ATRA; however, patients with either biochemical or clinical evidence of coagulopathy may be treated at the investigator's discretion.

- d. Additional electrolyte studies for calcium, magnesium, cholesterol and triglycerides should be obtained.
- e. Hydroxyurea therapy is permitted up to 24 hours before initiation of gemtuzumab ozogamicin (G.O.).
- f. All patients will be started on allopurinol 300 mg/day orally. For patients allergic to allopurinol, rasburicase may be substituted. Reversible abnormalities of metabolic function should be treated aggressively and corrected prior to institution of therapy.
- g. Investigators may contact the SWOG Study Chairs or Leukemia Committee Chair for assistance with the management of patients with high WBC count prior to confirmation of molecular diagnosis.

7.3 Induction Chemotherapy

AGENT	DOSE	ROUTE	Time	NOTES
ATRA ^ζ	45 mg/m ² /day (in 2 doses, 22.5 mg/m ² every 12 hours)	PO	every 12 hrs, Day 1 to CR [*]	With food. See Section 7.3a below.
Gemtuzumab Ozogamicin ^Δ	9 mg/m ²	IV infusion over 2 hours	Day 1 only ^π	
Arsenic Trioxide	0.15 mg/kg/d	IV infusion over 2 hours	5 days/wk beginning on Day 10 and continuing until CR ^ψ	

^{*} For maximum of 90 days, unless prohibited by either unacceptable toxicity or progressive disease.

^π G.O. may be delayed until Day 6 pending confirmation of APL diagnosis by FISH/cytogenetics, or RT-PCR. Hydroxyurea may be utilized during this time, up to 24 hours prior to initiation of gemtuzumab ozogamicin.

^ψ For a maximum of 60 days, unless prohibited by either unacceptable toxicity or progressive disease.

^Δ Recommended premedications prior to gemtuzumab: acetaminophen 1 gm orally, diphenhydramine 50 mg IV, and methylprednisolone 125 mg IV.

^ζ Day 1 of treatment will be the first day the patient is treated with ATRA, regardless of patient's registration status.

- a. ATRA will be "rounded" up to the nearest 10 mg, divided into 2 daily doses, given orally every 12 hours with food.

- b. **ATRA syndrome:** A spectrum of clinical manifestations of a cardiorespiratory distress syndrome has been described, including respiratory distress, hypoxemia, fever, erythematous rash, pulmonary infiltrates, pleural or pericardial effusions, congestive heart failure with impaired myocardial contractility and episodic hypotension. Patients with this syndrome may develop rapidly progressive cardiopulmonary failure.

If this syndrome is suspected, ATRA should be held and dexamethasone 10 mg IV or PO BID will be given for 3 days. ATRA will be resumed once the signs/symptoms of the syndrome have resolved. Patients with persistent signs/symptoms of the ATRA syndrome after 3 days of dexamethasone or who have recurrence of the ATRA syndrome after restarting ATRA should be discussed with the Study Chair.

- c. **Prolonged QT_c:** Prolongation of the QT_c has been reported with the use of arsenic trioxide in association with electrolyte abnormalities. Therefore, any identified electrolyte abnormalities of potassium, calcium, or magnesium should be promptly corrected to within normal limits prior to and during treatment with arsenic trioxide. EKG must be obtained twice weekly during induction therapy and as clinically indicated.
- d. Patients may be registered on this study and begin induction chemotherapy before the result of the required pretreatment RT-PCR assay for PML-RAR α is available (see Section 5.1b). If the patient is found to be PML-RAR α -negative, then the patient is removed from protocol treatment and should receive appropriate chemotherapy for non-APL acute myeloid leukemia.

7.4 Consolidation Cycles 1 and 2

- a. Patients who achieve A1 bone marrow, B1 peripheral blood, and C1 extramedullary disease status (see Section 10.1) may be eligible for registration to consolidation therapy (see Section 5.2). Consolidation Cycle 1 therapy should be started within 4 weeks and no later than 8 weeks following documentation of CR.

b. Consolidation Cycles 1 and 2 Treatment Plan

AGENT	DOSE	ROUTE	Time	NOTES
Arsenic Trioxide	0.15 mg/kg/day	IV over 2 hours	5 days/week x 5 weeks	Repeat after 2 weeks rest*

* Consolidation Cycle 2 may be given after 2 weeks of rest following Cycle 1.

- c. **Prolonged QT_c:** Prolongation of the QT_c has been reported with the use of arsenic trioxide in association with electrolyte abnormalities. Therefore, any identified electrolyte abnormalities of potassium, calcium, or magnesium should be promptly corrected to within normal limits prior to and during treatment with arsenic trioxide.
- d. MUGA or echocardiogram must be performed prior to initiation of Consolidation Cycle 3 (see Section 7.5c). If the test has been performed at baseline or any time prior to Consolidation Cycle 3, it does not need to be repeated immediately before Cycle 3.

7.5 Consolidation Cycles 3 and 4

- a. Patients who remain in A1 bone marrow, B1 peripheral blood, and C1 extramedullary disease status (see Section 10.1) may continue consolidation therapy. Consolidation Cycle 3 should be started within 4 weeks following completion of Consolidation Cycle 2 if possible.
- b. Consolidation Cycle 4 should be started no earlier than 2 weeks, and no later than 8 weeks from recovery to B1 peripheral blood status.
- c. MUGA or echocardiogram must be performed prior to initiation of Consolidation Cycle 3. If the test has been performed at baseline or any time prior to Consolidation Cycle 3, it does not need to be repeated immediately before Cycle 3. EKG should be obtained as clinically indicated thereafter.
- d. Patients who cannot receive daunomycin because of cardiac or other toxicity, or are unable to initiate Consolidation Cycle 4 within 8 weeks of recovering peripheral blood counts to B1 status, must be discussed with the Study Chair; if in CR, these patients will proceed to Consolidation Cycle 5.

e. Consolidation Cycles 3 and 4 Treatment Plan

AGENT	DOSE	ROUTE	Time	NOTES
ATRA	45 mg/m ² /day (in 2 doses, 22.5 mg/m ² every 12 hours)	PO	every 12 hours, Days 1-7	With food. See Section 7.5e below.
Daunomycin*	50 mg/m ² /day	IV bolus or 1 hour infusion	Days 1-3	

* Idarubicin, 12mg/m²/day, on Days 1-3, may be used in place of daunomycin only if daunomycin is unavailable due to the national shortage. This must be documented on the **S0535** Consolidation Cycles 3 and 4 Treatment Summary Form.

- f. ATRA will be “rounded” up to the nearest 10 mg, divided into 2 daily doses, given orally every 12 hours with food.
- g. Prior ATRA syndrome: Patients who experienced the ATRA syndrome during induction may receive ATRA during Consolidation Cycles 3 and 4, since the ATRA syndrome is not expected to occur during remission.

7.6 Consolidation Cycles 5 and 6

- a. Patients who remain in B1 peripheral blood, and C1 extramedullary disease status (see Section [10.1](#)) may continue consolidation therapy. Consolidation Cycle 5 should be started no earlier than 2 weeks and no later than 8 weeks after recovery of peripheral blood counts to B1 status (see Section [10.1](#)).
- b. Consolidation Cycle 6 should be started no earlier than 2 weeks, and no later than 8 weeks after recovery to B1 peripheral blood status.
- c. Patients who cannot receive gemtuzumab ozogamicin because of previous toxicity or who are unable to initiate Consolidation Cycle 6 within 8 weeks after recovering peripheral blood counts to B1 status must be discussed with the Study Chair; if in CR, these patients will proceed to Maintenance Therapy.
- d. Consolidation Cycles 5 and 6 Treatment Plan

AGENT	DOSE	ROUTE	Time	NOTES
Gemtuzumab Ozogamicin ^Δ	9 mg/m ²	IV infusion over 2 hours	Day 1	

^Δ Recommended premedications prior to gemtuzumab: acetaminophen 1 gm orally, diphenhydramine 50 mg IV, and methylprednisolone 125 mg IV.

7.7 Maintenance Therapy

- a. Patients who remain in A1 bone marrow, B1 peripheral blood, and C1 extramedullary disease status (see Section [10.1](#)), may be eligible for registration to maintenance therapy (see Section [5.3](#)). Maintenance should be started no earlier than 2 weeks and no later than 8 weeks after recovery of ANC > 1,000/mcl (1.0 x 10⁹/L) and platelets > 100,000/mcl (100 x 10⁹/L).

b. Maintenance Treatment Plan

AGENT	DOSE	ROUTE	Time	NOTES
ATRA	45 mg/m ² /day (in 2 doses, 22.5 mg/m ² every 12 hours)	PO	Days 1-7 every 14 days	With food. See Section 7.7c below.
6-MP	60 mg/m ² /d	PO	Daily	For 1 year
Methotrexate	20 mg/m ²	PO		Once per week for 1 year.

c. ATRA will be “rounded” up to the nearest 10 mg, divided into 2 daily doses, given orally every 12 hours with food.

d. Prior ATRA syndrome: Patients who experienced the ATRA syndrome during induction may receive ATRA during Maintenance, since the ATRA syndrome is not expected to occur during remission.

7.8 Assessment of Response

a. Induction

A bone marrow aspirate and biopsy will be obtained at the time of neutrophil recovery ($\geq 1,000/\text{mcl}$) or on Day 42 after beginning protocol ATRA (i.e. not counting any days of ATRA given prior to the patients registration to this study), whichever comes first. Specimens of marrow aspirate (or peripheral blood if dry tap) must be submitted for cytogenetics (for patients affiliated with CALGB or ECOG) and PCR (for all patients) as described in Section [15.0](#). Subsequently, the bone marrow aspirate and biopsy will be repeated every 2 weeks until criteria for CR are met. These subsequent samples will NOT be submitted centrally for cytogenetic or RT-PCR testing, but the tests will still be performed locally. Testing for clinical/hematological CR should be performed locally for all of these subsequent specimens. Patients will continue ATRA and arsenic trioxide until CR is achieved, up to a maximum of 90 days. Patients with a CR will proceed to consolidation therapy as outlined above in Section [7.4](#).

b. Consolidation

A bone marrow aspirate and biopsy will be obtained within 8 weeks (preferably within 4 weeks) preceding Consolidation Cycle 1. This should be performed at the time when peripheral blood counts have recovered to baseline or as clinically indicated. A bone marrow aspirate and biopsy are also required prior to Consolidation Cycle 3. The pre-Consolidation Cycle 3 specimens of marrow aspirate (or peripheral blood if dry tap) must be submitted for PCR as described in Section [15.0](#).

c. Maintenance

A bone marrow aspirate and biopsy will be obtained within 8 weeks (preferably within 4 weeks) prior to beginning maintenance therapy. Specimens of marrow aspirate (or peripheral blood if dry tap) must be submitted for PCR testing as described in Section [15.0](#).

d. A bone marrow aspirate and biopsy will be obtained every 3 months during Maintenance therapy. Specimens from these samples should NOT be submitted for RT-PCR testing or cytogenetics. Testing for clinical/hematological CR for these samples should be performed locally.

- e. A bone marrow aspirate will be obtained every 3 months for the first year following completion of maintenance therapy, every 6 months for the second year following completion of maintenance therapy and at the end of the third year following completion of maintenance therapy. At the time of relapse cytogenetic studies and RT-PCR testing must be performed as described in Section [15.0](#).

7.9 Supportive Care Guidelines

a. Infection Prophylaxis

1. Extremely careful hand washing by all members of health care team is required.
2. Diet should exclude raw fruits, vegetables and unprocessed foods.
3. Antibiotic prophylaxis with oral antimicrobial agents is strongly recommended for all patients as indicated in the following table.

AGENT	DOSE	ROUTE	COMMENTS
Fluconazole	200 mg/d or 100 mg q 12 hr	PO or IV	If empiric amphotericin preparations are used, hold fluconazole or voriconazole for the duration of amphotericin-based therapy.
Ciprofloxacin	500 mg q 12 hr	PO	Discontinue when broad-spectrum IV antibiotics are started. Note that bioavailability of cipro is reduced if co-administered with agents containing magnesium, aluminum or calcium (e.g., antacids, sucralfate).
Acyclovir	800 mg q 12 hr or 250 mg/m ² q 12 hr	PO or IV	Use only in patients who are seropositive for herpes simplex virus or have a history of HSV infection.

Antimicrobial prophylaxis should be given to all patients during the induction therapy. Treatment with all agents (except for fluconazole and acyclovir) will start at the initiation of induction chemotherapy, if not started previously, and stop when the absolute granulocyte count is >

500/mcl. During each cycle of consolidation it is recommended that the same treatment be resumed on Day 7 and stopped when the absolute granulocyte count is $> 500/\text{mcl}$. If the absolute granulocyte count does not drop below 500/mcl following chemotherapy, then the antimicrobial prophylaxis should be stopped on Day 21 of each cycle.

b. Management of Infection and Use of Antibiotics

1. Any neutropenic patient (absolute granulocyte count $< 500/\text{mcl}$) with an oral temperature exceeding 38°C on more than one occasion within a single (24 hour) day or a single temperature greater than 38.5°C should have broad-spectrum intravenous empiric antibiotics started expeditiously at the discretion of the treating physician. Prior to antibiotic administration urine culture, urinalysis and 2 sets of blood cultures should be obtained. Careful physical exam and chest radiograph should also be performed. Oral ciprofloxacin prophylaxis should be stopped when empiric intravenous antibiotics are started.
2. There are many appropriate choices of broad-spectrum empiric antibiotics for use in the febrile neutropenic patient. The regimen should be chosen based on the susceptibility pattern of the predominant pathogens at the treating hospital. Possible regimens to use are listed below.
 - i. Monotherapy with imipenem
 - ii. Combination therapy with an anti-pseudomonal penicillin (piperacillin) and a third generation cephalosporin (ceftazidime or cefoperazone).
 - iii. Combination therapy with an anti-pseudomonal penicillin (piperacillin) and an anti-pseudomonal aminoglycoside (amikacin).
 - iv. Combination therapy with a third generation cephalosporin (ceftazidime or cefoperazone) and an anti-pseudomonal aminoglycoside (amikacin).
3. If the patient is persistently febrile after 72 hours, additional antibiotic and/or antifungal coverage should be considered. If culture data indicate a more favorable antibiotic regimen, then the appropriate antibiotics will be substituted. An infectious disease consultant should be considered for patients with persistent fever at 72 hours while receiving adequate antibiotic coverage. Although vancomycin is not recommended for empiric use, it should be noted that the use of ciprofloxacin may increase the emergence of streptococci and coagulate-negative staphylococci.
4. Patients placed on aminoglycosides should be carefully followed for renal insufficiency and for appropriate serum drug levels. Any patient placed on amphotericin B should be carefully monitored for renal insufficiency, hypokalemia and hypomagnesemia.
5. The patient will be continued on broad-spectrum antibiotics until the absolute granulocyte count is $> 500/\text{mcl}$ and the patient is afebrile.

c. Blood Product Support

1. The hemoglobin should be maintained at a safe level, especially in severely thrombocytopenic patients (e.g., hemoglobin > 8 - 10 grams/dl).
2. The platelet count should be maintained greater than 10,000/mcl in non-bleeding patients. In the presence of fever or hypertension, platelet transfusion to 20,000/mcl is recommended. In the presence of active hemorrhage or suspected gastrointestinal bleeding, platelet transfusion to a minimum count of 50,000/mcl is recommended. Maintenance of platelet count of 30,000-50,000/mcl, particularly at or near the time of diagnosis and initiation of therapy, is recommended, particularly in the setting of active DIC.
3. Patients who are refractory to random donor platelets (single donor or pooled) should receive HLA-matched platelet transfusions if possible. An unsatisfactory one-hour platelet count increment is less than 20% of expected rise (expected rise is 5,000 per unit platelets transfused).
4. Cryoprecipitate should be administered to maintain the fibrinogen at a level of 100-150 mg/dl.

d. Mucosal and Nutritional Considerations

1. Mucositis may be severe. Although prophylactic use of fluconazole and acyclovir is expected to reduce infectious causes, mucosal lesions should be cultured for fungal, viral and bacterial organisms.
2. Malnutrition may be severe and prolonged in elderly patients undergoing intensive chemotherapy. Early institution of hyperalimentation is recommended when oral intake becomes inadequate.

e. Growth Factors

1. Growth factors (e.g., GM-CSF, G-CSF, or erythropoietin) may be used at the discretion of the treating physician in cases of serious or life-threatening infection. It should be pointed out that the benefit of growth factors in this setting is unclear.

7.10 Intake Calendar

ATRA, 6-MP, and methotrexate drug compliance will be recorded by patients on the Intake Calendar (see Appendix [18.3](#)). Institutional CRAs will review and ascertain patient adherence with protocol treatment. Do not submit the Intake Calendar to the Data Operations Center.

7.11 Criteria for Removal from Protocol Treatment

- a. Patients whose pretreatment RT-PCR assays are found to be PML-RAR α -negative will be removed from protocol treatment and receive no further treatment under this protocol (see Section [7.3d](#)).
- b. Delay of more than 5 days prior to initiation of gemtuzumab ozogamicin during induction.
- c. Patients who fail to achieve A1 marrow, B1 blood, and C1 extramedullary disease status (see Section [10.1](#)) within 90 days of initiation of induction therapy will not be eligible for consolidation therapy and will receive no further treatment under this protocol.

- d. Unacceptable toxicity as defined in Section [8.0](#).
- e. Patients who do not maintain CR or relapse before or while receiving consolidation or maintenance therapy.
- f. Patients who become pregnant.
- g. Successful completion of all stages of therapy.
- h. The patient may withdraw from the study at any time for any reason.

7.12 Discontinuation of Treatment

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

7.13 Follow-Up Period

All patients will be followed until death or a maximum of 3 years from time of initial registration.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events (CTCAE)

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 Toxicities to be Monitored

The toxicities of the agents included in this regimen are well established, and are outlined above in Section [3.0](#). Dose modifications of study medications will be made based upon attribution of toxicity to drug therapy rather than disease.

8.3 Induction Therapy

a. Dose Modifications for ATRA During Induction

- Commonly observed toxicities with ATRA include hepatotoxicity (increased AST and ALT), neurologic changes (headache or pseudotumor cerebri), mucocutaneous changes (dry skin, peeling of palms and soles) and others including cheilitis, epistaxis, fatigue, musculoskeletal pain, and conjunctivitis. If a patient experiences a Grade 3 toxicity, ATRA will be held until the toxicity has resolved to \leq Grade 1. At that time, restart ATRA at 75% dose. Recurrent episodes of \geq Grade 3 toxicity will result in discontinuation of ATRA until the toxicity resolves to \leq Grade 1; ATRA will then be resumed with an additional 25% dose reduction. Patients requiring dose reductions that would reduce the dose to less than 25% of the starting dose should be removed from ATRA (continue other therapy) for the remainder of the cycle. ATRA may be used again in subsequent cycles if toxicity has resolved to \leq Grade 1.
- The ATRA syndrome should be treated as outlined in Section [7.3b](#).
- If ATRA related Grade ≥ 3 toxicity (excluding ATRA syndrome) does not resolve to \leq Grade 1 within 14 days of occurrence, ATRA will be permanently discontinued.

b. Dose Modification for Arsenic Trioxide During Induction

Missed doses due to holidays or dose modifications will not be made up. Modification of the arsenic dose in these cycles should be made as follows:

- Renal Toxicity

Creatinine	Adjust Dose:
≥ 1.5 x baseline but < 3.0 mg/dL	Hold treatment until creatinine < 1.5 x baseline, then resume treatment at full dose.
≥ 3.0 mg/dL or oliguric renal failure	Hold treatment until creatinine < 1.5 x baseline, then resume treatment with a 50% dose reduction (0.075 mg/kg/day)*

* If toxicity persists for more than 14 days or recurrent renal toxicity occurs despite a dose reduction, then discontinue arsenic trioxide.

Hepatotoxicity: Give the following dose, based on lab values obtained within 2 days prior to therapy

AST (SGOT)	Bilirubin	Adjust dose:
	2-3 fold increase over upper limit of normal (ULN)	Hold treatment until bilirubin < 2x ULN, then resume at full dose
> 5-fold increase over ULN	and/or > 3-fold increase over ULN	Hold treatment until AST < 3x ULN or bilirubin < 2x ULN, then resume treatment with a 50% dose reduction (0.075 mg/kg/day)*

* If toxicity persists for more than 14 days or recurrent hepatotoxicity occurs despite a dose reduction, then discontinue arsenic trioxide.

Hematologic Acute Hemolysis: In the case of acute hemolysis (CTCAE 3.0 Grade ≥ 3), hold treatment until complete resolution, then resume treatment with a 50% dose reduction (0.075 mg/kg/day). No dose adjustment is necessary for pancytopenia of any grade. If toxicity persists for more than 14 days after holding treatment or recurrent acute hemolysis occurs despite dose reduction, then discontinue arsenic trioxide.

Dermatologic Toxicity: In the case of rash (CTCAE 3.0 Grade ≥ 3), hold treatment until clear clinical evidence of improvement to ≤ Grade 1, then resume treatment with a 50% dose reduction (0.075 mg/kg/day). If toxicity persists for more than 14 days after holding treatment or recurrent dermatologic toxicity occurs despite dose reduction, then discontinue As₂O₃.

Nausea/Vomiting: Nausea/vomiting of any grade should be handled with symptomatic treatment with anti-emetics. If CTCAE 3.0 Grade ≥ 3 vomiting occurs despite adequate trial of anti-emetics, then hold treatment until clinical improvement and then resume treatment at full dose. If treatment-refractory

nausea/vomiting recurs, then hold treatment until improvement is \leq Grade 1 and then resume treatment with a 50% dose reduction (0.075 mg/kg/day). If toxicity persists for more than 14 days after holding treatment or recurrent nausea and vomiting occur despite dose reduction and anti-emetics, then discontinue As_2O_3 .

- **Neurologic Toxicity:** In the case of moderate-severe objective sensory loss or paresthesias; motor weakness; clinically evident hearing loss; locomotor ataxia or dysmetria; agitation, confusion, or hallucination then hold treatment until clear clinical evidence of resolution to \leq Grade 1 and then resume treatment with a 50% dose reduction (0.075 mg/kg/day). If toxicity persists for more than 14 days after holding treatment or recurrent moderate-severe neurologic toxicity occurs despite dose reduction, then discontinue As_2O_3 .
- **Cardiac Toxicity:** Guidelines for the management of prolonged QTc interval are as follows:
 - EKG must be obtained twice weekly during induction therapy and as clinically indicated.
 - Measure the QT interval (from the start of the Q wave to the end of the T wave) and the preceding RR interval. The QTc interval will be calculated as the QT interval (msec) divided by the square root of the RR interval (msec).
 - QTc interval < 500 msec: No specific therapy needed. Continue As_2O_3 . Serum K^+ and Mg^{++} should be monitored and repeated only if low.
 - QTc interval 500-600 msec: Hold As_2O_3 temporarily and replete serum K^+ and Mg^{++} with IV and/or oral K^+ and Mg^{++} to minimum target levels of 4.0 and 2.0 mg/dL, respectively. Resume As_2O_3 on same day if target levels are achieved and re-check prior to next dose.
 - QTc interval > 600 msec: Hold As_2O_3 . Aggressive IV K^+ and Mg^{++} repletion (for adults MgSO_4 can be given as 2 g IV, followed by up to 12 g in 6 hours). If the QTc interval falls below 600 msec, the patient can be sent home with additional oral supplements and should return the following day for re-checking prior to further As_2O_3 treatment. If the QTc interval does not fall below 600 msec with this level of repletion, the patient should undergo EKG monitoring by telemetry, preferably in the hospital, along with continued IV K^+ and Mg^{++} .
 - **Other Arsenic Trioxide-Related Toxicity:** If Grade ≥ 3 , then hold treatment until clear clinical evidence of resolution to \leq Grade 1 and then resume treatment with a 50% dose reduction (0.075 mg/kg/day). If toxicity persists for more than 14 days after holding treatment or recurrent toxicity occurs despite dose reduction, then discontinue As_2O_3 .

8.4 Consolidation Therapy

a. Dose Modifications for ATRA Toxicity during Consolidation Therapy

- Follow dose modifications outlined in Section [8.3a](#).
- The ATRA syndrome (see Section [7.3b](#)) is not expected in patients in CR or PR; however, if the syndrome is suspected, discontinue ATRA, start dexamethasone at 10 mg IV or PO BID, and contact the Study Chair.
- Patients who experienced severe or recurrent ATRA-related toxicity during induction that necessitated permanent discontinuation should be discussed with the Study Chair before reinstituting ATRA during consolidation. Such patients can remain on protocol treatment without continuation of ATRA.

b. Dose Modifications for Gemtuzumab Ozogamicin (G.O.) during Consolidation

- Hepatotoxicity

If CTCAE 3.0 Grade 2-3 AST, ALT, or bilirubin elevation occurred during induction therapy (thought to be drug-related, and not disease related), G.O. dose will be reduced to 6 mg/m² during Consolidation Cycle 5. If Grade 2-3 AST, ALT, or bilirubin elevation recurs following Day 1 of G.O. during Consolidation Cycle 5, the dose of G.O. during Consolidation Cycle 6 will be decreased to 3 mg/m².

For patients in whom Grade 2-3 AST, ALT, or bilirubin elevation did NOT occur during induction, but occurs following Day 1 of Consolidation Cycle 5, the dose of G.O. during Consolidation Cycle 6 will be decreased to 6 mg/m².

For patients that experience Grade 4 AST, ALT, or bilirubin elevation following G.O. during any course, further G.O. will NOT be administered. In these instances, a hepatic doppler ultrasound is required to evaluate for hepatic sinusoidal obstructive syndrome.

In any case where there is Grade 3 bilirubin elevation, a hepatic doppler ultrasound is recommended to evaluate for hepatic sinusoidal obstructive syndrome.

- Hematologic Toxicity

Following the initiation of Consolidation Cycle 5, delayed recovery of peripheral blood to B1 status (see Section 10.1) beyond 8 weeks will require discontinuation of further G.O. therapy, and patients will proceed to Maintenance Therapy.

- Anaphylactic reaction

For patients experiencing anaphylactic reaction with this agent during induction, gemtuzumab ozogamicin will be permanently discontinued.

c. Dose Modification for Daunomycin during Consolidation

- Hepatotoxicity (for patients with evidence of hepatic dysfunction, reassess regularly during daunorubicin treatment).**

<u>Bilirubin</u>	<u>% Dose to Give</u>
> 3.0 mg/dL	75%

- Cardiotoxicity:** Adequate LV function will be required as described previously. Patients judged not to have adequate LV function should be discussed with the Study Chair.

d. Dose Modifications for Arsenic Trioxide during Consolidation

- See Section 8.3.b above. For patients requiring dose reduction of arsenic trioxide during induction due to toxicity, the starting dose for consolidation should be reduced to the acceptable dose determined during induction. For patients in whom arsenic trioxide was permanently discontinued during induction therapy, arsenic trioxide will be omitted from Consolidation Cycles 1 and 2, and patients will proceed to Consolidation Cycle 3. For patients experiencing toxicity from arsenic trioxide during consolidation (in the absence of previous toxicity during induction), dose adjustment guidelines as stated in Section 8.3b should be followed.

8.5 Maintenance Therapy

- Dose Modifications for 6-MP and MTX during Maintenance Therapy
 - Because patients begin maintenance therapy in CR, the non-leukemia NCI CTCAE scale should be used during maintenance therapy.

Grade	ANC/mcl	and/or Hgb (g/dl)	and/or Platelets /mcl	6-MP & MTX
1	< LLN - 1,500	< LLN – 10	< LLN - 75,000	100%
2	< 1,500 - 1,000	8 - <10	< 75,000 - 50,000	50%
3	< 1,000 - 500	6.5 - < 8	< 50,000 - 25,000	0*
4	< 500	< 6.5	< 25,000	0*

* Discontinue 6-MP and methotrexate. Treatment may resumed at 50% doses when toxicity has resolved to \leq Grade 1. Both drugs may then be escalated individually to tolerance.

If more than one of the dose modifications apply, use the most stringent (i.e., the greatest dose reduction). The intent of this treatment is to give the highest tolerable daily dosages of 6-MP and oral methotrexate (up to 100%). If hematologic toxicity does not resolve, a bone marrow exam should be performed to evaluate for relapse.

- Hyperbilirubinemia

Give the following percentages of full dose:

Bilirubin (md/dL)	6-MP & MTX
< 3.0	100%
≥ 3.0 but < 5.0	75%
≥ 5.0	0*

* Hold treatment for up to four weeks. Contact the Study Chair if toxicity does not resolve.

- Elevated ALT/AST

Grade	ALT/AST	6-MP & MTX
1	> ULN – 2.5 X ULN	100%
2	> 2.5 – 5.0 X ULN	100%
3	> 5.0 – 20.0 X ULN	0*
4	> 20.0 X ULN	0*

* Discontinue 6-MP and methotrexate. When toxicity has resolved to \leq Grade 1, treatment with both drugs may resume with a 50% dose reduction. Both drugs then may be escalated individually to tolerance. If toxicity recurs, discontinue both drugs. Treatment may resume again after another 50% dose reduction (i.e., 25% of original dose) when toxicity resolves to \leq Grade 1. If toxicity reoccurs after a second dose reduction then discontinue drugs and contact the Study Chair. Persistent hepatic transaminase elevation may require liver biopsy for diagnosis.

The intent of this treatment is to give the highest tolerable daily dosages of 6-MP and weekly methotrexate that produce < Grade 3 toxicity.

- **Mucositis**

For \geq Grade 2 oral ulceration, hold oral methotrexate until mucositis clears, then reinstate at 75% of previous dose. Observe for hematologic toxicity if mucositis is noted.

- Other 6-MP or MTX-Related Toxicities: If Grade \geq 3, then hold treatment. Treatment may resume after a 50% dose reduction when toxicity resolves to \leq Grade 1. If toxicity reoccurs after a first dose reduction, treatment may resume again after another 50% dose reduction (i.e., 25% of original dose) when toxicity resolves to \leq Grade 1. If toxicity reoccurs after a second dose reduction then discontinue drug(s).

- Dose Modification for ATRA during Maintenance Therapy

- See Section [8.4.a](#) above

8.6 Dose Modifications for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, all dosing is to be determined by the patient's actual weight. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation. Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients on this protocol.

8.7 Dose Modification Contacts

For treatment or dose modification questions, please contact the Study Chair, Dr. Lancet at 813-745-6841 or if Dr. Lancet is not available, Dr. Komrokji at 513/584-6915.

8.8 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in [Section 16.0](#) of the protocol must be reported to the Operations Office, Study Chair and NCI via ADEERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDARS

REQUIRED STUDIES		PRE- STUDY	INDUCTION	CONSOLIDATION		CONSOLIDATION		CONSOLIDATION		MAINTENANCE		Follow Up
				#1 through 2	#3 through 4	#5 through 6	Prior	During	Prior	During		
PHYSICAL												
History & Physical Exam		X	2X/week	X	X&	X	X α	X	X&	X	X&	X✓
Height, Weight and BSA		X		X	X†	X	X†	X	X†	X	X&	X✓
Performance Status (Zubrod)				X	X&	X	X α	X	X&	X	X&	X✓
Toxicity Notation			2X/week	X		X		X		X	X&	X✓
LABORATORY STUDIES												
CBC, Diff, Plts		X	2X/week	X	weekly	X	weekly	X	weekly	X	X&	X✓
Pregnancy test		X										
Electrolytes (incl. Ca ⁺ and Mg ⁺⁺), creatinine *		X	2X/week	X	weekly	X	weekly	X	weekly	X	X&	
Bilirubin, AST, ALT, Alkaline phosphatase *		X	2X/week	X	weekly	X	weekly	X	weekly	X	X&	
Cholesterol, triglycerides *		X				X		X		X	X&	
PTT, PT, fibrinogen, FDP, D-dimer Δ *		X	2X/week									
BM Aspirate/Biopsy Θ		X	X ψ	X		X				X	X Π	X
Cytogenetics Σ		X	Xú									Xú
RT-PCR for PML-RARα Σ		X	X							X		Xú
Lumbar Puncture (see Section 7.2b)				X								
X-RAYS AND SCANS												
Chest X-Ray %		X										
MUGA/ECHO						X#						
EKG \$		X	2X/week			X						
TREATMENT (See Section 7.0)												
Allopurinol/rasburicase			X									
ATRA			X f				X				X	
Daunomycin							X					
Arsenic trioxide			X		X							
6-mercaptopurine											X	
Methotrexate											X	
Gemtuzumab ozogamicin			X							X		

NOTE: Forms are found in Section 18.0. Forms submission guidelines are found in Section 14.0.

Click here to view [footnotes](#).

Footnotes:

- * Results of these tests do not determine eligibility but should be done prior to registration in accordance with good medical practice.
- & Monthly.
- ✓ After the patient is off treatment, the remaining of Months 3, 6, 9, 12, 18, 24 and 36 from the time of initial registration.
- Δ These tests should be done at pretreatment, twice weekly during induction until normal, and as clinically indicated thereafter.
- ⊖ Pretreatment, during induction (on Day 42, then q 2 wks until CR is met), prior to Consolidation #1, prior to Consolidation #3, prior to Maintenance, then every 3 months during maintenance. Once maintenance is complete, every 3 months for the 1st year, then every 6 months for the 2nd year, then at the end of the 3rd year from registration. Following completion of maintenance, only aspirate is required. Note that the marrow documenting CR may serve as the prior to Consolidation #1 marrow, providing it was performed within 8 weeks prior to Consolidation registration (see Section [5.2](#)).
- Σ See Section [15.0](#).
- % Chest X-Ray should be done pretreatment and as clinically indicated.
- \$ Obtain within 72 hours prior to the day of treatment. To be performed twice per week for the first 2 weeks of induction, prior to consolidation Cycle 3, and thereafter as clinically indicated.
- ψ On Day 42, then every 2 weeks until criteria for CR are met.
- Π Every 3 months during maintenance.
- α Every 2 weeks.
- # See Section [7.5c](#).
- † To be performed prior to each cycle of consolidation.
- f ATRA administration is permitted for up to 5 days prior to registration.
- ¶ RT-PCR required prior to Consolidation #3, but not #4.
- ¿ Follow-up cytogenetics and RT-PCR required at relapse only.
- ü Only submitted centrally for patients affiliated with CALGB or ECOG (see Section [7.8a](#)).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Disease Status Criteria:

NOTE that the kinds of cells considered equivalent to blasts and included in the calculation of blast percentages depend on the FAB classification (see Section [4.1a.2](#))

a. Bone Marrow:

A1. Maturation of all cell lines; and < 5% blasts; and no Auer rods.

A2. Same as A1, except blasts \geq 5% and < 25%.

A3. Failure to meet the criteria for A1 or A2.

b. Peripheral Blood:

B1. Neutrophils > 1,000/mcl; and platelets > 100,000/mcl; and no leukemia blasts in the peripheral blood.

B2. Failure to meet the criteria for B1.

c. Extramedullary Disease:

C1. None

C2. Any

10.2 Complete Remission (CR)

Attainment of A1 marrow status and B1 peripheral blood status and C1 extramedullary disease status.

10.3 Molecular Remission (MCR)

Attainment of CR with no evidence of the PML-RAR alpha transcript as measured by PCR.

10.4 Partial Remission (PR)

Attainment of A2 marrow status and B1 peripheral and C1 extramedullary disease status.

10.5 Treatment Failures

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

a. Resistant Disease: patient survives > 30 days following completion of initial treatment course and has persistent leukemia in the most recent peripheral blood smear or bone marrow after completion of therapy.

b. Not Assessable: patient survives > 30 days following completion of initial treatment course then dies with no persistent leukemia in the peripheral smear but no post-induction bone marrow examination.

c. Treatment Failure Due to Death:

1. patient survives < 30 days after completion of initial treatment course with evidence of persistent leukemia in the peripheral smear and post induction bone marrow examination.
2. patient survives < 30 days following completion of initial treatment course then dies without determination of response.

10.6 Relapse from CR

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 or reappearance of PML-RAR alpha (in patients who had achieved MCR) via cytogenetics, FISH, or PCR in the blood or bone marrow, confirmed at least once 4 - 8 weeks later. 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.

10.7 Event-free survival (EFS) at 3 years

For this study, EFS at 3 years is defined as a binary variable as follows: Yes if the patient achieves CR (Section [10.2](#)) and remains in continuous CR until at least 3 years after entering the study; otherwise No.

10.8 Toxicity Criteria

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

10.9 Performance Status

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

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

10.10 Time to Death

From date of registration until date of death from any cause.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Objective

The primary objective of this study is to test whether the regimen incorporating ATRA, arsenic trioxide, and gemtuzumab ozogamicin is sufficiently safe and effective among patients with previously untreated high-risk acute promyelocytic leukemia to warrant Phase III study. This objective will be met by analyzing the probabilities of continuous complete remission (CCR) at 3 years and of death from any cause within the first 6 weeks of protocol treatment. If the 3-year CCR rate is sufficiently high AND the 6-week mortality rate is sufficiently low, then Phase III study might be warranted; otherwise further study would not be recommended. To define a test criterion based on both outcomes, it is necessary to define null and alternative hypotheses in terms of the joint distribution of efficacy and toxicity.

The regimen would not warrant Phase III study if its true 3-year CCR rate is 50% or less OR its 6-week mortality rate is 30% or more. Therefore, the joint distribution of the null hypothesis with marginal probabilities is the following:

Null Hypothesis Joint Distribution:

Death within first 6 weeks	Died or relapsed within 3 years, or no CR	Alive in CR at 3 years
Yes	30%	0%
No	20%	50%

The regimen would warrant Phase III study if its true 3-year CCR rate is 70% or higher AND its true fatal toxicity rate is 15% or less. Therefore, the joint distribution of the alternative hypothesis with marginal probabilities is the following:

Alternative Hypothesis Joint Distribution:

Death within first 6 weeks	Died or relapsed within 3 years, or no CR	Alive in CR at 3 years
Yes	15%	0%
No	15%	70%

Because there is only limited Group-wide experience with this regimen, accrual will be conducted in two steps. In the first step, 32 eligible patients will be accrued. If more than seven of these patients die within the first 6 weeks, then the study will be terminated early with the conclusion that the study does not warrant Phase III study. Otherwise an additional 38 eligible patients will be accrued. Patients enrolled before RT-PCR results are known and who are subsequently found to be negative for PML-RAR α and RAR α -PML will not be counted towards these accrual goals.

If, among the total of 70 eligible patients, at least 41 are alive and in continuous CR at 3 years and fewer than 17 die in the first 6 weeks, then Phase III study will be warranted. For the null hypothesis joint distribution above, the probability of early stopping is 0.79, and the critical level (the probability of erroneously concluding that the regimen warrants Phase III study) of the study is 0.033. For the joint distribution of the alternative hypothesis, the probability of early stopping is 0.096, and the power (the probability of correctly concluding that Phase III study is warranted) is 0.89. The statistical characteristics are summarized in the following table:

Hypothesis	Null	Alternative
Probability of 8+ deaths within 6 weeks in first 32 patients	0.79	0.096
Probability of 41+ CCR at 3 yrs and < 17 deaths within 6 weeks in 70 patients	0.033	0.89

11.2 Molecular Response and Toxicity

With 70 eligible patients, the probabilities of molecular response and of any particular toxicity can be estimated to within at most $\pm 12\%$ (95% confidence interval). Any toxicity occurring with at least 5% probability is very likely to be observed in at least one patient (probability $\geq 97\%$).

11.3 Accrual

The recent intergroup APL study **C9710**, accrued about 25 eligible high-risk patients per year. Therefore accrual of 70 eligible patients to this study is expected to require approximately 34 months assuming there is not a lengthy delay between the two stages of accrual.

11.4 Data Safety Monitoring

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

NOTE: For non-SWOG member procedures (CTSU participation) see Appendix [18.4](#).

13.1 Registration Timing

Patients must be registered prior to initiation of Induction (Step 1—Initial Registration), Consolidation (Step 2—Consolidation Therapy Registration), or Maintenance (Step 3—Maintenance Therapy Registration) treatment no more than one working day prior to planned start of treatment.

13.2 Registration Requirements

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

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

13.3 Registration Procedures

- a. You may register patients from Member, CCOP and approved Affiliate institutions to a therapeutics study using the SWOG Registration program. To access the Registration program go to the SWOG Web site (<http://swog.org>) and click on the Logon link to go to the SWOG Members Area logon page (<https://swog.org/visitors/logon.asp>). This Web program is available at any time except for periods listed under Down Times. Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at <https://swog.org/visitors/logonhelp.asp>. After you have logged on, click on the Clinical Trials link and then the Patient Reg link to go

to the Entry Page for the Patient Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on Starter Kit link at the login page.

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

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN to the institution where a registration is occurring, and
3. You are granted permission to use the Patient Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Patient Registration program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred, and exactly what you were doing.

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

Member, Affiliate and CCOP Institutions

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

- 13.4 For either method of registration, exceptions to Southwest Oncology Group registration policies will not be permitted.
 - a. Patients must meet all eligibility requirements.
 - b. Institutions must be identified as approved for registration.
 - c. Registrations may not be cancelled.
 - d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

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

14.3 Data Submission Procedures

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

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

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

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

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

14.4 Data Submission Overview and Timepoints

- a. WITHIN 14 DAYS AFTER INITIAL REGISTRATION (STEP 1):

Submit the following:

S0535 Prestudy Form

Pathology Report

Pretreatment Cytogenetics Report (only required for patients from SWOG sites and other sites NOT affiliated with ECOG or CALGB)

Pretreatment RT-PCR Report (only required for patients from SWOG sites, CALGB sites and other sites NOT affiliated with ECOG)

See Section [15.0](#) for sample submission requirements.

- b. WITHIN 14 DAYS AFTER COMPLETING INDUCTION TREATMENT:

Submit the following:

S0535 Induction Treatment Summary Form

S0535 Adverse Event Summary Form

APL Disease Assessment Form

Off Treatment Notice (Please enter Step "1" on form.)

RT-PCR Report (only required for patients from SWOG sites, CALGB sites and other sites NOT affiliated with ECOG)

- c. WITHIN 14 DAYS AFTER COMPLETING EACH OF CONSOLIDATION CYCLES 1 AND 2 TREATMENT:

Submit the following:

S0535 Consolidation Cycles 1 and 2 Treatment Summary Form

S0535 Adverse Event Summary Form

- d. WITHIN 14 DAYS AFTER COMPLETING CONSOLIDATION CYCLE 2:

Submit the following:

APL Disease Assessment Form

RT-PCR Report (only required for patients from SWOG sites, CALGB sites and other sites NOT affiliated with ECOG)

- e. WITHIN 14 DAYS AFTER COMPLETING EACH OF CONSOLIDATION CYCLES 3 AND 4 TREATMENT:

Submit the following:

S0535 Consolidation Cycles 3 and 4 Treatment Summary Form

S0535 Adverse Event Summary Form

- f. WITHIN 14 DAYS AFTER COMPLETING EACH OF CONSOLIDATION CYCLES 5 AND 6 TREATMENT:

Submit the following:

S0535 Consolidation Cycles 5 and 6 Treatment Summary Form

S0535 Adverse Event Summary Form

- g. WITHIN 14 DAYS AFTER COMPLETING CONSOLIDATION CYCLE 6:

Submit the following:

APL Disease Assessment Form

- h. WITHIN 14 DAYS AFTER GOING OFF CONSOLIDATION TREATMENT:

Submit the following:

Off Treatment Notice (Please enter Step "2" on form.)

- i. WITHIN 14 DAYS AFTER REGISTRATION FOR MAINTENANCE THERAPY (Step 3):

Submit the following:

APL Disease Assessment Form

RT-PCR Report (only required for patients from SWOG sites, CALGB sites and other sites NOT affiliated with ECOG)

j. EVERY 3 MONTHS WHILE ON MAINTENANCE THERAPY:

Submit the following:

S0535 Maintenance Treatment Summary Form

S0535 Adverse Event Summary Form

APL Disease Assessment Form

k. WITHIN 14 DAYS AFTER GOING OFF MAINTENANCE TREATMENT:

Submit the following:

Off Treatment Notice (Please enter Step "3" on form.)

l. WITHIN 14 DAYS AFTER KNOWLEDGE OF A RELAPSE FROM COMPLETE REMISSION:

Submit the following:

A copy of the APL Disease Assessment Form documenting the date of and evidence for complete remission or relapse.

Submit Cytogenetics Report (only required for patients from SWOG sites and other sites NOT affiliated with ECOG or CALGB)

RT-PCR Report (only required from SWOG sites, CALGB sites and other sites not affiliated with ECOG)

m. AFTER OFF TREATMENT: THE REMAINING OF MONTHS 3, 6, 9, 12, 18, 24 AND 36 FROM THE TIME OF INITIAL REGISTRATION:

Submit the following:

Follow Up Form.

n. WITHIN 4 WEEKS AFTER KNOWLEDGE OF DEATH:

If death occurs while patient is on protocol treatment submit a copy of the Notice of Death, the **S0535** Adverse Event Summary Form and the Treatment Summary Form that corresponds with the Step and Cycle of treatment the patient was receiving at the time of death.

If the death occurs after off treatment submit a final Southwest Oncology Group Follow Up Form. Also submit a copy of the Notice of Death.

15.0 SPECIAL INSTRUCTIONS

15.1 Summary of all specimen submission

The table below outlines the required RT-PCR tests and cytogenetic studies for all patients. RT-PCR at each time listed below and cytogenetic studies at pretreatment and relapse are required for all patients, regardless of group affiliation. Additional details regarding mechanisms for obtaining these studies are Group specific. See Section 15.2 for SWOG (and other sites not affiliated with ECOG or CALGB), [Section 15.3](#) for ECOG and [Section 15.4](#) for CALGB.

Specimen collection time	RT-PCR*	Cytogenetics
Pretreatment (Prior to Induction)	BM, PB ^a	BM
At the time of neutrophil recovery or on Day 42 (see Section 7.8a)	BM, PB	BM ^b
Prior to Consolidation #3 (see Section 7.8b)	BM, PB	
Prior to Maintenance (see Section 7.8c)	BM, PB	
At relapse	BM, PB	BM

* SWOG institutions may only submit peripheral blood if bone marrow aspirate is “dry tap”.

RT-PCR analyses of specimens collected at pretreatment are time-sensitive and RT-PCR results will be reported by the testing laboratory to the institution within 10 days after the specimens are received. RT-PCR assays of the remaining specimens are not time sensitive, and results will not be reported to the institution.

If the RT-PCR result of the time-sensitive analysis is indeterminate (e.g. specimen damaged in shipment or extracted RNA yield or quality is inadequate), the testing laboratory may contact the institution to request collection and submission of an additional specimen in an attempt to obtain a positive or negative result before reporting the molecular status.

^a The pretreatment RT-PCR determines whether the patient is eligible for the study or, if already registered, should continue on protocol treatment; see Section 5.1b. If the pretreatment RT-PCR result is indeterminate (e.g. specimens damaged in shipment or extracted RNA yield or quality is inadequate), additional blood specimens should be submitted for RT-PCR testing to avoid indeterminate pretreatment results whenever possible.

^b Not required for SWOG sites and other sites not affiliated with ECOG or CALGB.

15.2 Southwest Oncology Group institutions and other institutions NOT affiliated with ECOG or CALGB

NOTE: No specimens will be banked for SWOG and other sites not affiliated with ECOG or CALGB.

a. Cytogenetic studies

Effective with Revision #5, 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, according to the schedule in Section 15.1, and reports of the results must be submitted as described in Section [14.0](#).

b. PCR testing

1. Effective with Revision #5, submission of specimens for RT-PCR testing through protocol **S9910** is no longer required. However, RT-PCR testing must still be performed at the following times:

- a. Pretreatment (prior to Induction)
 - b. At the time of neutrophil recovery ($\geq 1,000/\text{mcl}$) or on Day 42 after beginning ATRA (whichever comes first). (See Section 7.8a.)
 - c. Prior to Consolidation #3 (within 8 weeks [preferably within 4 weeks] before starting Consolidation #3 treatment; see Section 7.8b)
 - d. Prior to Maintenance
 - e. At Relapse
2. Specimens for PCR testing may be submitted to any CLIA-approved laboratory; reports of the results must be submitted as described in Section 14.0. CLIA certificates will be verified at the time of an audit.

15.3 ECOG Institutions

The sample submission schedule is indicated in Section [15.1](#). It is required that pretreatment specimens and karyotypes must be submitted via E3903 "Ancillary laboratory protocol for collecting diagnostic material on patients considered for ECOG treatment trials for leukemia or related hematologic disorders".

It is required that ALL biological sample submissions be logged into the ECOG Sample Tracking System (ECOG-STS) and a shipping manifest generated by this system is to accompany all submissions. See Section [15.3c](#).

If the ECOG-STS is unavailable at the time of shipping, submit a completed E3903 Material Submission Form and indicate the collection "TIME POINT" in the comment section of the form. The form MUST contain the treatment protocol number **S0535** and the patient's **S0535** case number. Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

NOTE: The E3903 Material Submission Form may be obtained from the ECOG website.

a. Specimens for PCR testing

1. Submissions

Baseline samples are to be submitted via E3903.

Copies of the patient's signed E3903 and **S0535** consents and signed authorizations must be submitted to the Leukemia Translational Studies Laboratory (LTSL) prior to or with the first sample submissions on these studies.

An ECOG-STS shipping manifest must be submitted with each shipment.

The following samples must be submitted **at each RT-PCR time point listed in Section 15.1:**

- a. Heparinized (10 units heparin/ml) bone marrow aspirate, two (2) 4-5mL tubes

Note: For patients with an inaspirable bone marrow (“dry tap”) call Dr. Paietta’s laboratory at (718) 920-9992 to discuss the case and the possibility for submitting peripheral blood only. Be prepared to report the WBC.

- b. Heparinized peripheral blood (green top tubes) (30-40 cc)
- c. One air dried smear must be submitted.

The bone marrow and peripheral blood must be sent fresh (on the day of collection) **on cool packs**, packaging so that samples DO NOT FREEZE by wrapping them at least in bubble wrap. 24 hours prior to arrival of the samples at the LTSL, the following must be done:

- If the ECOG – STS is unavailable, The Leukemia Translational Studies Laboratory **must** be notified by telephone. **Fax is not acceptable.**

Phone: 718/920-9992
Beeper (off hours): 917/729-7231

If you want to notify the laboratory of a sample submission during off hours, please leave a message on the laboratory’s answering machine (718-920-9992). Page Dr. Paietta at the beeper number above only if there are questions regarding the sample submission.

- Ship by overnight courier (preferably Federal Express) to arrive within 24 hours to:

Elisabeth Paietta, Ph.D.
Our Lady of Mercy Cancer Center
600 East 233rd Street
6th Floor, Immunology Laboratory
Bronx, NY 10466-2697
Phone: 718/920-9992

The laboratory is open to receive shipments Monday through Saturday. Shipments on Fridays for Saturday delivery must have “Saturday Delivery” marked on the overnight courier slip.

If you have questions, contact the Leukemia Translational Studies Laboratory 718/20-9992.

2. Notification of PCR test

The LTSL will process and forward the appropriate materials to Dr. Robert Gallagher for determination of molecular PML-RAR α status (positive or negative). The results for the time sensitive tests will be FAXed to the site within 10 days of receipt of the sample.

Copies of the reports will also be submitted to SWOG.

b. Cytogenetic Review

At each cytogenetic time point listed in Section 15.1, submit two original karyotypes and institution's cytogenetics laboratory report from the **bone marrow** cytogenetic studies performed by the institution's cytogenetic laboratory.

NOTE: Karyotypes from peripheral blood cytogenetic studies will **NOT** be accepted as a substitute for the bone marrow cytogenetic analysis.

Submit the karyotypes, reports and a completed ECOG Leukemia Cytogenetics Form (#365R) to the ECOG Cytogenetics Committee:

Gary Hicks
Mayo Clinic Cytogenetics Laboratory
970 Hilton
200 First Street, S.W.
Rochester, MN 55905
Phone: 507/284-2950
Fax: 507/284-0043

Failure to submit these materials will render the case unevaluable.

The cytogenetic reviews will be performed by the ECOG Cytogenetics Laboratory at Mayo Clinic. Original karyotypes will be returned when the review and analysis are complete. Copies of the karyotypes will be scanned and stored electronically for future reference.

c. ECOG Sample Tracking System (ECOG-STS)

It is required (barring special circumstances) that all samples be entered and tracked using the ECOG Sample Tracking System (ECOG-STS). As of June 2007, the software will allow the use of either 1) an ECOG user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking <https://webapps.ecog.org/Tst>.

Important: Please note that the ECOG-STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: <http://www.ecog.org/ecoginst/trans/>. Please take a moment to familiarize yourself with the software prior to using the system.

A shipping manifest must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the ECOG-STS to ecog.tst@jimmy.harvard.edu.

15.4 CALGB institutions

Information for specimen submissions for CALGB institutions.

a. Specimens for PCR Testing and **CALGB-9862**

1. Specimens for PCR Testing

Effective with Revision #7, submission of specimens for RT-PCR testing through protocol CALGB-9862 is no longer required. However, RT-PCR testing must still be performed at the time points listed in Section [15.4a.3](#).

Specimens for PCR testing may be submitted to any CLIA-approved laboratory; reports of the results must be submitted as described in Section [14.0](#). CLIA certificates will be verified at the time of an audit.

2. Specimens for **CALGB-9862**

For consenting patients, specimens for banking must be submitted to the CALGB Leukemia Tissue Repository at the time points listed in Section [15.4a.3](#).

3. PCR and Banking Specimen Submission Time Points

- a. Pretreatment (prior to Induction)
- b. At the time of neutrophil recovery ($\geq 1,000/\text{mcl}$) or on Day 42 after beginning ATRA (whichever comes first). (See Section [7.8a](#).)
- c. Prior to Consolidation #3 (within 8 weeks [preferably within 4 weeks] before starting Consolidation #3 treatment; see Section [7.8b](#))
- d. Prior to Maintenance
- e. At Relapse

b. Specimens for Cytogenetics

Enrollment on **CALGB 8461** will be required for patients participating through CALGB institutions. **Submission of samples to your local, CALGB-approved cytogeneticist is mandatory. The cytogenetic sample must be obtained prior to the initiation of therapy. Specimens must also be submitted at time of achievement of CR and at relapse.**

With the specimen sent to the local approved cytogeneticist, enclose a completed CALGB Cytogenetic Referral Form (C-030) with CALGB patient number. Send a copy of the form to the CALGB Statistical Center, Data Operations. As soon as it is available, a copy of the cytogenetic report must be faxed to the CALGB Cytogenetics Office (614-293-3575) and to the CALGB Statistical Center, Data Operations (919-668-9348). Questions concerning sample submission may be directed to the CALGB Cytogenetics Office at The Ohio State University (614-293-2542).

Cytogenetic Sample Procurement: Consult with the institutional CALGB cytogeneticist regarding how the sample(s) should be collected. An adequate NONDILUTE specimen of marrow is usually required to obtain metaphases. Two to 3 mLs of the initial aspiration (in a sterile heparinized syringe) from a repositioned needle is ideal. Success is often dependent on the prompt delivery of the specimen to the cytogeneticist.

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

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

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.

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.

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 CTEP's Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at <http://ctep.cancer.gov>. A CTEP-AERS report must be submitted to the Southwest Oncology Group Operations Office electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table [16.1](#)) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808. Once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table [16.1](#) or [16.2](#), as applicable.

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 to the Institutional Review Board responsible for oversight of the patient must also be reported according to local policies and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table [16.1](#). The investigational agent(s) used in Induction and Consolidation Cycles 5 and 6 of this study is gemtuzumab ozogamicin. 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 Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention¹ Gemtuzumab Ozogamicin

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or [Section 16.1f.]

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent under a non-CTEP-IND:**

1) **Group-specific instructions.**

Within 10 calendar days (5 calendar days if 24-hour reporting was required), submit the following to the Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

The Operations Office will notify drug companies as required.

2) **For this study, the adverse events listed below do not require expedited reporting via CTEP-AERS:**

- Grade 4 myelosuppression

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agent(s) used in this study are all trans retinoic acid (ATRA), arsenic trioxide, daunomycin, 6-mercaptopurine and methotrexate. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients on this study who have received the commercial drug(s) listed in 16.1f above.

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
<p>CTEP-AERS: Indicates an expedited report is to be submitted via NCI CTEP-AERS within 10 calendar days of learning of the event^b.</p> <p>^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.</p> <p>^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.</p>				

h. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

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

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

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

i. **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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18.0 APPENDIX

- 18.1 Determination of Expedited Adverse Event Reporting Requirements
- 18.2 Writing Committee
- 18.3 Intake Calendar
- 18.4 Cancer Trials Support Unit (CTSU) Participation Procedures

CLOSED EFFECTIVE 06/01/2013

18.1 Determination of Expedited Adverse Event Reporting Requirements

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

18.2 Writing Committee

A Writing Committee will be responsible for the publication of a manuscript that will describe the results of this study in a peer-reviewed journal. The members of this writing committee will be the co-authors of this manuscript. Dr. Lancet, the Study Chair, will be the primary author. Ms. Holly Gundacker, the SWOG statistician, will be the 2nd author; and Dr. Appelbaum, the Leukemia Committee Chair of the SWOG, will be the senior (last) author. The three laboratory investigators who will perform RT-PCR assays to determine eligibility on this trial (Drs. Willman, Gallagher, and Stock) will also be members of the writing committee.

The other members of the writing committee will be determined according to the level of participation in the study as measured by patient accrual from each group. The number of investigators on the Writing Committee from each participating cooperative group (e.g., SWOG, CALGB, ECOG, NCIC CTG, COG) will be based on the following accrual formula. Each group that enrolls at least 5% of the entire study population will have one member on the writing committee. Each group will be entitled to an additional member of the Writing Committee for each additional 10% of the overall accrual. For example, if a group enrolled 15% of the study patients, that group would have 2 co-authors on the committee; if 25% of the study patients were enrolled, that group would have 3 co-authors. The SWOG will be assigned additional members of the Writing Committee only after that group accrues > 25% of the total study patients. It will be the responsibility of each cooperating group to name the individual clinical or laboratory investigators to fill their allotted positions. By this method, it is anticipated that the final Writing Committee will include approximately 12-14 of the clinical and/or laboratory investigators who have most involved in the design, conduct, and analysis of this study.

A smaller number of individuals (such as Disease Committee or Correlative Science Committee chairs) may warrant acknowledgment (with their group affiliation) in the final manuscript for their support of the conduct of the study and for their critical review of this manuscript. The participation of each cooperative group that enrolls any patients on this intergroup study will be acknowledged in the final manuscript with their respective grant support.

18.3 Intake Calendar

Instructions for the participant:

This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month:

Year:

[illegible]

Patient Signature: _____

18.4 Cancer Trials Support Unit (CTSU) Participation Procedures

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. 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 (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU 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 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 member web site at www.ctsuo.org.

All forms and documents associated with this study can be downloaded from the **S0535** Web page on the CTSU registered member Web site (www.ctsuo.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for S0535 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Pre-study requirements for patient enrollment on S0535

*In order to participate in **S0535**, subjects must be enrolled on ancillary protocols as detailed below:*

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations (including bone marrow aspirate and blood samples) performed within the time period specified in the protocol.
- **CALGB sites:** CALGB patients must be registered on **CALGB 8461** and **CALGB 9862** prior to registration to **S0535**,
- **ECOG sites:** **PRIOR** to registering a patient to **S0535**, ECOG institutions must either register the patient to **E3903** through ECOG. The ECOG patient number will be required by the CTSU at the time of **S0535** registration.
- **All other non-SWOG sites:** Effective with Revision #5, registration on **SWOG-9007** and **S9910** is no longer required, although cytogenetic studies and RT-PCR testing must be performed as described in Section [15.2](#).

CTSU Procedures for Patient Enrollment**Registration (Step 1) Induction**

Patients must be registered prior to Induction no more than one working day prior to the planned start of treatment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Mon-Fri. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. Within one hour, call the registrar cell phone at 1-301-704-2376.
2. Complete the following forms:
 - CTSU Patient Enrollment Transmittal Form
 - Eligibility Criteria Checklist (Section [5.1](#) of the protocol)
 - Registration Form for Registration Step 1
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and will follow-up with the site to resolve any discrepancies.
4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the Southwest Oncology Group, to obtain assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

Registration (Step 2) Consolidation

1. After completing Induction, patients will be registered for Consolidation therapy provided that they were eligible for the initial registration and satisfy the additional criteria outlined in Section [5.2](#) of the protocol.
2. Complete the following forms:
 - CTSU Patient Enrollment Transmittal Form
 - Eligibility Criteria Checklist for Consolidation (Section [5.2](#) of the protocol)
 - Registration Form for Registration Step 2
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays). A confirmation fax will be sent to the enrolling site upon successful registration.

Registration (Step 3) Maintenance Therapy

1. After completing Consolidation, patients will be registered for Maintenance therapy provided that they were eligible for the initial registration; and were eligible for and completed protocol consolidation therapy and satisfy the additional criteria outlined in Section [5.3](#) of the protocol.
2. Complete the following forms:
 - CTSU Patient Enrollment Transmittal Form
 - Eligibility Criteria Checklist for Maintenance Therapy (Section [5.3](#) of the protocol)
 - Registration Form for Registration Step 3

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays). A confirmation fax will be sent to the enrolling site upon successful registration.

DATA SUBMISSION AND reconciliation

1. All case report forms (CRFs) associated with this study must be downloaded from the S0535 Web page located on the CTSU registered member Web site (www.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the SWOG Data Operations Center. The preferred method of sending data is via fax at 800/892-4007. Do NOT include a cover sheet for faxed data. Do not send study data to the CTSU.
3. The SWOG Data Operations Center will send query notices and delinquency reports directly to the site for reconciliation. Please fax query responses and delinquent data to the SWOG Data Operations Center and do not copy the CTSU Data Operations. When faxing data, include the query sheet that was originally sent from SWOG.
4. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current**. This will ensure timely communication between the clinical site and the SWOG data center.

Special Materials or Substudies

Cytogenetic studies and PCR as outlined in Section [15.0](#) are mandatory. The collection of pre-treatment specimens as outlined in Section [15.0](#) must be completed prior to registration to **S0535**. Additional submission time points are listed in Section [15.0](#). Submissions must be made utilizing one of the following mechanisms:

CALGB sites: Cytogenetic studies and RT-PCR testing must be obtained as described in Section [15.4](#).

ECOG sites: Submissions outlined in Section [15.3](#). It is required that baseline submissions be via **E3903**, ECOG's baseline submission and repository protocol.

All other sites: Submissions outlined in Sections [15.1](#) and [15.2](#). Submissions be made to a CLIA-approved laboratory.

All other sites: Requirements for cytogenetic studies and RT-PCR testing are outlined in Sections [15.1](#) and [15.2](#). Cytogenetic studies must be performed at each institution's preferred cytogenetics laboratory. RT-PCR testing must be performed at CLIA-approved laboratories.

SERIOUS Adverse Event (AE) Reporting (SECTION [16.1](#))

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Reporting System (CTEP-AERS) from either the Adverse Events tab of the CTSU member homepage (www.ctsus.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the protocol number Web page.
3. Do not send adverse event reports to the CTSU.
4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu CTEP-AERS. Submit the completed form and supporting documentation as outlined in the protocol.

Drug Procurement (SECTION [3.0](#))

Commercial agents: All Trans Retinoic Acid (Trentinoin), Arsenic Trioxide (Trisenox®), Daunomycin (Cerubidine)(daunorubicin hydrochloride), Gemtuzumab Ozogamicin (Mylotarg®), 6-Mercaptopurine, Methotrexate

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section [3.0](#) of the protocol.
2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center drop down list on the **S0535** Web page.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up can be found in the CTMB Monitoring Guidelines and are available for download from the CTEP web page <http://ctep.cancer.gov/monitoring/guidelines.html>.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data System–Web (CDS-Web) Monitoring

This study will be monitored by the Clinical Data System (CDS-Web). The sponsoring Group fulfills this reporting obligation by transmitting the CDS data collected from the study-specific case report forms, via the Web to the NCI Center for Biometrics (NCICB). Cumulative CDS data are submitted quarterly.

Informed Consent Model for S0535

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

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

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

Readability Statistics:

Flesch Reading Ease 61.8 (targeted above 55)
Flesch-Kincaid Grade Level 8.6 (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 the Southwest Oncology Group.

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

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

***NOTES FOR LOCAL INVESTIGATORS:**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "If You Have Cancer...What You Should Know about Clinical Trials". 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.

S0535, "A Phase II Study of ATRA, Arsenic Trioxide and Gemtuzumab Ozogamicin in Patients With Previously Untreated High-Risk Acute Promyelocytic Leukemia"

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 high-risk acute promyelocytic leukemia (APL) that has never been treated.

Why is this study being done?

The purpose of this study is to learn about the effects of treating your APL with chemotherapy. The chemotherapy for APL has three parts: induction therapy, consolidation therapy, and maintenance therapy. The purpose of the induction therapy is to eliminate the signs and symptoms of your APL from your body. If this happens, your APL will be in "remission". Consolidation therapy and maintenance therapy are intended to make your remission last as long as possible.

One of the main purposes of this trial is to study the effects, good and/or bad, of a unique combination and schedule of chemotherapy drugs for people who have difficult-to-treat APL. One of these chemotherapy drugs, gemtuzumab ozogamicin, is experimental.
(sentence added 10/5/10)

How many people will take part in the study?

About 70 people will take part in this study.

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

Before you begin the study ...

You may 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
- A chest x-ray
- Scans/tests of your heart function

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.

- Physical exam. This will take place twice per week during induction chemotherapy and once per month during the consolidation and maintenance chemotherapy.
- Blood tests, including test for your kidneys and liver. This will take place twice per week during induction chemotherapy and once per week during the consolidation and maintenance chemotherapy.
- Bone marrow aspirate and biopsy. This will take place on Day 42, then every 2 weeks during induction chemotherapy, before the first and third cycles of consolidation chemotherapy, before maintenance chemotherapy, and every 3 months during maintenance chemotherapy.

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- Heart scans/tests

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Bone marrow specimens from the aspirates and biopsies will be sent to a special lab for research purposes. This is required as part of the study. *(NOTE to institutions: This refers to the mandatory cytogenetic studies and RT-PCR testing.) (3/25/10)*

Induction Chemotherapy with ATRA, Gemtuzumab Ozogamicin, and Arsenic Trioxide

You will take ATRA by mouth twice every day with food starting on Day 1 until visible signs of your leukemia go away. Gemtuzumab ozogamicin will be given into your vein over two hours on Day 1. Arsenic Trioxide will be given into your vein starting on Day 10 over two hours every day for five days each week until your leukemia starts getting better. Samples of your bone marrow will be taken 42 days after beginning ATRA. Samples of your bone marrow then will be taken every two weeks if needed until signs of your leukemia are decreased or gone. If signs of your leukemia are decreased or are gone, you will go on to consolidation therapy.

(section added 5/30/08)

Drug	How Drug is Given	How Often	For How Long
ATRA	by mouth	2 times a day	until visible signs of leukemia are gone
Gemtuzumab ozogamicin	IV for 2 hours	once	on Day 1 only
Arsenic Trioxide	IV for 2 hours	5 days per week, starting on Day 10	until visible signs of leukemia are gone

Consolidation Chemotherapy

After your induction therapy, your bone marrow and blood samples will be tested for signs of APL. This is a standard part of the treatment for APL. You will be in complete remission (CR) if the signs of your APL are gone. If you are in CR after your remission induction therapy, you will receive six cycles of consolidation chemotherapy.

Consolidation #1 and #2 Chemotherapy with Arsenic Trioxide

You will receive arsenic trioxide into your vein over 2 hours 5 days per week for 5 weeks. You will then have 2 weeks of rest. You will then receive arsenic trioxide into your vein over 2 hours 5 days per week for 5 weeks.

(section added 5/30/08)

Drug	How Drug is Given	How Often	For How Long
Arsenic Trioxide	IV for 2 hours	5 days per week	five weeks of taking drug, two weeks of rest, five more weeks of taking drug

Consolidation #3 and #4 Chemotherapy with ATRA and Daunomycin

You will take ATRA by mouth twice each day with food on Days 1 - 7. Daunomycin will be given into your vein either in a very short time period or over an hour each day on Days 1 - 3. You will then have 2-8 weeks of rest. You will then take ATRA by mouth twice each day with food on Days 1 - 7. Daunomycin will be given into your vein either in a very short time period or over an hour each day on Days 1 - 3.

(section added 5/30/08)

Drug	How Drug is Given	How Often	For How Long
ATRA	by mouth	2 times a day	take drug for 7 days, rest for 2-8 weeks, then take drug again for 7 days
Daunomycin	IV (for up to 1 hour)	once daily	take drug for 3 days, rest for 2-8 weeks, take drug again for 3 days

Consolidation #5 and #6 Chemotherapy with Gemtuzumab Ozogamicin

You will receive gemtuzumab ozogamicin into your vein over 2 hours on Day 1. You will then have 2-8 weeks of rest and receive gemtuzumab ozogamicin once again. Samples of your bone marrow will be taken to see if you can go on to maintenance chemotherapy.

(section added 5/30/08)

Drug	How Drug is Given	How Often	For How Long
Gemtuzumab ozogamicin	IV for 2 hours	once	take drug for 1 day, rest for 2-8 weeks, take drug again for 1 day

Maintenance Chemotherapy

You will take ATRA by mouth twice each day with food for 7 days repeated every other week for 1 year. You will take 6-mercaptopurine by mouth each day for 1 year. You will take methotrexate by mouth once a week for 1 year. Samples of your bone marrow will be taken every 3 months during maintenance chemotherapy.

(section added 5/30/08)

Drug	How Drug is Given	How Often	For How Long
ATRA	by mouth	2 times a day	take drug for seven days, rest for seven days – repeat this cycle for one year
6-mercaptopurine	by mouth	once daily	one year
Methotrexate	by mouth	once a week	one year

How long will I be in the study?

You will be asked to take induction therapy (which could last up to 90 days unless you go into CR sooner), six courses of consolidation therapy (which could last about 6 months but may be longer if you have delays in treatment because of side effects), and maintenance therapy (for 1 year). After you are finished with these courses of treatment, the study doctor will ask you to visit the office for follow-up exams every 3 months for the first year, every 6 months for the second year, then at 3 years from the time you finish treatment. (11/1/11) At a minimum, you will have a physical exam and blood tests at each visit. Also, you will have a bone marrow aspiration, every 3 months for 1 year, then every 6 months for 1 year, then at the end of the third year.

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 ATRA, arsenic trioxide, daunomycin, gemtuzumab ozogamicin, 6-mercaptopurine, and methotrexate 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. If you are a female and become pregnant while in the study, you will be taken off of protocol treatment. (11/12/08)

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 drugs. In some cases, side effects can be serious, long lasting, or may never go away.

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

Risks and side effects related to the Induction Therapy (ATRA, Gemtuzumab Ozogamicin, and Arsenic Trioxide) include those that are:

Likely

- **Decreased number of a type of white blood cell (neutrophil/granulocyte)** (updated 5/26/10)
- **Decreased number of a type of blood cell that help to clot blood (platelet)** (updated 5/26/10)
- **Lack of enough red blood cells (anemia)** (updated 5/26/10)
- **Fever** (updated 5/26/10)
- **Chills** (updated 5/26/10)
- **Headache or head pain** (updated 5/26/10)
- **Nausea or the urge to vomit** (updated 5/26/10)
- **Vomiting** (updated 5/26/10)
- **Diarrhea** (updated 5/26/10)
- **Loss of appetite** (updated 5/26/10)
- **Belly pain** (updated 5/26/10)
- **Constipation**
- **Formation of sores in the lining of the mouth** (updated 5/26/10)
- **Inflammation (swelling and redness) or damage to the tissue surrounding where a drug was injected** (updated 5/26/10)
- **Muscle weakness of the whole body** (updated 5/26/10)
- **Shortness of breath** (updated 5/26/10)
- **Fatigue or tiredness** (updated 5/26/10)
- **Difficulty sleeping or falling asleep** (updated 5/26/10)
- **Depression**
- **Skin rash with the presence of macules (flat discolored area) and papules (raised bump)** (updated 5/26/10)
- **High blood pressure** (updated 5/26/10)
- **Low blood pressure** (updated 5/26/10)
- **Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)** (updated 5/26/10)

- **Increased blood sugar level** (*updated 5/26/10*)
- (*item deleted 5/26/10*)
- **Decreased blood level of potassium** (*updated 5/26/10*)
- **Low blood oxygen levels**
- **Chest pain not heart related** (*updated 5/26/10*)
- **Back pain**
- **Dryness of the lips** (*updated 5/26/10*)
- **Dry skin** (*updated 5/26/10*)
- **Fluid collecting in the lungs**
- **Sudden or traumatic injury to the kidney** (*updated 5/26/10*)
- **Toothache**
- **Sores or irritation of the lips**
- **Increased blood level of a form of fat called triglyceride** (*5/30/08*)
- **Nosebleed** (*5/30/08*)
- **Infection** (*added 5/26/10*)
- **Itching** (*updated and moved from Less Likely 5/26/10*)

Less Likely

- **Weight gain**
- **Fluid retention**
- **Upper respiratory infection**
- **Damage to the liver, which could cause yellowing in the skin and/or eyes**
- **Visual disturbances, eye problems**
- **Dry nose** (*updated 5/26/10*)
- **Dry mouth** (*updated 5/26/10*)
- (*updated and moved to Likely 5/26/10*)
- **Peeling skin**
- **Severe injury to liver (viral or alcoholic disease)** (*5/30/08*)
- **Fever associated with dangerously low levels of a type of white blood cell (neutrophils)** (*added 5/26/10*)
- **Decreased number of all blood cell types** (*added 5/26/10*)
- **Unpleasant sensation of irregular and/or forceful beating of the heart** (*added 5/26/10*)
- **Fast heartbeat; regular rhythm** (*added 5/26/10*)
- **Irregular heartbeat resulting from an abnormality in one of the lower chambers of the heart (ventricle)** (*added 5/26/10*)
- **Noise in the ears, such as ringing, buzzing, roaring, clicking** (*added 5/26/10*)
- **Swelling or feeling of fullness and tightness in the abdomen (belly)** (*added 5/26/10*)
- **Irritation or sores in the lining of the anus** (*added 5/26/10*)
- **Heartburn** (*added 5/26/10*)
- **Inflammation (swelling and redness) of the pancreas** (*added 5/26/10*)
- **Irritation or sores in the lining of the rectum** (*added 5/26/10*)

- **Irritation or sores in the lining of the small bowel** *(added 5/26/10)*
- **Swelling of the face** *(added 5/26/10)*
- **Swelling of the extremities (arms and/or legs)** *(added 5/26/10)*
- **Pain** *(added 5/26/10)*
- **Infection associated with a decrease in a type of white blood cell (lymphocyte)** *(added 5/26/10)*
- **Bruising** *(added 5/26/10)*
- **Increased blood level of a liver enzyme (ALT/SGPT)** *(added 5/26/10)*
- **Increased blood level of a liver enzyme (AST/SGOT)** *(added 5/26/10)*
- **Increased blood level of a liver pigment (bilirubin) often a sign of liver problems** *(added 5/26/10)*
- **Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)** *(added 5/26/10)*
- **Abnormal electrical conduction within the heart** *(added 5/26/10)*
- **Increased blood level of a liver enzyme (GGT)** *(added 5/26/10)*
- **Increased blood level of fat-digesting enzyme (lipase)** *(added 5/26/10)*
- **Increased blood level of a digestive enzyme (amylase)** *(added 5/26/10)*
- **Weight loss** *(added 5/26/10)*
- **Decrease in the total number of white blood cells (leukocytes)** *(added 5/26/10)*
- **More acid than normal in the blood** *(added 5/26/10)*
- **Increased blood level of potassium** *(added 5/26/10)*
- **Decreased blood level of magnesium** *(added 5/26/10)*
- **Joint pain** *(added 5/26/10)*
- **Bone pain** *(added 5/26/10)*
- **Shrinking of muscles** *(added 5/26/10)*
- **Muscle pain** *(added 5/26/10)*
- **Commonly known as “pins and needles”, where part of the body (typically a foot or hand) begins to tingle and becomes numb, or “falls asleep”** *(added 5/26/10)*
- **Weakness or paralysis (loss of muscle function) caused by damage to peripheral nerves (those nerves outside of brain and spinal cord)** *(added 5/26/10)*
- **Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning** *(added 5/26/10)*
- **Anxiety, feelings of dread or danger** *(added 5/26/10)*
- **More protein in the urine than usual, often a sign of kidney disease** *(added 5/26/10)*
- **Stuffy or runny nose, sneezing** *(added 5/26/10)*
- **Sudden constriction of the muscles in the walls of the bronchioles (small airways of the lung)** *(added 5/26/10)*
- **Cough** *(added 5/26/10)*
- **Irritation or sores in the lining of the voice box** *(added 5/26/10)*

- Irritation or sores in the lining of the throat *(added 5/26/10)*
- Build up of a large amount of fluid between the layers of tissue that line the lungs and chest cavity *(added 5/26/10)*
- A collection of symptoms including fever, difficulty breathing, chest pain, fluid in the lung (seen on chest X-ray), fluid around the lungs and heart, and lack of oxygen first seen in patients receiving the drug retinoic acid *(added 5/26/10)*
- Sore throat *(added 5/26/10)*
- Irritation or sores in the lining of the windpipe *(added 5/26/10)*
- Hair loss *(added 5/26/10)*
- Excess sweating *(added 5/26/10)*
- Area of bleeding within the skin causing a reddish purple discoloration *(added 5/26/10)*
- Inflammation (swelling and redness) of the skin *(added 5/26/10)*
- Thickening of the skin *(added 5/26/10)*
- Darkening of the skin *(added 5/26/10)*
- Hives *(added 5/26/10)*
- Increase in the number and size of the pores in the capillaries (small blood vessels) which causes leakage of fluid from the blood to the tissue spaces, resulting in dangerously low blood pressure, swelling and multiple organ failure *(added 5/26/10)*
- Sudden reddening of the face and/or neck *(added 5/26/10)*

Rare, but Serious

- Severe allergic reaction, which could be life threatening
- ATRA Syndrome: a combination of breathing problems including difficulty breathing, low level of oxygen in the blood, fever, rash, inflammation of the lungs, fluid around the heart and/or the lungs, heart failure
- *(moved 5/30/08)*

Risks and side effects related to Consolidation #1 and #2 Therapy (Arsenic Trioxide) include those that are:

Likely

- *(updated and moved to Less Likely 5/26/10)*
- Fatigue or tiredness *(updated 5/26/10)*
- Nausea or the urge to vomit *(updated 5/26/10)*
- Headache or head pain *(updated 5/26/10)*
- *(updated and moved to Less Likely 5/26/10)*
- Decreased number of a type of white blood cell (neutrophil/granulocyte) *(updated 5/26/10)*
- Decreased number of a type of blood cell that help to clot blood (platelet) *(updated 5/26/10)*
- *(updated and moved to Less Likely 5/26/10)*
- Shortness of breath

- *(item deleted 5/26/10)*
- **Diarrhea**
- *(updated and moved to Less Likely 5/26/10)*
- *(updated and moved to Less Likely 5/26/10)*
- *(item deleted 5/26/10)*
- *(updated and moved to Less Likely 5/26/10)*
- *(updated and moved to Less Likely 5/26/10)*
- *(updated and moved to Less Likely 5/26/10)*
- *(moved to Less Likely 5/26/10)*
- *(updated and moved to Less Likely 5/26/10)*
- **Vomiting** *(added 5/26/10)*
- **Fever** *(moved from Less Likely 5/26/10)*
- **Infection** *(added 5/26/10)*
- **Itching** *(moved from Less Likely 5/26/10)*
- **Skin rash with the presence of macules (flat discolored area) and papules (raised bump)** *(added 5/26/10)*

Less Likely

- *(moved to Likely 5/26/10)*
- **Chills**
- **Weight gain**
- *(item deleted 5/26/10)*
- *(item deleted 5/26/10)*
- *(moved to Likely 5/26/10)*
- *(item deleted 5/26/10)*
- **Abnormal electrical conduction within the heart** *(updated 5/26/10)*
- **Increased blood sugar level** *(updated and moved from Likely 5/26/10)*
- **Lack of enough red blood cells (anemia)** *(updated and moved from Likely 5/26/10)*
- **Belly pain** *(updated and moved from Likely 5/26/10)*
- **Chest pain not heart-related** *(updated and moved from Likely 5/26/10)*
- **Dry skin** *(updated and moved from Likely 5/26/10)*
- **Dry mouth** *(updated and moved from Likely 5/26/10)*
- **Build up of a large amount of fluid between the layers of tissue that line the lungs and chest cavity** *(updated and moved from Likely 5/26/10)*
- **Sudden or traumatic injury to the kidney** *(updated and moved from Likely 5/26/10)*
- **Toothache** *(moved from Likely 5/26/10)*
- **Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)** *(updated and moved from Likely 5/26/10)*
- **Fever associated with dangerously low levels of a type of white blood cell (neutrophils)** *(added 5/26/10)*

- **Decreased number of all blood cell types** *(added 5/26/10)*
- **Unpleasant sensation of irregular and/or forceful beating of the heart** *(added 5/26/10)*
- **Fast heartbeat; regular rhythm** *(added 5/26/10)*
- **Irregular heartbeat resulting from an abnormality in one of the lower chambers of the heart (ventricle)** *(added 5/26/10)*
- **Noise in the ears, such as ringing, buzzing, roaring, clicking** *(added 5/26/10)*
- **Swelling or feeling of fullness and tightness in the abdomen (belly)** *(added 5/26/10)*
- **Irritation or sores in the lining of the anus** *(added 5/26/10)*
- **Constipation** *(added 5/26/10)*
- **Heartburn** *(added 5/26/10)*
- **Irritation or sores in the lining of the mouth** *(added 5/26/10)*
- **Inflammation (swelling and redness) of the pancreas** *(added 5/26/10)*
- **Irritation or sores in the lining of the rectum** *(added 5/26/10)*
- **Irritation or sores in the lining of the small bowel** *(added 5/26/10)*
- **Swelling of the face** *(added 5/26/10)*
- **Swelling of the extremities (arms and/or legs)** *(added 5/26/10)*
- **Inflammation (swelling and redness) or damage to the tissue surrounding where a drug was injected** *(added 5/26/10)*
- **Pain** *(added 5/26/10)*
- **Infection associated with a decrease in a type of white blood cell (lymphocyte)** *(added 5/26/10)*
- **Bruising** *(added 5/26/10)*
- **Increased blood level of a liver enzyme (ALT/SGPT)** *(added 5/26/10)*
- **Increased blood level of a liver enzyme (AST/SGOT)** *(added 5/26/10)*
- **Increased blood level of a liver pigment (bilirubin) often a sign of liver problems** *(added 5/26/10)*
- **Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine)** *(added 5/26/10)*
- **Increased blood level of a liver enzyme (GGT)** *(added 5/26/10)*
- **Increased blood level of a fat-digesting enzyme (lipase)** *(added 5/26/10)*
- **Increased blood level of a digestive enzyme (amylase)** *(added 5/26/10)*
- **Weight loss** *(added 5/26/10)*
- **Decrease in the total number of white blood cells (leukocytes)** *(added 5/26/10)*
- **Loss of appetite** *(added 5/26/10)*
- **More acid than normal in the blood** *(added 5/26/10)*
- **Increased blood level of potassium** *(added 5/26/10)*
- **Decreased blood level of potassium** *(added 5/26/10)*
- **Decreased blood level of magnesium** *(added 5/26/10)*
- **Joint pain** *(added 5/26/10)*
- **Bone pain** *(added 5/26/10)*
- **Muscle weakness of the whole body** *(added 5/26/10)*
- **Shrinking of muscles** *(added 5/26/10)*
- **Muscle pain** *(added 5/26/10)*

- Commonly known as “pins and needles”, where part of the body (typically a foot or hand) begins to tingle and becomes numb, or “falls asleep” *(added 5/26/10)*
- Weakness or paralysis (loss of muscle function) caused by damage to the peripheral nerves (those nerves outside of brain and spinal cord) *(added 5/26/10)*
- Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning *(added 5/26/10)*
- Anxiety, feelings of dread or danger *(added 5/26/10)*
- Difficulty sleeping or falling asleep *(added 5/26/10)*
- More protein in the urine than usual, often a sign of kidney disease *(added 5/26/10)*
- Stuffy or runny nose, sneezing *(added 5/26/10)*
- Sudden constriction of the muscles in the walls of the bronchioles (small airways of the lung) *(added 5/26/10)*
- Cough *(added 5/26/10)*
- Nose bleed *(added 5/26/10)*
- Irritation or sores in the lining of the voice box *(added 5/26/10)*
- Irritation or sores in the lining of the throat *(added 5/26/10)*
- A collection of symptoms including fever, difficulty breathing, chest pain, fluid in the lung (seen on chest X-ray), fluid around the lungs and heart, and lack of oxygen first seen in patients receiving the drug leucovorin *(added 5/26/10)*
- Sore throat *(added 5/26/10)*
- Irritation or sores in the lining of the windpipe *(added 5/26/10)*
- Hair loss *(added 5/26/10)*
- Excess sweating *(added 5/26/10)*
- Area of bleeding within the skin causing a reddish purple discoloration *(added 5/26/10)*
- Inflammation (swelling and redness) of the skin *(added 5/26/10)*
- Thickening of skin *(added 5/26/10)*
- Darkening of skin *(added 5/26/10)*
- Hives *(added 5/26/10)*
- Increase in the number and size of the pores in the capillaries (small blood vessels), which causes leakage of fluid from the blood to the tissue spaces, resulting in dangerously low blood pressure, swelling and multiple organ failure *(added 5/26/10)*
- Sudden reddening of the face and/or neck *(added 5/26/10)*
- High blood pressure *(added 5/26/10)*
- Low blood pressure *(added 5/26/10)*

Risks and side effects related to Consolidation #3 and #4 Therapy (ATRA and Daunomycin) include those that are:

Likely

- Lower white blood count that may lead to infection, which could be life-threatening
- Lower platelets, which may lead to bruising or bleeding and could be life-threatening. This side effect may require you to receive a transfer of blood platelets from a donor.
- Lower red blood counts that may cause you to feel tired or have shortness of breath and require a transfer of red blood cells from a donor. Low red blood counts could be life-threatening.
- Nausea, vomiting, abdominal pain, or diarrhea
- Loss of appetite
- Sores in the mouth and/or rectum. The sores in the mouth may cause difficulty in swallowing or a sore throat.
- Headache
- Hair loss
- Skin rash
- Fever
- Bone pain
- Flu-like symptoms
- Changes in nail growth
- Taste changes
- Fatigue

CLOSED EFFECTIVE 06/01/2013

- **Rash**
- **Red urine and/or tears while receiving daunomycin**
- **Eye problems, visual disturbances (5/30/08)**
- **Increased blood level of a fat called triglyceride (11/12/08)**

Less Likely

- **Heart damage, which could lead to irregular heart beats or heart failure**
- **Dryness of the skin and lips**
- **Damage to the liver, which could cause yellowing of the skin and/or eyes**
- **Damage to the kidneys, which could result in the need for dialysis**
- **Chills**
- **Itching, inflammation, and redness of the skin on the palms of the hands or soles of the feet**
- **Muscle pain**
- **Bleeding from the nose, gums, or skin**
- **Mood changes**
- **Problems with coordination, speech impairment, seizures, or paralysis**

Rare but Serious

- **Inflammation of the lining of the bowel, which could lead to abdominal pain and swelling and require surgery**
- **ATRA Syndrome: a combination of heart and lung problems including difficulty breathing, lowered oxygen in the blood, fever, rash, inflammation of the lungs, fluid around the heart and/or the lungs, heart failure**

Risks and side effects related to Consolidation 5 and 6 therapy (Gemtuzumab Ozogamicin) include those that are:

Likely

- **Lower white blood count that may lead to infection which could be life-threatening**
- **Lower platelets, which may lead to bruising or bleeding and could be life-threatening. This side effect may require you to receive a transfer of blood platelets from a donor.**
- **Lower red blood counts that may cause you to feel tired or have shortness of breath and require a transfer of red blood cells from a donor. Low red blood counts could be life-threatening.**
- **Fever, chills, headache**
- **Nausea, vomiting, diarrhea**
- **Loss of appetite, abdominal pain**
- **Constipation**
- **Low levels of potassium in the blood, which may affect the heartbeat or cause muscle cramps**
- **Sores in the mouth**
- **Pain at the site of injection/local reaction**
- **Weakness**

- Difficulty breathing
- Fatigue
- Difficulty sleeping
- Fluid in the lungs
- Depression
- Rash
- Changes in blood pressure
- Dizziness

Less Likely

- Damage to the liver, which could cause yellowing of the skin and/or eyes
- Severe injury to the liver (veno-occlusive disease), which could be life-threatening

Rare, but Serious

- Severe allergic reaction, which could be life-threatening

Risks and side effects related to Maintenance Therapy with ATRA, 6-mercaptopurine, and Methotrexate include those that are:

Likely

- Lower white blood count that may lead to infection, which could be life-threatening
- Lower platelets, which may lead to bruising or bleeding and could be life-threatening. This side effect may require you to receive a transfer of blood platelets from a donor.
- Lower red blood counts that may cause you to feel tired or have shortness of breath and require a transfer of red blood cells from a donor. Low red blood counts could be life-threatening.
- Headache
- Nausea
- Stomach and/or intestinal ulcers
- Vomiting of blood
- Stomach pain
- Hair loss
- Skin changes
- Cough
- Sensitivity to light

Less Likely

- Dryness of the skin and lips
- Bladder irritation and blood in urine (this may be prevented with drinking lots of fluids and/or getting them in an IV and/or with medicine)
- Eye problems, visual disturbances
- Dryness of the skin and lips

- Itching, inflammation, and redness of the skin on the palms of the hands or soles of the feet
- Muscle pain
- Bleeding from the nose, gums, or skin
- Mood changes
- Weight loss
- Diarrhea
(moved 1/28/09)

(Section deleted 5/30/08)

Rare but Serious (added 1/28/09)

- **ATRA Syndrome:** A combination of heart and lung problems including difficulty breathing, lowered oxygen in the blood, fever, rash, inflammation of the lungs, fluid around the heart and/or lungs, heart failure. (11/12/08)
(moved 1/28/09)

In a recent clinical trial using gemtuzumab ozogamicin, in a higher dose than is used in this study and combined with a different chemotherapy, no benefit was seen and there was a higher rate of early death. Due to these findings, the company that makes gemtuzumab ozogamicin has withdrawn the drug from the market. However, every effort will be made to ensure availability of gemtuzumab ozogamicin for this trial.

Currently there is no evidence that gemtuzumab ozogamicin at a lower dose (as used in this trial) in combination with ATRA and/or arsenic trioxide causes increased toxicity, although experience is limited. The safety of the study therapy in patients on this trial will continue to be closely monitored. (re: paragraph added 10/5/10)

(Section deleted 5/30/08)

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.

Pregnancy testing is required for women with reproductive potential before induction and is strongly recommended before the third course of consolidation therapy and before maintenance therapy.

Women should be fully counseled on the serious risk to the fetus should they become pregnant while undergoing treatment with ATRA. An effective form of contraception should be used for at least one month before and also throughout ATRA therapy, and two months after. If pregnancy does occur during treatment, you should discuss this with your doctor immediately, and you will be removed from protocol therapy. (11/12/08)

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

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope the treatment used in this study will be more useful against APL 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 using these drugs as a treatment for APL. 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:

- The Southwest Oncology Group
- A qualified representative from Pfizer, Inc., the manufacturer of gemtuzumab ozogamicin (added 1/28/09) (4/6/11)
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- (For patients registered via the CTSU) The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to clinical trials. (added 5/30/08)

[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 the 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 free of charge). (local institutions must choose the option that best fits the hospital situation)

All trans retinoic acid, arsenic trioxide, daunomycin, 6-mercaptopurine and methotrexate are commercially available. (1/28/09)

Gemtuzumab ozogamicin is investigational and will be provided free of charge by Pfizer, Inc. for this study. (added 1/28/09) (4/6/11)

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 4/25/13) 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.

1. 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

2. Banking of specimens for future research

*[The following example of tissue consent has been taken from the NCI Cancer Diagnosis Program's model tissue consent form found at the following url
<http://www.cancerdiagnosis.nci.nih.gov/specimens/model.pdf>]*

[Note to investigators: This section is applicable only to CLGP and ECOG institutions.] (sentence added 3/25/10)

About Using Bone Marrow and/or Peripheral Blood for Research

If you participate in this study, your doctor will remove some blood and bone marrow to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care. Additionally, some of your bone marrow will be used for research that is part of this study.

We would like to keep some of the blood and/or bone marrow that is left over for future research. If you agree, this blood and/or bone marrow will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How are Specimens Used for Research?" to learn more about tissue research.

The research that may be done with your blood and/or bone marrow is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood and/or bone marrow will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over blood and/or bone marrow for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood and/or bone marrow can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your blood and/or bone marrow. Then any blood and/or bone marrow that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Southwest Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood and/or bone marrow is used for genetic research (about diseases that are passed on in families). Even if your blood and/or bone marrow is used for this kind of research, the results will not be put in your health records.

Your blood and/or bone marrow will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Benefits

The benefits of research using blood and/or bone marrow include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at RB's phone number.

No matter what you decide to do, it will not affect your care.

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

Yes No

2. **My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**

Yes No

3. **Someone may contact me in the future to ask me to allow other uses of my specimens.**

Yes No

(section deleted 3/25/10)

[For patients participating through ECOG use the following] *(section added 5/30/08)*

If you decide to withdraw your specimens from an Eastern Cooperative Oncology Group Repository in the future, a written withdrawal of consent should be submitted through your treating physician to the Eastern Cooperative Oncology Group Coordinating Center. Upon withdrawal of consent, your specimens will not be considered for use in any future research projects.

Where can I get more information?

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

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

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

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

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

Signature

I have been given a copy of a _____ *[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 _____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done and decides if any of the samples can be used. The Southwest Oncology Group gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. The Southwest Oncology Group will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example, are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

Where will my specimens be kept?

Your blood and/or bone marrow will be kept at:

(deleted 4/25/13)

[For patients participating through ECOG use the following] (section and addresses added 5/30/08)

Elisabeth Paietta, Ph.D.
Our Lady of Mercy Cancer Center
600 East 233rd Street
6th Floor, Immunology Laboratory
Bronx, NY 10466-2697
Tel: 718/920-9992

OR

Mayo Clinic Cytogenetics Laboratory
970 Hilton
200 First Street, S.W.
Rochester, MN 55905
Tel: 507/284-2250
FAX: 507/284-0000

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).