ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A041701

A RANDOMIZED PHASE II/III STUDY OF CONVENTIONAL CHEMOTHERAPY +/- UPROLESELAN (GMI-1271) IN OLDER ADULTS WITH ACUTE MYELOID LEUKEMIA RECEIVING INTENSIVE INDUCTION CHEMOTHERAPY

NCI-supplied agent: Uproleselan (GMI-1271) (NSC #801708, IND #[redacted] IND holder: DCTD
Commercial agent(s): Daunorubicin (NSC #82151), Cytarabine (NSC #63878)

This is an FDA Registration Study.

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Activation
[ ]	Therapy / Dose Modifications / Study Calendar changes	[X]	Closure
[ ]	Informed Consent changes	[ ]	Suspension / temporary closure
[X]	Scientific / Statistical Considerations changes	[ ]	Reactivation
[X]	Data Submission / Forms changes		
[X]	Editorial / Administrative changes		
[X]	Other: Updated CTSU Boilerplate Language		

***If your site utilizes the CIRB as your IRB of record:* No recommended IRB level of review is provided by the Alliance since the CIRB is the IRB of record for this trial. The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the amendment application and CIRB guidelines for further instructions.**

***If your site utilizes a local IRB as your IRB of record:* IRB approval (or disapproval) is required within 90 days. Please follow your local IRB guidelines. Expedited IRB Approval is allowed. The proposed changes in this amendment are minor and do not affect the overall risk/benefit ratio.**

As of Amendment #04, there will be no additional accrual to the Phase III component of the trial regardless of the outcome of the Phase II analysis and the study will be permanently closed to accrual.

UPDATES TO THE PROTOCOL:

Cover Page

- Drs. Wendy Stock and Geoffrey L. Uy have replaced Dr. Richard M. Stone as the Leukemia Committee Co-Chairs. All contact information has been updated accordingly.
- Dr. Marina Konopleva has replaced Dr. John C. Byrd as the Correlative Study Co-Chair. All contact information has been updated accordingly.
- Dr. Ken Byrd has replaced Dr. Stephen Strickland as the ECOG-ACRIN Study Champion. All contact information has been updated accordingly.
- Dr. Jun (Vivien) Yin's email address has been updated.
- Per the updated Alliance protocol template, the institution names associated with the co-chairs and study champions have been removed.

Study Resources (Page 2)

- Per the updated Alliance protocol template, Ilene Galinsky's institution name and phone number have been removed.
- Caroline Harvey has replaced Ryan Daley has the A041701 Pharmacy Contact. All contact information has been updated accordingly.
- The telephone number for the Alliance Hematologic Malignancy Biorepository (HEME) has been updated.

CTSU Address and Contact Information (Page 3)

This section has been changed to reflect the updated boilerplate language.

Section 4.1 (Investigator and Research Associate Registration with CTEP)

This section has been changed to reflect the updated boilerplate language.

Section 4.2 (Cancer Trials Support Unit Registration Procedures)

This section has been changed to reflect the updated boilerplate language.

Section 4.5 (Patient Registration/Randomization Procedures)

This section has been changed to reflect the updated boilerplate language.

Section 6.1 (Data Collection and Submission)

- This section has been changed to reflect the updated boilerplate language.
- Section 6.1.3 (Data Quality Portal) has been changed to reflect the updated boilerplate language.
- Section 6.1.4 (Rave-CTEP-AERS integration) has been added to reflect the Alliance protocol template

Section 9.1.1 (Rave-CTEP-AERS integration)

This section has been changed to reflect the updated boilerplate language.

Section 13.1.1 (Primary Endpoint)

The following information has been added to the end of the section: "As of Amendment 04, there will be no additional accrual to the Phase III component of the trial regardless of the outcome of the Phase II analysis."

Section 13.1.2 (Sample Size and Power Justification)

The following information has been added to the end of the section: "As of Amendment 04, there will be no additional accrual to the Phase III component of the trial regardless of the outcome of the Phase II analysis."

Section 13.2.1 (Primary Endpoint)

- The first sentence of the Phase II component's final analysis paragraph has been updated to the following: "The Phase II decision-making will be conducted when at least 191 events are observed (approximately expected 37 months after the first patient enrolled). If less than 191 events are observed 2 years after Phase II accrual ends, then the Phase II decision will occur at the target data lock."
- The second sentence of the Phase II component's final analysis paragraph has been moved to be its own paragraph in the "Phase II component" subsection.
- The second paragraph in the "Phase II component" subsection has been updated to the following: "At the final analysis of the Phase II, it will be concluded that the experimental arm regimen is promising ~~and suggest proceeding to the Phase III component of the trial~~, if we a one-sided p-value < 0.10 from the log-rank test ~~observe an HR <= 0.831~~ favoring the experimental arm."
- The following information has been added as a third paragraph in the "Phase II component" subsection: "As of Amendment 04, there will be no additional accrual to the Phase III component of the trial regardless of the outcome of the Phase II analysis. Given the maturity of follow-up on the current patients and no additional accrual to the trial, the final Phase III OS analysis will also be performed at the time of final Phase II EFS analysis. All Phase III alpha (one-sided 2.5%) will be spent at this analysis. The target data lock date is August 12, 2024."
- The first sentence of the Phase II component's interim analysis paragraph has been updated to the following: "We will conduct a futility interim analysis which will take place after 50% of the total events ~~are~~ have occurred (approximately 25 months after the first patient enrolled)."
- The following information has been added after the table as a second paragraph in the "Phase III component" subsection: "As of Amendment 04, there will be no additional accrual to the Phase III component of the trial regardless of the outcome of the Phase II analysis. Given the maturity of follow-up on the current patients and no additional accrual to the trial, the final Phase III OS analysis will also be performed at the time of final Phase II EFS analysis. The final Phase III of analysis of OS will conclude that the novel regimen significantly improves the OS compared to the daunorubicin and cytarabine arm if the one-sided p-value from the stratified log-rank test is < 0.025. The target data lock date is August 12, 2024."

Section 13.3 (Accrual Time and Study Duration)

The following information has been added to the end of the section: "As of Amendment 04, there will be no additional accrual to the Phase III component of the trial regardless of the outcome of the Phase II analysis."

Section 13.5 (Study Monitoring)

The following information has been added to the end of the section: "All EFS and OS outcome data will be requested for release after DSMB review at the time of the final Phase II EFS analysis, with patient follow-up continuing per protocol."

Section 13.7 (Inclusion of Women and Minorities)

This section has been changed to reflect the updated boilerplate language.

Section 14.1.3 (Methods)

- The fifth sentence of the first paragraph has been moved to the second paragraph of the section.
- The second paragraph has been completely revised to list of time points of the samples in a bullet list format.
- The second sentence of the first bullet point under the "Submission of Cytogenetic Samples" subsection to be the following: "Include the karyotype description or clone number in the bottom of the high resolution electronic image ~~(.jpeg or .tiff files)~~ with arrows placed indicating abnormalities."
- After the second sentence of the first bullet point under the "Submission of Cytogenetic Samples" subsection, the following information has been added: "Images (karyotype, metaphase, and FISH) are preferred to be submitted together in one PowerPoint (PPT) file. If this is not possible, individual .jpeg or .tiff files are accepted."
- Under the "Submission of Cytogenetic Samples" subsection, the fourth bullet point has been updated to the following: "If case is abnormal, non-clonal (has one or more of the characteristic abnormalities specified on the list), enter the ISCN of each cell and provide a karyotype and corresponding metaphase representing each type of abnormality present."
- After the first sentence of the seventh bullet point under the "Optional Additional Procedures" subsection, the following information has been added: "Abnormal FISH results are encouraged to be submitted."
- Under the "Optional Additional Procedures" subsection, the third sentence of the seventh bullet point has been updated to the following: "Provide FISH information and two images (in the PowerPoint file with karyotypes and metaphases (preferred) or as individual .jpeg or .tiff files) for each assay performed."
- The heading of the third subsection has been updated to the following: "Questions regarding karyotype submission can be directed to Lisa Sterling, Cytogenetic Data Manager, at"
- Under the "Questions regarding karyotype submission can be directed to Lisa Sterling, Cytogenetic Data Manager, at" subsection, the address for the Alliance Cytogenetics Committee Office has been completely removed.

Section 14.1.4 (Analyses)

The first sentence has been completely removed.

Section 15.0 (Monitoring Plan and Regulatory Considerations)

- The section heading has been updated to the following: "Monitoring Plan and Regulatory Considerations."
- Section 15.3 (Early Study Closure at Sites) has been added to provide guidance regarding early study closure at sites.

UPDATES TO THE MODEL CONSENT:

No changes have been made to the model consent.

Replacement protocol and model consent documents have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A041701

A RANDOMIZED PHASE II/III STUDY OF CONVENTIONAL CHEMOTHERAPY +/- UPROLESELAN (GMI-1271) IN OLDER ADULTS WITH ACUTE MYELOID LEUKEMIA RECEIVING INTENSIVE INDUCTION CHEMOTHERAPY

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This is an FDA Registration Study.

ClinicalTrials.gov Identifier: NCT03701308

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Study Resources:

Expedited Adverse Event Reporting http://eapps-ctep.nci.nih.gov/ctepaers/	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

Protocol Contacts:

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Protocol-related questions may be directed as follows:

Questions	**Contact (via email)**
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox regulatory@allianceNCTN.org
Questions regarding CTEP-AERS reporting:	Alliance Pharmacovigilance Inbox pharmacovigilance@allianceNCTN.org
Questions regarding specimens/specimen submissions:	appropriate Alliance Biorepository
Questions regarding drug supply	PMB
Questions regarding drug administration	Pharmacy Contact

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION

For regulatory requirements:	For patient enrollments:	For data submission:
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org).

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.

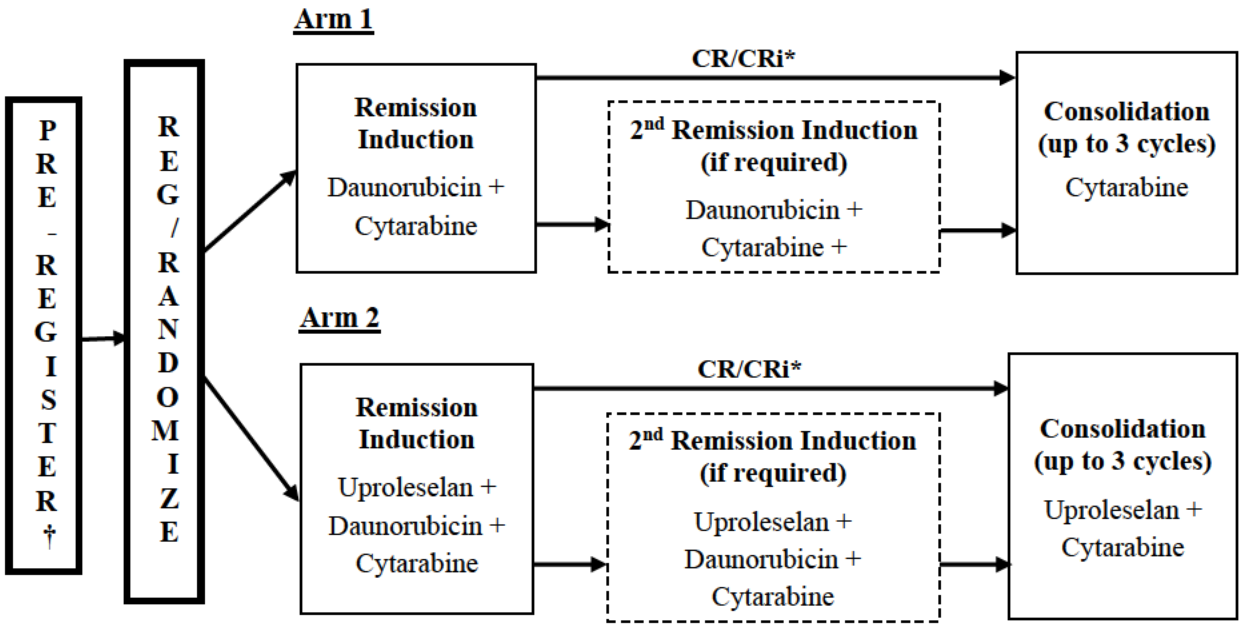
For clinical questions (i.e., patient eligibility or treatment-related)
Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager

For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

Eligibility Criteria (see Section 3.0)

- Diagnosis of AML based on 2017 WHO criteria excluding acute promyelocytic leukemia with PML-RARA
- No activating mutation in Fms-like tyrosine kinase-3 (FLT3)
- No evidence of CNS involvement of AML
- No prior chemotherapy for MDS, MPN or AML including hypomethylating agents or lenalidomide (see Section 3.3.2 for exceptions)
- Age ≥ 60 years
- Total Bilirubin ≤ 3 x upper limit of normal (ULN)
- Creatinine ≤ 3 x upper limit of normal (ULN)
  OR Creatinine Clearance ≥ 30 mL/min/1.73m^2

Schema



† All patients must be pre-registered in order to submit the required bone marrow and peripheral blood specimens to the Alliance HEME Biorepository (see Sections 4.3 and 6.2).

* During Remission Induction, a bone marrow examination (aspirate and biopsy) on Day 14 (+3 days) is required in all patients. Patients with evidence of persistent leukemia on day 14 or a subsequent bone marrow biopsy will receive a second induction course (See Section 7.0). Patients who achieve either a CR or CRi are eligible to proceed to consolidation therapy.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Table of Contents

1.0 BACKGROUND

1.1 Treatment of Older Adults with AML

For more than 40 years, "7+3" regimens (ie, cytarabine infused for 7 days with 3 days of an anthracycline) have been a standard for AML induction therapy [1]. Despite widespread use in older adults, 7+3 induction in these patients is associated with lower complete remission rates (50-60%), increased early mortality (up to 20%), and higher relapse rates compared with younger adults [2, 3]. Attempts at improving 7+3 through the addition of novel agents or intensification of post-remission therapy has largely failed to improve outcomes [4-6].

The reasons for the poor outcome of older adults with AML are poorly understood and include both unfavorable tumor biology as well as patient-specific characteristics such as increased comorbidity. Furthermore, within this patient population, there is significant heterogeneity in physical and psychological functioning and little consensus on optimal assessment strategies for determining which individuals are candidates for intensive remission and post-remission therapies. Currently, the choice of intensive versus nonintensive therapy is largely based on physician perceptions of patient tolerability and probability of success with little empirical data.

In 2017, the landscape of AML treatment changed with the regulatory approval of new agents midostaurin, CPX-351, gemtuzumab ozogamicin (GO) and enasidenib for AML. Midostaurin was approved by the FDA based on the results of a randomized Phase III study performed in adults ages 18-60 years with AML harboring a mutation in the FLT3 tyrosine kinase. With a median follow-up of 59 months, the median overall survival was 74.7 months (95% confidence interval [CI], 31.5 to not reached) in the midostaurin group compared to 25.6 months (95% CI, 18.6 to 42.9) in the placebo group (one-sided P=0.009) [7].

CPX-351 is a liposomal encapsulation of cytarabine and daunorubicin at a fixed 5:1 drug ratio. In an open-label, phase III trial, 309 patients aged 60-75 years with untreated secondary AML and de novo AML with MDS related cytogenetic changes were randomized to receive 1-2 induction cycles of CPX-351 or conventional 7+3, followed by consolidation therapy. CPX-351 significantly improved median overall survival compared with 7+3 (9.56 vs 5.95 months; hazard ratio=0.69 [95% confidence interval, 0.52-0.90]; 1-sided P=0.003). Response rate was also significantly higher with CPX-351 versus 7+3 (47.7% vs 33.3%; 1-sided P=0.008).

The approval of GO was based primarily on the ALFA-0701 study which was a randomized trial comparing daunorubicin and cytarabine with or without GO 3 mg/m^2 days 1, 4 and 7 for treatment of patients 50-70 years old with newly-diagnosed AML. The primary endpoint was event-free survival (EFS). There were 271 patients randomized. The analysis of EFS showed a statistically significant improvement with a hazard ratio (HR) of 0.56 (95% CI 0.42, 0.76; p<0.001), but analysis of the secondary endpoint OS did not show statistically significant improvement (HR 0.81; 95% CI, 0.60, 1.09; p=0.16).

A series of meetings between leukemia experts in the United States and Canada were convened to address the issues of improving the treatment of older adults with AML and to design the next series of studies within the NCTN. Two separate studies were proposed, one using intensive therapies in older adults comparing novel regimens to a 7+3 control arm and a study of non-intensive therapy which would utilize a hypomethylating agent as the control. These studies would share a similar phase II/III design with an intermediate endpoint which would facilitate a more rapid screening of regimens that should be tested in larger phase III comparisons. The SWOG 1612 Intergroup Less Intense AML Platform (LEAP) trial which will study less intensive therapies for this older adult population against an azacitidine control arm. The current proposed study is designed to be complementary to SWOG 1612. Both SWOG1612 and this study contain a common comprehensive geriatric assessment platform to identify patient

characteristics which may predict excess toxicity and suitability for intensive chemotherapy vs. non-intensive chemotherapy.

1.2 Role of E-selectin AML

The small molecule uproleselan is a glycomimetic specific E-selectin antagonist that binds to the adhesion molecule E-selectin that is expressed on endothelial cells. E-selectin expression is transient in the normal vasculature during an inflammatory response and constitutive in the bone marrow resulting in sequestration of AML cells. It binds a trisaccharide domain common to both sialyl Lewis^{a} (sLe^{a}) and its isomer, sialyl Lewis^{x} (sLe^{x}) on cells. E-selectin binding ligands that include CD15, CD44, and CD65 have been defined on histologically diverse normal and malignant cells, including AML.

E-selectin inhibition is hypothesized to disrupt the adhesion of AML cells in bone marrow. In a murine model of AML generated by retroviral transduction of the MLL-AF9 fusion oncogene into human HSCs, leukemic blasts were found to upregulate E-selectin on the bone marrow vasculature 5- to 10-fold [8]. Targeted disruption of potential E-selectin-mediated interactions by uproleselan was sufficient to mobilize leukemic blasts into the peripheral circulation. Studies in which wild-type or E-selectin knock-out mice engrafted with MLL-AF9 leukemic cells were treated with high dose cytarabine demonstrated that although the absence of E-selectin had no effect on total LSC numbers per femur, the absence of E-selectin increased chemosensitivity of LSCs by 20-fold. Uproleselan was also evaluated in combination with cytarabine and daunorubicin in an orthotopic model of human AML for its ability to eliminate patient-derived AML tumor cells from bone marrow and spleen and affect survival [9]. Mice treated with 40 mg/kg uproleselan in combination with cytarabine and daunorubicin had fewer numbers of AML blasts than mice treated with cytarabine and daunorubicin alone. In uproleselan and chemotherapy treated animals, the number of blasts were significantly lower in the combined compartments of the spleen and bone marrow.

Adhesion of AML blasts to E-selectin initiated up-regulation of pathways critical to leukemia progression that include members of Wnt signaling [10]. The magnitude of this response correlated with expression of E-selectin ligands on blasts. The Wnt pathway is associated with the regulation of cell proliferation, differentiation, and apoptosis in AML and has been identified as a target for therapy. uproleselan inhibits the E-selectin-mediated activation of the Wnt pathway and may improve response in treatment of AML. Similarly, E-selectin is unique among vascular adhesion molecules in being able to directly activate NF-κB. Upstream blockade of E-selectin by uproleselan has been shown to inhibit NF-κB activation [11]. NF-κB signaling was identified as a pathway potentially dampened in AML blasts following uproleselan administration, suggesting that adhesion to E-selectin activates pro-survival NF-κB signaling in AML cells leading to enhanced chemoresistance. Collectively, these results suggest that E-selectin is a key vascular niche component in the bone marrow mediating LSC resistance to chemotherapy.

Expression of E-selectin or its binding epitope (sialyl Le$^{a/x}$) may predict the clinical course and patient outcomes in AML [12-16]. Soluble E-selectin (sE-selectin) may be shed from the cell membrane and detected by enzyme-linked immunosorbent assay (ELISA) in the peripheral blood. AML is associated with increased vessel density, and sE-selectin release by activated/proliferating endothelial cells in the bone marrow may contribute to increased E-selectin levels in patients with untreated AML [13, 17]. sE-selectin levels were increased in the serum of patients with newly diagnosed AML compared with that in the serum of healthy subjects [12-14]. sE-selectin levels have also been correlated with the extramedullary infiltration of AML cells (P<0.001) and predicted the occurrence of relapse of AML (P=0.01); sE-selectin

levels at diagnosis of AML predicted low survival (P<0.001); and decrease in sE-selectin levels correlated with durable remission of AML [12, 15].

Data also suggest an important role for E-selectin in chemotherapy-induced mucositis through the regulation macrophage trafficking to the site of injury in the gut lining. Chemotherapy causes initial cell damage, and through a series of inflammatory and adhesion-molecule-mediated stages, the damage is propagated with resulting loss of mucosal integrity. E-selectin knockout mice are protected against chemotherapy-induced mucositis using 5-fluorouracil (5-FU). Similar results were demonstrated where mice administered uproleselan with 5-FU had enhanced neutrophil recovery [18], less mucositis and improved weight loss [19] as compared with mice treated with 5-FU alone. Furthermore, E-selectin was up-regulated in the intestines following chemotherapy or radiation damage. Both genetic deletion of E-selectin and pharmacologic inhibition using uproleselan effectively blocked secondary migration of inflammatory F4/80+ Ly-6C+ macrophages to intestines of mice following chemotherapy or irradiation.

1.3 Clinical Data of uproleselan in AML

A Phase I/II, open-label, multicenter trial evaluating the safety, PK, PD, and efficacy of uproleselan as an adjunct to standard chemotherapy in 91 subjects with acute myeloid leukemia (AML). The Phase I of GMI-1271-201 was a repeat dose-escalation study of 3 doses (5 mg/kg, 10 mg/kg, and 20 mg/kg) in adult subjects with relapsed/refractory (R/R) AML treated with mitoxantrone, etoposide and cytarabine (MEC) chemotherapy No dose-limiting toxicity was observed at any dose level. Pharmacodynamic analysis demonstrated on-target activity as measured by reduction in shed E-selectin (sE-sel) in the plasma at all 3 dose levels and no dose-response was observed, suggesting that the dose levels assessed were all above a plateau level for PD effect.

The Phase II consisted of two patient populations. Arm A dose expanded this population at the RP2D level of 10 mg/kg. Phase II Arm B evaluated uproleselan in older adult patients ≥ 60 years of age with newly diagnosed AML in combination with 7+3, cytarabine and idarubicin.

Enrollment and dosing in this trial is complete. Sixty-six (66) R/R subjects and 25 older adult newly diagnosed subjects were administered uproleselan with cytotoxic chemotherapy. Clinically relevant improvements in remission and overall response rates were observed. Preliminary data as of the December 2017 data cut-off are shown in **Table 1** and **Table 2**.

Table 1 GMI-1271-201 Baseline Demographics

Sub-group	**Phase I R/R (MEC) N (%)**	**Phase II R/R (MEC) N (%)**	**Total R/R (MEC) N (%)**	**Phase II Older Adult Newly Diagnosed (7+3) N (%)**
Subjects with available data	19	47	66	25
Age, median (range)	51 (26-77)	61 (27-84)	59 (26-84)	67 (60-79)
Primary Refractory, n (%)	7 (37)	15 (32)	22 (33)	-
Relapsed, All, n (%)	12 (63)	32 (68)	44 (67)	-
Relapsed <6 months	5 (26)	17 (36)	22 (33)	-
Frontline, All, n(%)	-	-	-	25 (100)
de novo	-	-	-	12 (48)

Sub-group	Phase I R/R (MEC) N (%)	Phase II R/R (MEC) N (%)	Total R/R (MEC) N (%)	Phase II Older Adult Newly Diagnosed (7+3) N (%)
Secondary AML	-	-	-	13 (52)
Prior Therapies, n (%)				
HSCT	4 (21)	7 (15)	11 (17)	-
≥2 Induction Regimens	6 (32)	16 (34)	22 (33)	-
Risk Category (ELN), n (%)				
Intermediate	2 (11)	9 (19)	11 (17)	7 (28)
Adverse	11 (58)	22 (47)	33 (50)	12 (48)
Unknown	4 (21)	11 (23)	15 (23)	3 (12)
Mutations				
FLT3-ITD	0	3 (6)	3 (5)	-
TP53 mutation; del (17p)	1 (5)	3 (6)	4 (6)	-

AML = acute myeloid leukemia; ECOG = Eastern Cooperative Oncology Group; ELN = European Leukemia Net; HSCT = hematopoietic stem cell transplantation; MEC = mitoxantrone + etoposide + cytarabine; R/R = relapsed/refractory; 7+3 = cytarabine + idarubicin

Table 2 Summary of Outcomes Observed in GMI-1271-201

Outcome	Phase I R/R (MEC)	Phase II R/R (MEC)	Total R/R (MEC)	RP2D R/R (MEC)	Older Adult Newly Diagnosed (7+3)
N Completing Induction Period	**19**	**47**	**66**	**54**	**25**
BONE MARROW RESPONSE, n (%)					
CR	8 (42)	14 (30)	22 (33)	19 (35)	13 (52)
CR/CRi	9 (47)	18 (38)	27 (41)	23 (43)	17 (68)
ORR (CR/CRi/MLFS/PR)	10 (53)	22 (47)	32 (48)	27 (50)	20 (80)
All-Cause Mortality 0-30 days, n (%)	0	1 (2)	1 (2)	1 (2)	2 (8)
All-Cause Mortality 0-60 days, n (%)	2 (11)	4 (9)	6 (9)	5 (9)	3 (12)
Outcomes by Subgroup (CR/CRi Rate and %)					
Primary Refractory	4/7 (57)	4/15 (27)	8/22 (36)	5/17 (29)	-
Relapsed (all)	5/12 (42)	14/32 (44)	19/44 (43)	18/37 (49)	-
Duration, prior remission <6 mos	1/5 (20)	5/17 (29)	6/22 (27)	6/19 (32)	-
Duration, prior remission ≥24 mos	3/3 (100)	3/4 (75)	6/7 (86)	6/7 (86)	-
AML Type					

Outcome	Phase I R/R (MEC)	Phase II R/R (MEC)	Total R/R (MEC)	RP2D R/R (MEC)	Older Adult Newly Diagnosed (7+3)
De novo	-	-	-	-	9/12 (75)
Secondary AML	-	-	-	-	8/13 (62)
ELN Risk Category					
Favorable risk	-	-	-	-	3/3 (100)
Intermediate risk	-	-	-	-	4/7 (57)
Adverse risk	-	-	-	-	8/12 (67)

MEC = mitoxantrone + etoposide + cytarabine; R/R = relapsed/refractory; 7+3 = cytarabine + idarubicin

The subjects enrolled are representative of the high-risk, poor prognosis populations expected to be seen at tertiary academic cancer research centers participating in this trial. In the phase I/II study overall complete response rates (CR/CRi) of 43% were observed in the R/R AML population and 68% in older adult AML population. The 30- and 60-day all-cause mortality was extremely low. These data compare favorably with published data where higher induction mortality rates are expected in the older population, with rates of 15-20% commonly reported.

The adverse events (AEs) observed in these AML patient populations were typical for induction chemotherapy and no specific uproleselan-related concerns have been identified. While most events were reported at similar rates as reported in the literature for MEC and 7+3, the incidence and severity of mucositis was low overall with only 2 Grade 3/4 events reported in 2 R/R subject treated with MEC (3%). These data suggest that uproleselan may reduce the incidence and severity of chemotherapy-induced mucositis, thereby providing an important safety advantage over chemotherapy alone

Table 3 Oral Mucositis Adverse Events Reported During Induction in GMI-1271-201, N (%)

Oral Mucositis Adverse Event	Phase I R/R (MEC)	Phase II R/R (MEC)	Total R/R (MEC)	RP2D R/R (MEC)	Older Adult Newly Diagnosed (7+3)
Evaluable Patients	**19**	**47**	**66**	**54**	**25**
Grades 1/2*	**5 (26)**	**9 (19)**	**14 (21)**	**9 (17)**	**5 (20)**
Grades 3/4*	**1 (5)**	**1 (2)**	**2 (3)**	**2 (3)**	**0**

*AE grade definitions follow CTCAE v4.03.

1.4 Selection of uproleselan dose

In the phase I clinical trial of uproleselan, three dose levels of uproleselan (5, 10, and 20 mg/kg BID) were assessed. Clinical outcomes (bone marrow response to uproleselan with induction chemotherapy) were similar across the dose levels. The concentration for IC_{50} and IC_{90} in the binding assay for E-selectin has been established for uproleselan. A comparison of plasma concentrations achieved with uproleselan and IC_{50} and IC_{90} levels was performed, using area under the curve (AUC), time above IC_{50} ($T>IC_{50}$), and time above IC_{90} ($T> IC_{90}$). Target exposure levels for efficacy in terms of AUC, $T>IC_{50}$ or $T> IC_{90}$, were established based on *in vitro* data and preclinical efficacy data. Population PK analysis on the Phase 1 was conducted

to understand the pharmacokinetics of uproleselan in AML patients. Clearance of uproleselan varies with renal function and exhibits dose-linear PK with no accumulation of uproleselan at any dose was observed, as expected from the short half-life. Clearance did not vary with body size or weight in AML patients. The target exposure levels in terms of AUC and time above IC_{50} and IC_{90} were attained at all doses in the Phase 1 portion of the study. However, the daily AUC nonclinical no-observed-adverse-effect level (NOAEL) limits for mouse were exceeded in a majority of patients at the 20 mg/kg dose level. Based on these observations in the Phase 1, the Recommended Phase 2 Dose was 10 mg/kg which provided the highest levels of exposure that do not exceed the nonclinical safety limits for a majority of patients. Simulation of flat-fixed dosing was performed and compared to a weight-based dose of 10 mg/kg. The simulation suggests that the flat-fixed dose of 800 mg will provide less variability in PK metrics while achieving the target exposure levels necessary for efficacy. Further, in an exposure-response analysis of patients with AML administered uproleselan with cytotoxic chemotherapy in the Phase 1/2 trial, no exposure-response relationships for efficacy and safety were identified. While exposure was found to vary with renal function, simulations of the 800 mg dose over a wide range of renal function demonstrated that exposure remains within the range attained in the Phase 1/2 trial. Therefore, the flat, fixed dose of 800 mg is expected to provide exposure consistent with that already evaluated at the RP2D of 10 mg/kg in the Phase 1/2 trial and will be used in this and other trials of uproleselan in AML.

1.5 Rationale

We will conduct a randomized study testing the addition of uproleselan to a standard daunorubicin/cytarabine regimen in older adults with previously untreated AML. E-selectin inhibition with uproleselan in AML is attractive in that it targets both disease biology (adherence/activation of AML blasts) and a host response contributing to treatment morbidity (macrophage trafficking to the site of chemotherapy injury in the gut mucosa). The administration of uproleselan with chemotherapy in the initial Phase I/II study resulted in 1) higher than expected CR/CRi rates, 2) low induction-related mortality rates, and 3) low Grade 3/4 events of mucositis and warrants further investigation in a randomized study.

We propose a randomized phase II/III trial using EFS as the phase II endpoint and OS as the phase III endpoint. Although we are ultimately interested in agents that provide an overall survival benefit to patients, a shorter, intermediate endpoint is desirable to screen potential novel agents more quickly for phase III testing. In AML, the lack of surrogate endpoints that predict OS remains a major barrier for clinical development. There are several reasons for this including the availability of potentially effective salvage regimens including allogeneic HCT (alloHCT). The most common endpoint used in phase II AML studies are rates of morphologic CR. A drawback of the use of CR as a phase II endpoint in an upfront study is that it does not take into consideration the potential beneficial effects of the study agent in consolidation therapy. Another drawback to CR as an endpoint is that promising improvements in CR have later been demonstrated to show no benefit to overall survival as a result of increased toxicity and non-relapse mortality.

The choice of EFS has several benefits in that it incorporates measures of efficacy such as CR and remission duration as well as toxicity including nonrelapse mortality. Like CR, EFS has a modest correlation with overall survival due to the potential for patients to be salvaged by nonprotocol therapy including alloHCT [20]. For older adults with AML, the median remission duration and the effectiveness of salvage chemotherapy and alloHCT is less of a consideration than in a younger patient population. Furthermore, EFS may be considered a desirable endpoint as patients in CR may have an improved quality of life from normalization of their blood counts because of transfusion independence and decreased risk of infection. Recently, the FDA has

accepted EFS as evidence of clinical efficacy in older patients with newly diagnosed AML supportive of the full approval of Mylotarg [21].

2.0 OBJECTIVES

2.1 Primary objectives

2.1.1 Phase II

Compare the event-free survival (EFS) of daunorubicin, cytarabine plus uproleselan versus daunorubicin and cytarabine in subjects ≥ age 60 with previously untreated acute myeloid leukemia

2.1.2 Phase III

Compare the overall survival (OS) of the daunorubicin, cytarabine plus uproleselan to daunorubicin and cytarabine in this patient population.

2.2 Secondary objectives

2.2.1 Determine the rates of complete remission (CR), complete remission with incomplete count recovery (CRi), complete remission with incomplete hematopoietic recovery (CRh) and cytogenetic complete remission (CCyR) for each chemotherapy regimen.

2.2.2 Determine the overall survival (OS), and remission duration of patients for each chemotherapy regimen.

2.2.3 Describe the frequency and severity of adverse events for patients for each chemotherapy regimen

2.2.4 Describe the interaction of pretreatment disease and patient characteristics including morphology, cytogenetics, molecular genetic features, WBC count and hemogram, and performance status on clinical outcomes.

- Note: Analysis of cohort with performance status of 4 will be done separately from patients with an ECOG performance status of 0-3, as most phase III trials only include patients with a performance score of 0-3.

2.3 Correlative science objective(s)

2.3.1 Assessment of Cytogenetics and ELN Risk Categories

- Correlate specific karyotype groups (normal or various primary and secondary chromosomal abnormalities) with clinical and laboratory parameters and with response rates, response duration, survival and cure in patients treated with various induction and post-induction regimens.
- Correlate specific karyotype groups with selected molecular abnormalities and with measurable residual disease.
- To determine karyotype changes at end of consolidation and the influence of the type of change (or no change) in karyotype at the end of consolidation on subsequent clinical course.
- To determine karyotype changes at relapse and the influence of the type of change (or no change) in karyotype at relapse on subsequent clinical course.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this 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. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient. HIV infected patients on effective antiretroviral therapy with undetectable viral load within 6 months are eligible for this trial.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.

3.2 Pre-Registration Eligibility Criteria (Step 0)

___ 3.2.1 Bone Marrow and Peripheral Blood Submission

All patients must be pre-registered in order to submit the required bone marrow and peripheral blood specimens to the Alliance HEME Biobank (see Section 6.2).

Note: Bone marrow aspirate and peripheral blood for patients who consent to A041701-LC1 and/or banking should also be submitted at this time as outlined in Section 6.2.

Please ensure patient has suspected diagnosis of AML and meets on study guidelines per Section 3.1 prior to informed consent and biospecimen collection.

3.3 Registration Eligibility Criteria (Step 1)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

___ 3.3.1 Documentation of Disease

- Diagnosis of AML based on 2017 WHO criteria [22] excluding acute promyelocytic leukemia with PML-RARA.

  Note: Patients with myeloid sarcoma without bone marrow involvement, acute leukemia of ambiguous lineage or blast transformation of CML are not eligible.

- No activating mutation in the Fms-like tyrosine kinase-3 (FLT3) defined as a ratio of mutant to wild-type allele ≥ 0.05 by capillary electrophoresis or a

variant allele fraction of ≥ 5% by next generation sequencing from either bone marrow or peripheral blood.

- No evidence of CNS involvement of AML

___ **3.3.2 Prior Treatment**

- No prior chemotherapy for MDS, MPN or AML including hypomethylating agents (e.g. azacitidine and decitabine), ruxolitinib or lenalidomide with the following exceptions:
    - Emergency leukapheresis
    - Hydroxyurea
    - Growth factor/cytokine support
    - All-trans retinoic acid (ATRA)
    - Single dose of intrathecal cytarabine and/or methotrexate for patients undergoing lumbar puncture to evaluate for CNS involvement

___ **3.3.3 Age ≥ 60 years**

___ **3.3.4 Required Initial Laboratory Values**

Total Bilirubin	≤ 3 x upper limit of normal (ULN)
Creatinine	≤ 3 x upper limit of normal (ULN)
OR	
Creatinine Clearance	≥ 30 mL/min/1.73m^2

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes four person registration types that are applicable to this study.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non-Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges; and
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✓	✓		
Financial Disclosure Form	✓	✓	✓	
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓	
GCP training	✓	✓	✓	
Agent Shipment Form (if applicable)	✓			
CV (optional)	✓	✓	✓	

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting or treating investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

This study is supported by the NCI CTSU.

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating through the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email (CTSURegPref@ctsu.coccg.org) or by calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;

- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

4.2.1 Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.2 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org);
- Click on *Protocols* in the upper left of the screen:
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select *Alliance*, and protocol number *A041701*.
- Click on *Documents, Protocol Related Documents,* and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission*.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

4.2.4 Checking Site's Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on Site Registration; and
- Enter the sites 5-character CTEP Institution Code and click on Go:

- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.2.5 Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application which is accessible via the Delegation Log link on the CTSU members' website or directly at https://dtl.ctsu.org. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

4.3 Patient Pre-Registration Requirements

- **Informed consent:** The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Bone marrow and peripheral blood submission:** All patients are required to be pre-registered to A041701 in order to submit bone marrow aspirate and peripheral blood samples to the HEME Biobank for the required banking for molecular genetic analysis (see Section 6.2).

4.4 Patient Registration Requirements

- **Pre-registration (Step 0) Completed:** After patient pre-registration, specimens must be submitted as outlined in Section 6.2. Pre-registration (Step 0) must be completed in order to complete patient registration (Step 1). Once patient registration eligibility is confirmed (see Section 3.3), the patient may be registered (Step 1).

4.5 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs' registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;

- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in the Registration and Credential Repository (RCR). If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.6 Registration to Correlative and Companion Studies

4.6.1 Registration to Substudies described in Section 14.0

There are two substudies within Alliance A041701. These substudies do not require separate IRB approval. The substudies included within Alliance A041701 are:

- E-selectin studies (Section 14.3), Alliance A041701-LC1

If a patient answers "yes" to "I agree that my samples and related information may be used for the laboratory study described above," Question #1 in the model consent, they have consented to participate in the substudy described in Section 14.3. The patient should be registered to Alliance A041701-LC1 at the same time they are registered to the treatment trial (A041701). Samples should be submitted per Section 6.2.

4.7 Stratification Factors, Grouping Factors, and Treatment Assignments

Stratification factors: age (60-69 vs. 70 and older), performance status (0-1 vs. 2-4), de novo vs. secondary/therapy related AML

Grouping factors: phase II vs. phase III

The randomization routine is found in Section 13.0 (Statistical Considerations).

5.0 STUDY CALENDAR

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

	Baseline*	Induction	End of Induction	Consolidation	End of Treatment	Follow-up**
Tests & Observations						
History and physical	X	X		X	X	X
Performance Status	X					
Height and weight	X	X		X		
MUGA or ECHO	X					
ECG	X					
Adverse Event Assessment	X	X	X	X	X	
Laboratory Studies						
FLT3 Mutation analysis	X					
CBC with differential	X	X(2)	X	X(2)		X
Serum Creatinine	X	X(3)		X(3)		
Bilirubin, AST, ALT, Alk. Phos.	X	X(3)		X(3)		
INR, PTT, fibrinogen	X					
Uric Acid	X					
LDH	X					
Molecular genetic testing	X(1)					
Cytogenetics	X		B		B	B
Staging						
BM biopsy/aspirate	X(4)	A	X		X	C
Correlative studies: For patients who consent to participate						
Bone marrow and blood samples	*Prior to treatment, end of induction, end of consolidation, and relapse. See Section 6.2.*					

* Baseline studies are to be completed ≤ 14 days prior to registration.

** Follow-up should occur at least every 2 months (+/- 14 days) in year 1, every 3 months (+/- 14 days) in year 2, then every 6 months (+/- 30 days) until 5 years from registration (See Section 12.3). Cytogenetics reports for applicable time points should be submitted until 15 years following registration.

1 Molecular testing is to be performed according institutional standards but should include testing for mutations in *FLT3*, *NPM1*, *CEBPA*, *RUNX1*, *ASXL1*, *IDH1*, *IDH2* and *TP53* to allow classification of patients by 2017 WHO criteria and stratification by 2017 ELN genetic risk classification [23].

2 CBC should be performed daily while inpatient and at least twice weekly until hematopoietic recovery. Please submit induction lab tests and results in Rave from either the labs drawn at the end of the cycle, or the lab that that will correspond to the disease response.

3 Monitoring of serum creatinine, bilirubin, AST/ALT/Alk Phos should be performed prior to the start of each cycle of treatment and then as clinically indicated.

4 Baseline bone marrow biopsy/aspirate should be obtained at the time of pre-registration and specimens should be submitted as outlined in Section 6.2 (see also Sections 3.2 and 4.4).

A Day 14 of first course (+3 days)

B Cytogenetics are required prior to initiation of therapy, at achievement of first complete remission (if diagnostic specimen is abnormal), at the end of consolidation (if CR cytogenetics are abnormal), and at first relapse. After local review is complete, the designated local cytogeneticist will submit electronic karyotypes, metaphases, karyotype processing information, and FISH information (if applicable). See Section 14.1.

C Bone marrow assessments post-treatment are only required if clinical or laboratory signs of relapse are present.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associate (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. Site staff will not be able to access the study in Rave until all required Medidata and study-specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the *Data Management* section under the Data Management Help Topics > Rave resource materials (*Medidata Account Activation and Study Invitation*). Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management > Rave* section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

6.1.1 Data submission schedule

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

6.1.2 Supporting Documentation to be Submitted to the Alliance

This study requires supporting documentation for diagnosis, response, and relapse. Supporting documentation will include CBC, bone marrow pathology, molecular genetic testing, cytogenetics, and FISH reports (if applicable) which must be submitted at the following time points:

Diagnosis: CBC, bone marrow pathology, molecular genetic testing, cytogenetics, and FISH reports (if applicable)

Day 14: Bone marrow pathology

End of induction: CBC, bone marrow pathology, cytogenetics, and FISH reports (if applicable)

End of treatment: CBC, bone marrow pathology, cytogenetics, and FISH reports (if applicable)

Time of relapse: CBC, bone marrow pathology, cytogenetics, and FISH reports (if applicable)

Supporting documentation is to be submitted via Rave.

6.1.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.1.4 Rave-CTEP-AERS integration

See Section 9.1.1 for information regarding submission of adverse event information utilizing the Rave-CTEP-AERS integration.

6.2 Specimen collection and submission

The Alliance A041701 Correlative Science Manual (CSM) contains instructions for specimen collection, processing and shipping. The manual can be found on the BioMS and CTSU websites. Questions regarding the CSM should be address to the contacts specified in the manual.

For all patients registered to Alliance A041701: Bone marrow and peripheral blood will be collected and banked for molecular genetic analysis described in Section 14.2.

For patients registered to substudy A041701-LC1 and/or patients who consent to banking: All participating institutions must ask patients for their consent to participate in Alliance A041701-LC1 and the banking of their specimens for future studies, although patient participation is optional. Rationale and methods for the scientific components of these studies are described in Section 14.0. For patients who consent to participate, bone marrow and blood samples will be collected at the following time points for these studies:

	At Pre-registration	End of Induction	End of Consolidation	Relapse	Storage/ Shipping conditions	Submit to:
	For all patients registered to A041701, submit the following					
Bone marrow aspirate[1] (EDTA/lavender top)	5 mL				Ambient	HEME
Peripheral blood (EDTA/lavender top)	10 mL				Ambient	HEME
	For patients registered to A041701-LC1[A], submit the following					
Bone marrow aspirate (heparin/green top)	2 mL	2 mL	2 mL		Ambient	Hematologics
Peripheral blood (Na citrate/light blue top)	2.7 mL	2.7 mL			Frozen/dry ice	HEME

	For patients who consent to banking[B], submit the following					
Bone marrow aspirate[1] (EDTA/lavender top)	5 mL	5 mL	5 mL	5 mL	Ambient	HEME
Peripheral blood (EDTA/lavender top)	10 mL	10 mL	10 mL	10 mL	Ambient	HEME

1 Or submit 30 mL peripheral blood (EDTA/lavender top) if marrow inaspirable or if the patient has had a bone marrow aspiration prior to pre-registration and refuses to have another one performed. This peripheral blood is in addition to the 10 mL required prior to treatment.

A Collect and submit only from patients who consent to model consent question #2. No additional specimen will be required for RNA testing. The sample collected for E-selectin ligand testing will provide sufficient material for RNA aliquoting. If marrow inaspirable or if the patient has had a bone marrow aspiration prior to pre-registration and refuses to have another one performed, then the submitted 30 mL peripheral blood (EDTA/lavender top) used for all patients registered to A041701 will be used.

B Collect and submit only from patients who consent to model consent question #4.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 7 days of registration.

For questions regarding treatment, please see the study contacts page.

Patients may be removed from protocol treatment at any time post-induction to undergo allogeneic hematopoietic cell transplantation. In rare cases where a subject is discovered to have acute promyelocytic leukemia with PML-RARA or AML with BCR-ABL only after starting protocol treatment, these patients should be removed from protocol therapy in order to receive targeted agents.

7.1 Arm 1 Treatment: 7+3

7.1.1 Remission Induction

- Daunorubicin 60 mg m^2/day IV Days 1-3 (total dose 180 mg/m^2)
- Cytarabine 100 mg/m^2/day CIVI Days 1-7 (168 hour infusion, total dose 700 mg/m^2)

During the Remission Induction, a bone marrow examination (aspirate and biopsy) on Day 14 (+3 days) is required in all patients. Recommendations regarding the need for second induction are provided in the table below. Consult with the study chair if there are questions about the need for reinduction,

Bone Marrow Cellularity	Bone Marrow Leukemic Blasts	Action
≥ 20%	≥ 5%	Second remission induction
	< 5%	Do not start second remission induction therapy. Repeat bone marrow biopsy upon count recovery or by Day 42
< 20%	≥ 5%	Repeat bone marrow biopsy in one week, and follow guidelines in table.

	< 5%	Do not start second remission induction therapy. Repeat bone marrow biopsy upon count recovery or by Day 42

Patients with residual disease as indicated above on Day 14 or subsequent biopsy following the first course of induction chemotherapy are eligible to receive a second remission induction course. It is recommended that a second induction course start within 7 days of bone marrow documentation of residual disease but may be delayed based on the clinical status of the patient. Removal of a patient following a single cycle of induction chemotherapy to receive non-protocol therapy is highly discouraged as the results of the day 14 bone marrow (i.e. high cellularity, blast percentage) do not predict the outcome of second remission induction course.

7.1.2 Second Remission Induction (if required)

- Daunorubicin 60 mg/m^2/day IV Days 1-2 (total dose 120 mg/m^2)
- Cytarabine 100 mg/m^2/day CIVI Days 1-5 (120 hour infusion, total dose 500 mg/m^2)

7.1.3 Consolidation (up to 3 cycles)

Patients who achieve either a CR or CRi are eligible to receive up to 3 cycles of Consolidation. Each Consolidation cycle is four weeks (28 days) in duration, and should begin within two weeks following hematologic recovery (ANC ≥ 1000/μL +/- platelet count ≥ 100,000/μL), but not sooner than four weeks from the beginning of the previous cycle.

- Cytarabine 2000 mg/m^2/day by IV infusion over 3 hours on Days 1-5 (total dose 10000 mg/m^2)

7.2 Arm 2 Treatment: 7+3 + Uproleselan

7.2.1 Remission Induction

- Uproleselan 800 mg IV, once a day on Day 1, and q12 hours on Days 2-10 (total of 19 doses)
- Daunorubicin 60 mg m^2/day IV Days 2-4 (total dose 180 mg/m^2)
- Cytarabine 100 mg/m^2/day CIVI Days 2-8 (168 hour infusion, total dose 700 mg/m^2)

The first dose of uproleselan will be given 24 hours (+/- 2 hours) prior to the first dose of chemotherapy as a single sentinel dose. On days 2-10, uproleselan will be administered every 12 hours (+/- 1 hour). On days in which both uproleselan and daunorubicin are administered, administer uproleselan approximately 2 hours (+/- 15 minutes) prior to daunorubicin.

During the Remission Induction, a bone marrow examination (aspirate and biopsy) on Day 14 (+3 days) is required in all patients. Recommendations regarding the need for second induction are provided in the table below. Consult with the study chair if there are questions about the need for reinduction.

Bone Marrow Cellularity	Bone Marrow Leukemic Blasts	Action
≥ 20%	≥ 5%	Second remission induction
	< 5%	Do not start second remission induction therapy. Repeat bone marrow biopsy upon count recovery or by Day 42

< 20%	≥ 5%	Repeat bone marrow biopsy in one week, and follow guidelines in table.
	< 5%	Do not start second remission induction therapy. Repeat bone marrow biopsy upon count recovery or by Day 42

Patients with residual disease as indicated above on Day 14 or subsequent biopsy following the first course of induction chemotherapy are eligible to receive a second remission induction course. It is recommended that a second induction course start within 7 days of bone marrow documentation of residual disease but may be delayed based on the clinical status of the patient. Removal of a patient following a single cycle of induction chemotherapy to receive non-protocol therapy is highly discouraged as the results of the day 14 bone marrow (i.e. high cellularity, blast percentage) do not predict the outcome of second remission induction course.

7.2.2 Second Remission Induction (if required)

- Uproleselan 800 mg IV, once on Day 1, and q12 hours on Days 2-8 (total of 15 doses)
- Daunorubicin 60 mg/m^2/day IV Days 2-3 (total dose 120 mg/m^2)
- Cytarabine 100 mg/m^2/day CIVI Days 2-6 (120 hour infusion, total dose 500 mg/m^2)

The first dose of uproleselan will be given 24 hours (+/- 2 hours) prior to the first dose of chemotherapy as a single sentinel dose. On days 2-8, uproleselan will be administered every 12 hours (+/- 1 hour). On days in which both uproleselan and daunorubicin are administered, administer uproleselan approximately 2 hours (+/- 15 minutes) prior to daunorubicin.

7.2.3 Consolidation (up to 3 cycles)

Patients who achieve either a CR or CRi are eligible to receive up to 3 cycles of Consolidation. Each Consolidation cycle is four weeks (28 days) in duration, and should begin within two weeks following hematologic recovery (ANC ≥ 1000/μL +/- platelet count ≥ 100,000/μL), but not sooner than four weeks from the beginning of the previous cycle.

- Uproleselan 800 mg IV, once on Day 1, and q12 hours on Days 2-8 (total of 15 doses)
- Cytarabine 2000 mg/m^2/day by IV infusion over 3 hours on Days 2-6 (total dose 10000 mg/m^2)

Uproleselan is to be administered 24 hours (+/- 2 hours) prior to the first dose of cytarabine. On days 2-8, uproleselan will be administered every 12 hours (+/- 1 hour). On days in which both uproleselan and cytarabine are administered, administer uproleselan approximately 2 hours (+/- 15 minutes) prior to cytarabine.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Ancillary Therapy

Patients should not receive any other therapy which would be considered treatment for their AML while on protocol treatment. Per the FDA approved indication, oral azacitidine (Onureg) may be administered at the discretion of the treating physician for the continued treatment of patients who achieve CR or CRi and are not able to complete consolidation therapy. Patients who receive oral azacitidine in this manner should remain on study and

in clinical follow up with the administration of oral azacitidine recorded in the case report forms. Additional guidance on the use of oral azacitidine for patients enrolled in this study will be provided as an amendment prior to the opening of the phase 3 portion of the study after consultation with the company sponsor and the FDA

8.1.2 Supportive Care

Patients should receive full supportive care while on this study according to institutional practices including the use of blood products, antibiotics, and antiemetics.

Tumor lysis prophylaxis including hydration, allopurinol, or rasburicase should be administered during induction chemotherapy.

Steroid eye drops are recommended for patients during consolidation with cytarabine.

8.1.3 Myeloid Growth Factors

The routine administration of Myeloid Growth Factors (e.g. filgrastim (G-CSF), pegfilgrastim, or sargramostim (GM-CSF)) is prohibited during remission induction chemotherapy. Myeloid Growth Factors are permitted as part of the supportive care during consolidation therapy per institutional practice.

8.2 Dose Modifications

8.2.1 Dose Modifications for Hepatotoxicity

Daunorubicin doses during both remission induction and second remission induction (if required) should be modified as follows:

Total Bilirubin (mg/dL)	% Daunorubicin Dose
≤ 2	60 mg/m^2 (100%)
> 2 – ≤ 3	45 mg/m^2 (25% dose reduction)
> 3	30 mg/m^2 (50% dose reduction)

8.2.2 Dose Modifications for Impaired Renal Function

Daunorubicin doses during both remission induction and second remission induction (if required) should be modified as follows:

Serum Creatinine (mg/dL)	% Daunorubicin Dose
> 3	30 mg/m^2 (50% dose reduction)

During consolidation, cytarabine should be modified as follows:

Serum Creatinine(mg/dL)	Cytarabine Dose
≤ 2	2000 mg/m^2 (100%)
> 2 – ≤ 3	1000 mg/m^2 (50% dose reduction)
> 3	Do not administer cytarabine

8.2.3 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 solely by actual weight without any modification. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

9.1 Routine Adverse Event Reporting

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 according to the study calendar in Section 5.0. For this trial, the Form, "Adverse Events" is used for routine AE reporting in Rave.

9.1.1 Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave**.

Pre-treatment AEs: AEs that occur after informed consent is signed and prior to start of treatment are collected in Medidata Rave using the Pre-treatment Adverse Event form.

Pre-existing medical conditions (formerly referred to as baseline AEs) identified during baseline assessment are not considered AEs and therefore should not be reported on the Pre-treatment Adverse Event form. If these pre-existing conditions worsen in severity, the

investigator must reassess the event to determine if an expedited report is required. Whether or not an expedited report is required, the worsened condition should be reported in Rave as a routine AE.

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational study agent/intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query-free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: Protocols > Documents> Protocol Related Documents> Adverse Event Reporting; and
- Additional resources: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

9.1.2 Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment by CTCAE, PRO-CTCAE, or both.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)

Febrile neutropenia	Blood and lymphatic system disorders
Nausea	Gastrointestinal disorders
Diarrhea	Gastrointestinal disorders
Oral mucositis	Gastrointestinal disorders
Alanine aminotransferase increased	Investigations
Aspartate aminotransferase increased	Investigations
Blood bilirubin increased	Investigations

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible		a	a, b	a, b	a, b
Probable		a	a, b	a, b	a, b
Definite		a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date.

9.3 Expedited Adverse Event Reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE.

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

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.

<table>
<tr><th>Hospitalization</th><th>• Grade 1 Timeframes</th><th>• Grade 2 Timeframes</th><th>• Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour;
5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

[1] Serious 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 ≤ 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

9.3.2 Expedited AE reporting timelines defined

"24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.

"10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.

Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

9.3.3 Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND

All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.

Alliance A041701 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.

Grade ≤4 cytopenias (anemia, decreased white blood cell, lymphocyte, neutrophil, or platelet counts) and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, and in situ tumors.

Secondary Malignancy:

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.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE 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 unless otherwise specified. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available.

Treatment expected adverse events include those listed in Section 10.0 and in the package insert.

CTEP-AERS reports should be submitted electronically.

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at http://ctep.cancer.gov/). 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.

9.4 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Uproleselan (GMI-1271, NSC 801708)

The Comprehensive Adverse Events 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 Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 184 patients.* Below is the CAEPR for GMI-1271.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, July 9, 2019[1]

Adverse Events with Possible Relationship to Uproleselan (GMI-1271) (CTCAE 5.0 Term) [n= 184]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Febrile neutropenia		
GASTROINTESTINAL DISORDERS			
		Abdominal pain	
	Dyspepsia		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Platelet count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		
	Headache		
	Somnolence		
PSYCHIATRIC DISORDERS			
	Restlessness		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Oropharyngeal pain		

[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.

Adverse events reported on Uproleselan (GMI-1271) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Uproleselan (GMI-1271) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia
EYE DISORDERS - Eye disorders - Other (retinal hemorrhage)
GASTROINTEST
INAL DISORDERS - Colitis; Enterocolitis; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Fatigue; Fever
INFECTIONS AND INFESTATIONS - Bacteremia; Lung infection; Sepsis
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Electrocardiogram QT corrected interval prolonged; Neutrophil count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (malnutrition); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Myalgia; Neck pain; Pain in extremity

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Dyspnea; Hypoxia; Nasal congestion; Pulmonary edema
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Rash maculo-papular

Note: Uproleselan (GMI-1271) 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.

10.0 DRUG INFORMATION

10.1 General Considerations:

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

It is not necessary to change the doses of chemotherapy due to changes in weight unless the calculated dose changes by ≥10%.

All study agents are to be administered at the registering institution.

10.2 Uproleselan (GMI-1271) (NSC #801708) (IND # [redacted] IND holder: DCTD)

Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Sites may request a maximum of 10 vials when a patient is being screened.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current version of the Uproleselan IB will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, and a "current"

password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB Online Agent Order Processing (OAOP) application:

  https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm

Characteristics

Chemical Name: Sodium (1*R*,3*R*,4*R*,5*S*)-3-({2-N-acetylamino-2-deoxy-3-O-[(1S)-1-carboxylato-2-cyclohexylethyl]-β-D-galactopyranosyl}oxy)-4-({6-deoxy-α-L-alactopyranosyl}oxy)-5-ethyl-cyclohexan-1-yl-(38-oxo-2,5,8,11,14,17,20,23,26,29,32,35-dodecaoxa-39-azahentetracontan-41-yl) carboxamide

Other Names: GMI-1271

Chemical Formula: $C_{60}H_{108}N_3NaO_{27}$

Molecular Weight: 1326.5

Classification: Uproleselan is a specific E-selectin antagonist

Mode of Action: The proposed mechanism of action is by competitive inhibition of E-selectin, thereby interrupting E-selectin-mediated interactions. Pre-clinical data collectively suggest that Uproleselan-mediated disruption of E-selectin interactions between the endothelium and various tumor cells, such as those in leukemia and myeloma, confers increased sensitivity to cytotoxic agents by preventing these cancerous cells from remaining in the bone marrow niche and attenuating stroma-induced resistance to chemotherapy.

Description: White to off white solid

Formulation

Uproleselan is supplied by GlycoMimetics, Inc. and distributed by PMB, CTEP, DCTD, NCI. Uproleselan Injection is a sterile, isotonic solution for IV administration, supplied in single-use vials at a concentration of 50 mg/mL. Each 16 mL, single dose vial contains 800 mg of Uproleselan. The solution contains sodium chloride, water, and TRIS buffer to stabilize the pH at 7.4 (6.4 to 8.4).

Storage and Stability

Uproleselan Injection 50 mg/mL is stored refrigerated (2°C to 8°C), prior to administration.

If a storage temperature excursion is identified, promptly return uproleselan to 2°C to 8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability studies are ongoing.

Preparation

Uproleselan solution should be clear, colorless to slightly yellow, and free from visible particulates. Uproleselan can be administered undiluted or diluted. If dilution is preferred, use only normal saline and dilute to a concentration of not less than 5 mg/mL.

Uproleselan may be prepared prior to administration and stored in syringes or IV bags for 24 hours at room temperature or 72 hours at refrigerated conditions, except when using administration sets composed of PVC with DEHP where the storage time is limited to 2 hours (see Administration section below). While it is highly recommended that uproleselan prepared prior to administration be refrigerated until one hour prior to dosing, solutions kept at room temperature can be administered within 24 hours of preparation

Administration

Uproleselan Injection should be administered through a peripheral line, a central catheter, or a peripherally inserted central line catheter (PICC). Infusion should take place at a steady rate over a period of 20 minutes using a syringe pump or IV pump. Microbore tubing is preferred. In-line filtration with a 0.2-micron filter is highly recommended.

The storage time for an IV line primed with uproleselan solution is dependent on the tubing composition. Tubing composed of PVC with DEHP has a maximum storage time of 2 hours prior to administration. The storage time for administration sets composed of PVC without DEHP is 24 hours at room temperature or 72 hours at refrigerated conditions, including administration.

Uproleselan is compatible with IV bags composed of PVC (with or without DEHP), polyolefin, or ethylene vinyl acetate, glass bottles, and syringes. IV administration sets composed of PVC without DEHP or lined with polyethylene are compatible with uproleselan. IV admin sets composed of PVC with DEHP should not exceed 2 hours of contact with uproleselan.

Compatibility with other therapeutic agents has not been determined, therefore uproleselan should not be administered concurrently with anything other than saline. If a flush is used, saline flush is preferred.

Pharmacokinetics

PK evaluations in healthy volunteers showed a dose-linear relationship in mean PK parameters after IV infusion of 2 mg/kg, 5 mg/kg, 10 mg/kg, 20 mg/kg and 40 mg/kg uproleselan. Uproleselan is characterized by a half-life of 1.4-2.5 hours and does not accumulate after doses up to 20 mg/kg BID. Population PK analysis in healthy volunteers and patients with AML demonstrate similar PK profiles, PK parameters, and dose-proportionality. Clearance was found to depend on renal function and have a similar magnitude in both healthy volunteers and in patients with AML. The PK of uproleselan does not appear to be affected when co-administered with chemotherapy.

Adverse Events

Uproleselan continues to be evaluated in clinical trials. In AML and MM trials, the AE profile at the doses and regimens tested to date does not indicate concerns about safety or tolerability

of uproleselan when administered alone or with MEC, cytarabine/idarubicin (7+3 or 5+2), or cytarabine alone in patients undergoing induction or consolidation chemotherapy for AML, or bortezomib-based chemotherapy for MM. No anticipated toxicities, or target organ for toxicity, have been identified thus far in nonclinical studies or in clinical trials.

Potential Drug Interactions

Uproleselan is not expected to undergo extensive hepatic metabolism in humans. Uproleselan does not cause direct or time-dependent inhibition of CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4. Uproleselan also showed no evidence of induction of CYP1A2, CYP2B6 or CYP3A4. Active transporter substrate analysis revealed that uproleselan is a substrate for the efflux transporters P-gp and MRP2, may be a weak substrate for BCRP, and is not a substrate of the efflux transporter BSEP. In addition, uproleselan is not a substrate for the following uptake transporters: OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2-K. Uproleselan is not an inhibitor of the efflux transporters P-gp, BCRP, or BSEP, and is not an inhibitor of the following substrate transporters: OATP1B1, OATP1B3, OAT1, OAT3, OCT2 and OCT1.

Patient Care Implications

Women of childbearing potential and men must use highly effective methods of contraception during the study and for 3 months after the last dose of study drug. Do not administer uproleselan to pregnant or lactating women.

See CAEPR in 9.4.

10.3 Daunorubicin (Cerubidine®, Daunomycin, DNM) (NSC #82151)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection as:
Injection, powder for reconstitution: 20 mg
Injection, solution: 5 mg/mL (4 mL, 10 mL)

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials of powder for injection at room temperature of 15°C to 30°C (59°F to 86°F); intact vials of solution for injection should be refrigerated at 2°C to 8°C (36°F to 46°F). Protect from light. Dilute vials of powder for injection with 4 mL SWFI for a final concentration of 5 mg/mL. May further dilute in 100 mL D5W or NS. Reconstituted solution is stable for 4 days at 15°C to 25°C. Further dilution in D5W, LR, or NS is stable at room temperature (25°C) for up to 4 weeks protected from light.

Administration

Daunorubicin is not for I.M. or SubQ administration. Administer as a slow I.V. push over 1-5 minutes into the tubing of a rapidly infusion I.V. solution of D5W or NS or dilute in 100 mL of D5W or NS and infuse over 15-30 minutes. Daunorubicin is a potent vesicant; it is best to administer IV infusion doses through a central venous access device.

Drug Interactions

Avoid Concomitant Use of Daunorubicin with any of the following: BCG; Natalizumab; Pimecrolimus; Tacrolimus (Topical); Vaccines (Live).
Increased Effect: Daunorubicin may increase the levels/effects of: Leflunomide; Natalizumab; Vaccines (Live).
The levels/effects of Daunorubicin may be increased by: Bevacizumab; Denosumab; P-Glycoprotein inhibitors; Pimecrolimus; Tacrolimus (Topical); Taxane Derivatives; Trastuzumab
Decreased Effect: Daunorubicin may decrease the levels/effects of: BCG; Cardiac Glycosides; Sipuleucel-T; Vaccines (Inactivated); Vaccines (Live)
The levels/effects of Daunorubicin may be decreased by: Cardiac Glycosides; Echinacea; P-Glycoprotein Inducers
Ethanol/Herb/Nutraceutical Interactions: Avoid ethanol (Due to GI irritation).

Pharmacokinetics

Distribution: V_d: 40 L/kg; to many body tissues, particularly liver, spleen, kidney, lung, heart; does not distribute into the CNS; crosses placenta
Protein binding, plasma: 70% to 76%
Metabolism: Primarily hepatic to Daunorubicinol (active), then to inactive aglycones, conjugated sulfates, and glucuronides
Half-life elimination:
Distribution: 2 minutes
Elimination: 14-20 hours
Terminal: 18.5 hours
Daunorubicinol plasma half-life: 24-48 hours
Excretion: Feces (~40%); urine (~25% as unchanged drug and metabolites)

Nursing Guidelines

- Drug is a potent vesicant. Establish patency of IV before and frequently during administration as to avoid extravasation. If drug is being administered IV push administer through side port of rapidly running IV solution. If suitable vein cannot be used, central venous access may become necessary. Discuss with treating MD. If extravasation occurs treat per your institution's policy.
- Drug is not compatible with heparin. Be sure to flush heparin locked IV's or central lines before administering agent.
- Moderate to severe nausea occurs in up to 50% of patient within first 24 hours. Administer antiemetics as ordered and assess for their effectiveness.
- Inform patient about alopecia
- Potent myelosuppressive agent. Monitor CBC closely. Inform patient to report any signs or symptoms of infection, or unusual bruising or bleeding.
- Drug is cardiotoxic. Maximum lifetime dose limit is 550 mg/m^2. Monitor for signs of acute cardiac toxicity, which is possible within hours after administration. This is unrelated to cumulative dose and may manifest symptoms of pump or conduction dysfunction. Watch for signs or symptoms of CHF, pericardial effusion, and transient ECG abnormalities.
- Monitor liver function tests. Dose reduction is necessary in patients with impaired liver function.
- Radiation recall is a possibility with this drug. Monitor patient's skin at site of previous irradiation for damage.
- Inform patient that urine may be pink or red for up to 48 hours after administration.

Adverse Events

The most common adverse reactions associated with daunorubicin include hematologic, gastrointestinal, and cardiovascular. Leukopenia and thrombocytopenia are often dose-limiting. Daunorubicin causes nausea and vomiting, but is generally considered moderately emetogenic. Stomatitis is also common. Acute cardiovascular reactions include EKG abnormalities which are usually asymptomatic and self-limiting. Chronic cardiomyopathy manifests as congestive heart failure. Risk factors include age (> 70 years), mediastinal irradiation and cumulative lifetime dose (e.g., > 450 mg/m^2). Dermatologic reactions (alopecia, "radiation recall") are also common. Less common are red/orange urine (more alarming than of notable consequence to patients) and skin "flare." The flare consists of redness and itching along the distribution of the vessel through which daunorubicin was administered. It is usually self-limiting and of short duration, but should be distinguished from an extravasation reaction. Extravasation of daunorubicin does not occur very often, but can result in severe skin and tissue necrosis. Cold should be applied to the site of a suspected or actual extravasation of daunorubicin.

Please refer to the package insert for the comprehensive list of adverse events.

10.4 Cytarabine Intravenous (Cytosar, Ara-C) (NSC #63878)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection, powder for reconstitution: 100 mg, 500 mg, 1 gram, 2 gram. Commercially available solution for injection in concentrations of 20 mg/mL and 100 mg/mL. Commercially available preparations may be preservative-free or preservative-containing.

Preparation, Storage and Stability

Store intact vials of powder at room temperature 15ºC to 30ºC (59ºF to 86ºF). Reconstitute with bacteriostatic water for injection. Reconstituted solutions are stable for up to 8 days at room temperature, although the manufacturer recommends use within 48 hours. Further dilution in 250-1000 mL of D5W or 0.9% NaCL is stable for 8 days at room temperature (25°C). Note: Solutions containing bacteriostatic agents should not be used for the preparation of either high doses or intrathecal doses of cytarabine.

Administration

Refer to the drug treatment section of the protocol for specific administration directions and infusion rates. May be given IV or subcutaneously.

Drug Interactions

Cytochrome P450 Effect: None known

Increased Effect/Toxicity: Cytarabine may increase the levels/effects of: Clozapine, Leflunomide, Natalizumab, Vaccines (Live). The levels of Cytarabine may be increased by: Denosumab, Pimecrolimus, Roflumilast, Tacrolimus (Topical); Trastuzumab

Decreased Effect: Cytarabine may decrease the levels/effects of: BCG, Cardiac Glycosides, Coccidiodin Skin Test, Flucytosine, Sipuleucel-T, Vaccines (inactivated); Vaccines (live).

Herb/Nutraceutical Interactions: Avoid Echinacea.

Pharmacokinetics

Distribution: V_d: Total body water; widely and rapidly since it enters the cells readily; high-dose cytarabine crosses the blood-brain barrier with CSF levels of 40% to 50% of plasma level

Metabolism: Primarily hepatic; metabolized by deoxycytidine kinase and other nucleotide kinases to aracytidine triphosphate (active); about 86% to 96% of dose is metabolized to inactive uracil arabinoside.
Half-life elimination: I.V.: Initial: 7-20 minutes; Terminal: 1-3 hours.
Excretion: Urine (~80%) within 24 hours

Nursing Guidelines

- Can be a potent myelosuppressive agent. Monitor CBC closely. Anemia, leukopenia, and thrombocytopenia are expected. Nadir within 5-7 days with recovery expected in 2-3 weeks. Hematological toxicity is more intense if ARA-C is given as a continuous IV infusion versus an IV bolus.
- Nausea and vomiting is dose-related, common, and often preventable with antiemetic drugs. Administer as ordered and assess for their effectiveness.
- Instruct patient of possibility of metallic taste. The use of sugarless hard candies may lessen this effect.
- Stomatitis is possible.
- May cause pancreatitis or peritonitis. Instruct patient to report any severe or worsening abdominal pain immediately.
- Monitor LFT's-elevations of LFT's may occur.
- Cerebellar toxicity can occur in 16-40% of patients with more severe symptoms at higher doses. Monitor for these toxicities with each dose of ARA-C. Signs and symptoms of cerebellar toxicity can include: lethargy with progressive confusion, ataxia, nystagmus, slurred speech. Report any of these or other neurological changes to the MD immediately.
- Instruct patient to report any shortness of breath or difficulty breathing as this may be a sign of a rare but life threatening pulmonary complication.
- Monitor for signs of conjunctivitis and/or keratitis. This is usually prevented with prophylactic glucocorticoid eye drops.
- Assess for skin rash. This may present itself as an erythema without exfoliation, or a generalized rash. Report to MD.
- Monitor for "ARA-C" syndrome. This is characterized by bone and muscle pain, chest pain, fever, general weakness, reddened eyes, and skin rash. Report these to the MD, as patient may need to be treated with corticosteroids.

Adverse Events

The most common adverse reactions reported with cytarabine ("usual dosage" e.g., ≤ 200 mg/m^2/day) include hematologic, gastrointestinal, dermatologic, and hepatic. Myelosuppression includes neutropenia, thrombocytopenia and anemia. Cytarabine is considered highly emetogenic. In addition to nausea and vomiting, diarrhea and mucositis are reported in > 10% of patients receiving cytarabine. Alopecia is common. Rash, including hand-foot syndrome, is reported also. Mild jaundice, and elevated transaminase levels also are reported in > 10% of patients. Fever (non-infectious) is also reported among the most common adverse reactions associated with cytarabine. Less commonly, a "cytarabine syndrome" or "ara-C syndrome" has been reported. The syndrome may be characterized by fever, myalgia, bone pain, rash, malaise, and chest pain.

In addition to the above, the following adverse reactions have been described with high dose (≥ 1 gm/m^2/day) cytarabine. Neurologic toxicity is primarily cerebellar (nystagmus, dysarthria, dysdiadochokinesia, ataxia, abnormal gait) but cerebral toxicity (somnolence, confusion, psychosis, seizures) may also be seen. Ocular toxicity including photophobia and conjunctivitis are described with high dose cytarabine. Steroid ophthalmic solution should be administered, beginning 6-12 hours before cytarabine and continuing for 24 hours after the

last “high dose”, to prevent conjunctivitis. Pulmonary edema has been rarely reported in association with high dose cytarabine.

Please refer to the package insert for the comprehensive list of adverse events.

11.0 MEASUREMENT OF EFFECT

Response to treatment will be assessed according to the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia [24].

11.1 Morphologic complete remission (CR)

Defined as morphologic leukemia-free state, including < 5% blasts in BM aspirate, no blasts with Auer rods, no persistent extramedullary disease, ANC ≥ 1,000/µl and platelet count ≥ 100,000/µl. The patient must be free of the need for RBC transfusions.

11.2 Cytogenetic complete remission (CCyR)

Only patients with an identified cytogenetic abnormality pretreatment may receive this designation. Defined as a morphologic complete remission plus reversion to a normal karyotype (no clonal abnormalities detected in a minimum of 20 metaphase cells).

11.3 Morphologic complete remission with incomplete blood count recovery (CRi)

Defined as CR with the exception of neutropenia <1,000/µl or thrombocytopenia <100,000/µl.

11.4 Treatment failure (TF)

Treatment failure includes those patients for whom treatment has failed to achieve a CR or CRi and will be classified as follows:

- Treatment failure due to resistant disease includes patients who survive at least 7 days after completion of the final dose of the initial course of treatment but whose last posttreatment peripheral blood smear and/or bone marrow sample showed persistent AML.
- Treatment failure due to complications from aplasia includes patients who survive at least 7 days after the final dose of the initial course of treatment and die while cytopenic, but whose last posttreatment bone marrow was aplastic or hypoplastic, as determined by the institutional morphologist or pathologist, without evidence of leukemia, provided that marrow was obtained within 7 days of death.
- Treatment failure of indeterminate cause includes three categories of patients:
  - Patients who die less than 7 days after conclusion of the initial course of treatment, and
  - Patients who die 7 or more days after the conclusion of treatment whose most recent peripheral blood smear did not show persistent leukemia and who did not have a bone marrow examination subsequent to therapy
  - Patients who die without completing the first course of therapy.

11.5 Recurrence/morphologic relapse

Defined as reappearance of blasts in the blood or the finding of ≥ 5% blasts in the BM, not attributable to any other cause.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Protocol Treatment

Patients will continue with the therapy specified in this protocol until one of the following occurs:

- Completion of all protocol-specific treatments.
- Unacceptable toxicity.
- Treatment failure due to resistant disease or death.
- Recurrence / morphologic relapse.
- Withdrawal of consent by the patient to continue on study.

12.2 Criteria for Discontinuation of Protocol Treatment/Intervention

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Completion of all protocol-specified therapy
- Recurrence/morphologic relapse
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Termination of the study by sponsor

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

12.3 Follow-up

12.3.1 Duration of Follow-up

Patients who complete protocol therapy will go to clinical follow-up, followed every 2 months until 1 year after completion of therapy, every 3 months between 1 and 2 years after completion of therapy, then every 6 months for up to 5 years from study registration or until relapse.

12.3.2 Follow-up for Patients who Stop Study Treatment/Intervention Early

Patients who end treatment for reasons other than relapse and subsequent treatment other than oral azacitidine per Section 8.1.1 will go to clinical follow-up, followed every 2 months until 1 year from the date of discontinuation, then every 3 months until 2 years from the date of discontinuation, then every 6 months for up to 5 years from registration or until relapse.

Patients who relapse or receive a subsequent treatment other than transplantation or azacitidine per Section 8.1.1 will go to survival follow-up, followed every 6 months from the date of discontinuation for 5 years from registration.

Patients who receive transplantation will be removed from this protocol and go to clinical follow-up, followed every 3 months for 2 years and then every 6 months up to 5 years from registration.

Patients who withdraw prior to starting any protocol treatment will go to survival follow-up, followed every 6 months for up to 5 years in observation from registration.

12.2.3 Follow-up for Specimen Submission

Specimen submission must continue during all treatment stages, observation and clinical follow-up. Specimen submission are not required if patient is in survival follow-up.

12.4 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.5 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patient

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline, off treatment, and post-treatment follow up (i.e., relapse, progression, and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Design

This is an open-label, randomized phase II/III study.

The primary objective of the Phase II study is to determine based on the event-free survival (EFS) whether the combination of uproleselan plus daunorubicin/cytarabine should be tested further against standard of care: daunorubicin/cytarabine in the phase III component of this trial.

The primary objective of the Phase III study is to compare the OS between uproleselan plus daunorubicin/cytarabine versus the control arm (daunorubicin/cytarabine). Patients accrued during the Phase II portion of the trial will be used in the Phase III analysis.

Randomization: Randomization will be stratified on the following stratification factors: age (60-69 vs. 70 and older), performance status (0-1 vs. 2-4), de novo vs. secondary/therapy related AML. Patients will be randomized to receive one of the two treatment regimens with equal allocation using a permutated block method to balance the stratification factors.

13.1.1 Primary Endpoint

- Phase II component: Event-free survival (EFS). EFS is defined as the time from the date of randomization to the first of failure to achieve a CR/CRi during induction, relapse, or death due to any cause, with patients last known to be alive and event-free censored at the date of last contact. Patients who are removed from protocol treatment for allogeneic HCT or azacitidine per Section 8.1.1 will not be censored for EFS, and will be continued to be followed for relapse or death. Patients who receive other non-protocol therapy without relapse or CR/CRi during induction will be censored at the time they discontinue the treatment. All randomized patients meeting the eligibility criteria will be evaluable for the primary endpoint (EFS) analysis based on an intention to treat.

- Phase III component: Overall survival (OS) – measured from the date of randomization to death from any cause, with patients last known to be alive censored at the date of last contact. All randomized patients will be evaluable for this endpoint.

  As of Amendment 04, there will be no additional accrual to the Phase III component of the trial regardless of the outcome of the Phase II analysis.

13.1.2 Sample Size and Power Justification

Phase II component

Patients will be randomized to receive daunorubicin and cytarabine or the novel regimen with equal allocation using a permutated block method. E2906 study[6] reported a 1-year EFS of 29%. Therefore, we estimate that the 1-year EFS in the daunorubicin and cytarabine arm will be 30%. We are interested in testing the alternative hypothesis that the 1-year EFS in the novel experimental arm will be at least 47% (a 17% improvement in the 1-year EFS). This translates to an improvement in the median EFS from 7 to 11 months (HR = 0.64), assuming exponential distributions of EFS in both control and experimental arm. A sample size of 131 evaluable patients per arm (262 total) provides 96% power to detect an improvement in median EFS from 7 months to 11 months (a hazard ratio of 0.64), using a one-sided log-rank test at a significance level of 10%.

Phase III component

A median OS of 12 months is anticipated on the control arm.[6] We are interested in testing the alternative hypothesis that the median OS in the novel experimental arm will be at least 16 months (a 33% improvement in the median OS, for a HR of 0.75). This translates into an improvement in the 1-year OS from 50% to 60%, assuming exponential survival. A randomized trial comparing the novel agents passing the Phase II component against the standard arm (daunorubicin and cytarabine) will be conducted using a 1:1 randomization

scheme. A sample size of 335 evaluable patients per arm (670 total) provides 90% power to detect an improvement in median OS from 12 months to 16 months (a hazard ratio of 0.75), using a one-sided log-rank test at a significance level of 2.5%. The overall power for the phase II/III design is 86% (=0.96*0.9). The total sample size for the Phase III component will include the patients rolled over from the Phase II component.

As of Amendment 04, there will be no additional accrual to the Phase III component of the trial regardless of the outcome of the Phase II analysis.

13.2 Analysis Plan

13.2.1 Primary Endpoint

The analysis for both phase II and III component would be intention-to-treat (ITT), which means that all patients who signed a consent form and are randomized are included in the analysis and will be analyzed in the arms to which they are randomized.

Phase II component

Final analysis: The Phase II decision-making will be conducted when at least 191 events are observed (approximately expected 37 months after the first patient enrolled). If less than 191 events are observed 2 years after Phase II accrual ends, then the Phase II decision will occur at the target data lock.

At the final analysis of the Phase II, it will be concluded that the experimental arm regimen is promising, if we a one-sided p-value < 0.10 from the log-rank test favoring the experimental arm.

As of Amendment 04, there will be no additional accrual to the Phase III component of the trial regardless of the outcome of the Phase II analysis. Given the maturity of follow-up on the current patients and no additional accrual to the trial, the final Phase III OS analysis will also be performed at the time of final Phase II EFS analysis. All Phase III alpha (one-sided 2.5%) will be spent at this analysis. The target data lock date is August 12, 2024.

Interim analysis: We will conduct a futility interim analysis which will take place after 50% of the total events have occurred (approximately 25 months after the first patient enrolled). If at the planned interim analysis the hazard ratio is >1.0 in favor of the control arm, the recommendation will be to stop further accrual to the experimental arm and conclude that the novel regimen does not have improved EFS.

We will suspend accrual between phase II and III. In order to protect the phase III comparison, the results of the phase II portion will only be released to the FDA and/or industry sponsors for regulatory purposes, contingent upon the approval and recommendation from the Alliance Data Monitoring Committee. Other than that, the Alliance DMC will only release whether the criteria for continuation to Phase III have been satisfied and not any of the actual results.

Phase III component

The final analysis will be conducted after 521 deaths have been observed. In addition, we will conduct 2 interim analyses which will take place after approximately 50% and 75% of the total events have occurred. The first interim analysis is for futility only, and the second interim for both futility and efficacy. If in the second interim evaluation, sufficient evidence (per criteria outlined below) is observed that the experimental arm is superior to the control arm in terms of OS, then accrual to the control arm may be suspended and terminated. To preserve the Type I error rate control on superiority, the Lan-DeMets error spending function with the O'Brien-Fleming stopping boundaries is utilized. Futility boundaries

have also been developed for the comparison against control, where if at any of the planned interim analyses the hazard ratio is >1 in favor of the control arm, the recommendation will be to stop further accrual to the experimental arm (if the trial is still accruing) and conclude that the novel regimen does not have improved OS. At the final analysis, if we observe a p-value <= 0.022 from the log-rank test (equivalently, HR <= 0.838 favoring the experimental regimen, assuming the exponential distribution) we will conclude that the novel regimen significantly improves the OS, compared to the daunorubicin and cytarabine arm. The interim and final analysis boundaries and characteristics were generated using the East clinical trial software program (version 6.3, Cytel Inc).

Information Fraction	**Cum. events**	**Cum. alpha spent**	**Cum. beta spent**	**Efficacy Boundaries**			**Futility Boundaries**	
				HR	**P-value**	**Z score**	**HR**	**p-value**
50%	261	0	0.01	NA	NA	NA	1	0.5
75%	391	0.010	0.011	0.789	0.010	-2.339	1	0.5
100%	521	0.025	0.1	0.838	0.022	-2.012	0.838	0.022

As of Amendment 04, there will be no additional accrual to the Phase III component of the trial regardless of the outcome of the Phase II analysis. Given the maturity of follow-up on the current patients and no additional accrual to the trial, the final Phase III OS analysis will also be performed at the time of final Phase II EFS analysis. The final Phase III of analysis of OS will conclude that the novel regimen significantly improves the OS compared to the daunorubicin and cytarabine arm if the one-sided p-value from the stratified log-rank test is < 0.025. The target data lock date is August 12, 2024.

13.2.2 Secondary Endpoints

- **1-year EFS rate:** The 1-year EFS rate is the proportion of efficacy evaluable patients event-free 1 year from registration. Patients who fail to achieve a CR/CRi during the induction, relapse, or die prior to 1 year after randomization/registration will be considered as a failure for this endpoint. Patients who are removed from protocol treatment for allogeneic HCT will continue to be followed for relapse or death at 1 year. Patients who are removed from study for other non-protocol therapy without relapse or CR/CRi during induction are also considered as a failure for the 1-year EFS endpoint.
- **Disease-free survival (DFS):** DFS will be calculated as the time from achieving a CR/CRi to the time of relapse and/or death. Any patients who have not achieved the event of interest will be censored at the time of their last evaluation.
- **Complete Remission (CR) and overall response rates:** Response to treatment will be assessed according to the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia.
- **Toxicity and tolerability:** As per NCI CTCAE v5.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to the study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either “unrelated” or “unlikely to be related” to study treatment in the event of an

actual relationship developing. The incidence of severe (grade 3+) adverse events or toxicities will be described for each treatment arm, but will also be compared between the arms. Fisher's exact tests will be used to quantitatively compare the incidence of severe as well as specific toxicities of interest between the treatment arms and we will graphically assess differences in maximum grades observed for toxicities between the arms. Toxicity and tolerability will be monitored regularly. The study will be reviewable by the Alliance DSMB every 6 months to identify any toxicity or tolerability issues in either of the treatment arms.

- Association of clinical outcomes with pretreatment disease and patient characteristics. We will examine whether CR, EFS, DFS, and OS are predicted by pretreatment characteristics such as age, morphology, cytogenetics, immunophenotype, molecular genetic features, WBC count and hemogram, and performance status with clinical outcomes. The associations between these baseline factors and CR, EFS, DFS, and OS will be analyzed using Kaplan-Meier curves, log-rank test, contigency table and chi-square test whenever appropriate. Multivariable analysis including Cox proportional hazards models and logistic regression models will be used as well to evaluate the associations.

13.2.3 Primary Analysis of the Key Secondary Endpoint of EFS

In the event that the primary endpoint OS for phase III is significant as determined by the primary analysis, then the key secondary endpoint of EFS will be formally tested hierarchically in a confirmatory setting at an overall one sided alpha of 0.025 level at the same time as the primary endpoint. Both hazard ratio and p-value for EFS will be presented.

13.2.4 Sensitivity Analysis

To evaluate the impact of off-protocol transplantation, sensitivity analyses will be conducted. Approaches will include but not limited to: 1) considering transplantation as a competing risk, 2) censoring patients who go off study for transplant without relapse at the time they discontinue the treatment, 3) multi-state model. In addition, the proportion of patients who received transplantation in the two arms will be summarized and compared using a chi-square test. We acknowledge that censoring patients at the time of HCT may potentially lead to informative censoring and biased efficacy results. Similar sensitivity analyses will be conducted for patients who take other off-protocol treatment due to MRD.

13.2.5 Subgroup Analyses

Subgroup analyses by potential prognostic factors at baseline will be conducted, to evaluate the consistency of the treatment effect among each subgroup. Non-parametric methods such as Kaplan-Meier and log-rank tests will be used within each subgroup. Univariate/multivariate Cox models will be fit within each subgroups; hazard ratios will be used to quantify the treatment effect within each subgroup, along with the 95% confidence intervals.

13.3 Accrual Time and Study Duration

The anticipated accrual rate is approximately 5 pts/month in the first year, 10 pts/month second year, and 14 patients per month afterwards. The phase II component is expected to accrue in 30 months after trial activation. Accrual will be suspended between the phase II and phase III component for primary endpoint analysis from phase II; the suspension between the Phase II and Phase III is expected to be 12 months to allow for follow-up on the last phase II patients and completion of the primary analysis for phase II. The phase III component is expected to accrue in approximately 59 months. Including the suspension between Phase II and III, the total

study duration is expected to be approximately 83 months, or until the last Phase III patient accrued has been observed for at least 12 months.

As of Amendment 04, there will be no additional accrual to the Phase III component of the trial regardless of the outcome of the Phase II analysis.

13.4 Adverse Event Stopping Rule

Early stopping rule will be based on 30-day mortality rate. If 3 or more of the first 20 Phase II patients enrolled or 15% or more of the Phase II patients enrolled thereafter die within 30 days after start of treatment, enrollment to the study will be suspended. The study team will review all adverse event data in light of the early deaths. A trial recommendation will be formulated and presented to the Alliance DSMB – the study may permanently close or may re-open to accrual after any needed modifications to the dose, the design etc., and after discussion with CTEP.

13.5 Study Monitoring

As a randomized phase II/III trial this study will be monitored by the Alliance Data and Safety Monitoring Board (DSMB) twice per year. The DSMB follows the Alliance Policies and Procedures for all randomized phase II trials. The DSMB will review accrual, toxicity, and interim analyses results. All summary findings of the DSMB will be communicated to study investigators by the Alliance. In addition the Alliance Statistical Data Center will submit quarterly reports to CTEP by electronic means using the Clinical Data Update System.

All EFS and OS outcome data will be requested for release after DSMB review at the time of the final Phase II EFS analysis, with patient follow-up continuing per protocol.

13.6 Clinical Data Update System (CDUS) Reporting

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

13.7 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

The geographical region served by the Alliance, has a population which includes approximately 18% minorities. Based on prior Alliance studies involving similar disease sites, we expect about 18% of patients will be classified as minorities by race and about 40% of patients will be women. Expected sizes of racial by gender subsets for patients registered randomized to this study are shown in the following table.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	6	2	2	6	16
Asian	8	15	2	2	27
Native Hawaiian or Other Pacific Islander	2	4	2	2	10
Black or African American	30	38	2	0	70
White	186	282	29	50	547
More Than One Race	0	0	0	0	0
Total	232	341	37	60	670

14.0 CORRELATIVE AND COMPANION STUDIES

There will be three substudies within A041701. Cytogenetics (Section 14.1) and Molecular Genetic Analysis (Section 14.2) are required for all patients. A041701-LC1 (Section 14.3) is an integrated substudy and patients are encouraged to participate.

14.1 Cytogenetic Correlative Science (Alliance A041701)

14.1.1 Background

Cytogenetic analyses in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) have revealed a great number of non-random chromosome abnormalities. In many instances, molecular studies of these abnormalities identified specific genes implicated in the process of leukemogenesis. The more common chromosome aberrations have been associated with specific laboratory and clinical characteristics, and are now being used as diagnostic and prognostic markers guiding the clinician in selecting the most effective therapies. Specific chromosome aberrations and their molecular counterparts have been included in the World Health Organization classification of hematologic malignancies, and together with morphology, immunophenotype and clinical features are used to define distinct disease entities. The European Leukemia Net Classification also uses specific chromosome aberrations and molecular information to classify patients.

Pretreatment cytogenetic findings have been repeatedly shown to be among the most important, independent prognostic factors in AML Consequently, cytogenetic analyses are considered mandatory for analyzing outcome of many clinical trials and are currently used to stratify patients for different types of therapy. For instance, based on the European Leukemia Net (ELN) 2017 risk categories (Döhner et al, Blood, 2017; 129:424-47), patients with inv(16)(p13.1q22) or t(16;16)(p13.1;q22) and t(8;21)(q22;q22.1) are associated with a better risk and survival. Patients with t(6;9)(p23;q34.1), t(v;11q23.3), t(9;22)(q34.1;q11.2), inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2), −5 or del(5q), −7, −17/abn(17p) and complex or monosomal karyotype are associated with adverse risk and poor survival. The remaining patients, those with t(9;11)(p21.3;q23.3) or cytogenetic abnormalities not classified as favorable or adverse are associated with intermediate risk and survival.

Clonal chromosome abnormalities, that is, an identical structural aberration or gain of the same, structurally intact chromosome detected in at least two metaphase cells or the same chromosome missing from a minimum of three cells, are consistently found in the majority of AML patients at diagnosis. However, in contrast to patients diagnosed with CML, who are invariably positive for t(9;22) or its variants, the cytogenetic picture of AML is much more complex. To date, approximately 200 different structural and numerical aberrations such as reciprocal translocations, inversions, insertions, deletions, unbalanced translocations, isochromosomes, isodicentric chromosomes, isolated trisomies and monosomies have been found to be recurring chromosome changes in AML. Many of these aberrations are very rare, being so far detected in a few patients worldwide, whereas others occur more frequently [25].

14.1.2 Objectives

- Correlate specific karyotype groups (normal or various primary and secondary chromosomal abnormalities) with clinical and laboratory parameters.
- Correlate specific karyotype groups with response rates, response duration, survival and cure in patients treated with various induction and post-induction regimens.
- Correlate specific karyotype groups with selected molecular abnormalities.
- To correlate specific karyotype groups with measurable residual disease.
- To correlate CR karyotype with outcome.

- To determine karyotype changes at end of consolidation and the influence of the type of change (or no change) in karyotype at end of consolidation on subsequent clinical course.
- To determine karyotype changes at relapse and the influence of the type of change (or no change) in karyotype at relapse on subsequent clinical course.

14.1.3 Methods

Specimens for cytogenetic and FISH analysis must be performed for the required time points at each institution's preferred CLIA-approved cytogenetic and FISH laboratory.1 A copy of the Cytogenetic Form from the Case Report Forms in Medidata Rave® should be printed and submitted to the institution's preferred cytogenetic lab along with the contact information for the CRP and the specimen; the Cytogenetic Form can be found in the A041701 All Forms Packet on the Alliance and CTSU websites.2 An editable PDF of the forms can also be obtained by contacting the Alliance Cytogenetics Committee Office (see below). 3Use of an Alliance approved cytogeneticist is encouraged but not required; a list of Alliance-approved cytogeneticists can be found on the study-specific webpage on the Alliance and CTSU websites.4

Cytogenetics samples obtainedare required to be submitted at the following timepoints:

- Prior to initiation of therapy
- 1st complete remission (if diagnostic specimen is abnormal)
- End of consolidation (if cytogenetics are abnormal at CR)
- Relapse.

Required processing of specimen includes 24 or 48 hour culture of bone marrow specimen (unstimulated blood culture required if marrow tap is dry), G-banding, and analysis of first 20 analyzable metaphase spreads.

Submission of Cytogenetic Samples

After local review has been performed, the designated local cytogeneticist will complete the Cytogenetic Form and provide the required karyotype, metaphase images, and FISH information (if applicable) to the institution. The responses provided by the local cytogeneticist on the Cytogenetic Form will be entered in Medidata Rave® by site staff, and the required supporting documentation will be uploaded in Medidata Rave® for the use of the Alliance Cytogenetic Committee Office. The cytogenetic data from the prior to registration time point should be entered in Medidata Rave® within 28 days of patient registration; data for all other time points should be entered within 14 days of institution's receipt of local review results.

- Karyotypes and metaphases must be submitted via Medidata Rave®. Include the karyotype description or clone number in the bottom of the high resolution electronic image with arrows placed indicating abnormalities. Images (karyotype, metaphase, and FISH) are preferred to be submitted together in one PowerPoint (PPT) file. If this is not possible, individual .jpeg or .tiff files are accepted. Photocopies, faxes, and low-resolution PDF scans of karyotypes and metaphases will not be accepted. Write "Random Loss" next to the homologue when appropriate. If one copy (or both copies) of a given chromosome is overlapped or distorted, please submit a partial karyotype from another cell from the same clone showing both homologues of this chromosome intact, so that the reviewers are able

to evaluate each chromosome pair without distortion or overlap in at least two cells from the same clone.

- For any abnormal, non-clonal cell not on the "List of Specific Abnormalities" (Appendix I), submit the International System for Human Cytogenetics Nomenclature (ISCN), karyotype is not required.
- Two karyotypes of each abnormal clone and the corresponding metaphase spreads are required for submission. For any abnormal, non-clonal cell related to a clone, or for any abnormal, non-clonal cell not related to a clone and not on the "List of Specific Abnormalities" (Appendix I), submit the ISCN, but do not submit karyotype.
- If case is abnormal, non-clonal (has one or more of the characteristic abnormalities specified on the list), enter the ISCN of each cell and provide a karyotype and corresponding metaphase representing each type of abnormality present.
- If case is normal, submit two karyotypes and corresponding metaphase spreads for the normal clone. Submit karyotypes and associated metaphases for any abnormal non-clonal cell present in a normal case if it contains an abnormality on the “List of Specific Abnormalities” (Appendix I).
- If the presence of a constitutional abnormality is suspected, the laboratory should perform analysis necessary to confirm or refute such suspicion (e.g., PHA-stimulated cultures of peripheral blood) and submit the results.
- Unsuccessful cytogenetic studies at the required time points are still required to be submitted.
- For samples of peripheral blood only abnormal outcome will be accepted.
- Follow-up will continue for required cytogenetic samples until relapse, withdrawal of consent, or death for up to 15 years.

Optional Additional Procedures:

- Direct preparations of AML specimens are acceptable only if the case is abnormal.
- Unstimulated 24-48 hour cultures of peripheral blood.
- Standard PHA-stimulated cultures of peripheral blood.
- Other banding procedures.
- Counting and/or analysis of additional metaphase spreads.
- Submission of additional karyotypes.
- Appropriate metaphase or interphase fluorescence in situ hybridization (FISH) analyses. Abnormal FISH results are encouraged to be submitted. Provide FISH information and two images (in the PowerPoint file with karyotypes and metaphases (preferred) or as individual .jpeg or .tiff files) for each assay performed.

Questions regarding karyotype submission can be directed to Lisa Sterling, Cytogenetic Data Manager, at:

Alliance Cytogenetics Committee Office
Tel: 614-688-9750
Lisa.sterling@osumc.edu

Central Karyotype Review

Karyotypes will be sent to the Central Karyotype Review Committee if the material is adequate in terms of numbers of metaphases and required numbers of karyotypes.

14.1.4 Analyses

Analyses will be conducted using the analysis dataset used for the analysis of the clinical endpoints to ensure consistent data is reported for the primary and secondary endpoints (e.g. data associated with censoring, proper inclusion of crossover data, and data to be excluded in cases of consent withdrawals for follow-up and correlative studies). In this study, we plan to group the patients into ELN 2017 risk categories using centrally reviewed cytogenetics, see Section 14.1.3: Central Karyotype Review. We will then use that data as a factor in analyses as it is well known that cytogenetics play a role in outcome of patients. Since we are focusing on these ELN 2017 risk categories, we will be able to avoid making false conclusions due to multiple testing. For correlative studies, we will use per family error rate by setting the expected false discovery rate to 1. Using this we will be able to determine the multiplier needed to adjust for various hypotheses contained in the objectives of the study.

14.2 Molecular Genetic Analysis

An amendment for the molecular genetic testing will be submitted to CTEP, NCI for review and approval according to NCTN guidelines. Amendments to the protocol and/or proposals for use of banked bone marrow or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

14.2.1 Background

Large scale DNA sequencing studies have identified over 250 recurring somatic mutations in AML and have defined the genomic landscape of the disease [26]. Understanding the genetics of AML has led to refinements in disease classification, informs prognosis, and has identified potential targets for therapeutic intervention.

Molecular genetic testing using either single gene or next generation sequencing assays has become a routine and essential part of the clinical care of patients with AML. As a corollary, interpretation of clinical trial data in AML requires and understanding of the genetic context of the patient population. In clinical practice, however, heterogeneity exists in commercially available next generation sequencing assays for AML due to differences including sequencing platform, library generation, sequencing platform, sequencing coverage, read depth and variant interpretation. Furthermore, because the field of molecular genetics is a rapidly evolving area in AML with constant refinements in gene panels and sequencing technology. Genetic information that would be considered clinically meaningful and relevant in the future at the time of study analysis may not be currently available through routine clinical testing for patients enrolled earlier in the course of the study.

For these reasons, a baseline, pretreatment bone marrow and blood sample will be required from all patients to allow for centralized genetic molecular profiling. The information obtained will complement cytogenetic analysis to refine prognostic groups and response to treatment.

14.2.2 Objectives

- To prospectively obtain specimens required for a baseline molecular characterization of patients treated on study.
- To determine the frequency of specific gene alterations.
- To determine the association of specific gene alterations with pretreatment characteristics and clinical outcomes.

14.2.3 Methods

The specific details of the molecular genetic testing for the samples will be determined after all patients are enrolled and will reflect the best available information about the molecular genetics of AML and sequencing technology at the time of analysis.

14.2.4 Analysis

The objectives are to examine three types of associations: (1) association of molecular features with pretreatment characteristics, (2) association among molecular markers, and (3) the association of molecular markers with clinical endpoints, such as CR, DFS, EFS, CIR, and OS. The type of analysis will be determined based on the nature of the variables analyzed. Fisher's exact and Wilcoxon rank-sum tests will compare categorical and continuous variables, respectively. To analyze multiple factors related to the probability of achieving CR, logistic regression models will be constructed. For DFS, EFS, and OS, Kaplan-Meier curves will be constructed and the log-rank test will be used to examine the impact of single molecular markers on outcome. In addition, combinations of molecular markers along with other potentially important variables will be examined in multivariable analyses, using Cox regression.

14.3 E-selectin studies (Alliance A041701-LC1)

14.3.1 Background

E-selectin mediated interactions may play a role in AML and the expression of E-selectin or its binding epitope (sialyl $Le^{a/x}$) may predict the clinical course and patient outcomes in AML. Increased expression of E-selectin, as seen in inflammatory conditions, malignant states such as leukemia, and during chemotherapy, is also associated with increased shedding of E-selectin from the cell surface resulting in higher levels of sE-selectin in the circulation.

We will measure the levels of E-selectin ligand on pretreatment bone marrow blasts in patients treated with or without uproleselan to describe the cell-surface expression pattern of E-selectin ligand on AML blasts and to determine the effect on clinical outcomes. We will also examine plasma sE-selectin at baseline and after treatment with chemotherapy with or without uproleselan to determine if E-selectin inhibition affects sE-selectin levels and to correlate plasma levels with clinical outcomes.

E-selectin (E-sel) is a cell adhesion glycoprotein that is expressed on endothelial cells and has been implicated in therapeutic resistance. In most myeloid leukemias, leukemic blasts express E-selectin ligands, which contain the glycan epitope of the carbohydrate sialyl Le^x (sLe^x). This sequestration in the bone marrow vascular niche, leading to cell adhesion-mediated drug resistance and resultant poor clinical outcome. Uproleselan is an E-selectin antagonist which interrupts leukemic cell homing to the vascular niche, increases susceptibility to cytotoxic and targeted therapies and can be a potent adjunct to therapeutics. In deed data has demonstrated a correlation between leukemic cell surface

levels of E-selectin ligands using multiparameter flow cytometry and response to uproleselan.

Recently, transciptome profiling of E-selectin ligand-forming glycosylation genes have been explored from public data sets to identify elevated E-selectin ligand expression in patients with AML. RNA-seq data from patients treated in COG AAML1031 ($N = 1,074$) was available for evaluation. Of 24 genes examined, Fucosyltransferase 7 (FUT7) and ST3 beta-galactoside alpha-2,3-sialyltransferase 4 (ST3GAL4) were significantly associated with adverse outcome ($HR = 1.013$, $p < 0.0001$, and $HR = 1.023$, $p < 0.0001$, respectively). and directly synthesize sLe^x. Patients highly expressing *FUT7* (highest quartile of expression) had significantly worse outcome than lower expressors (lowest 3 quartiles of expression), with a 5-year OS of 50.3% vs. 68.3% ($p < 0.0001$). Similarly, those with high *ST3GAL4* expression had a 5-year OS of 51.3%, compared to 68.1% for low expressors ($p < 0.0001$). High expression of these genes was shown to be associated with cell surface E-selectin ligand expression. Taken together these data suggest a strong correlation between transcriptome measurements of E-selectin ligand-forming glycosylation genes and cell surface glycosylation levels of E-selectin ligands, and lend support for the use of E-selectin ligand glycosylation genes as predictive biomarkers.

We will measure the expression of E-selectin ligand-forming glycosylation genes from pretreatment bone marrow blasts treated with or without uproleselan to describe the RNA expression levels of these genes on AML blasts and to determine the effect on clinical outcomes.

Traditional measures of response in AML rely on the morphological characterization of blasts after therapy with complete remissions requiring less than 5% blasts to be present in the bone marrow. The morphological determination of blasts lacks sensitivity to identify low levels of residual disease and is subject to both sampling and interpretation error. Measurable residual disease (MRD) denotes the presence of leukemia cells down to levels of $1:10^4$ to $1:10^6$ white blood cells (WBCs), compared with 1:20 in morphology-based assessments. Multiple studies have demonstrated that the achievement of a negative MRD status is associated with improved clinical outcomes. In this study, we will utilize a flow cytometry-based MRD assessment at the end of induction and consolidation to explore potential differences in the experimental and control arms and correlate these results with clinical outcomes.

14.3.2 Exploratory Objectives

- To examine the correlation of E-selectin ligand expression of leukemic blasts with clinical outcome.
- To examine the correlation of plasma soluble E-selectin concentrations with clinical outcomes.
- To examine the correlation of MRD after induction and consolidation chemotherapy with clinical outcomes.
- To examine the correlation of E-selectin ligand-forming glycosylation genes of leukemic blasts with clinical outcome.

14.3.3 Methods

E-selectin ligand will be measured on bone marrow blasts using multiparameter flow cytometry using a standardized panel of monoclonal antibodies designed to identify the blast population. The percentage of cells and mean fluorescence intensity will be used to quantify the extent of E-selectin ligand in this population.

sE-Selectin will be measured from plasma samples obtained at baseline and after induction using a commercially available enzyme-linked immunosorbent assay (ELISA) to human E-selectin.

Expression levels of the E-selectin ligand-forming glycosylation genes, Fucosyltransferase 7 (FUT7) and ST3 Beta-Galactoside Alpha-2,3-Sialyltransferase 4 (ST3GAL4), in RNA extracted from residual bone marrow aspirates of patients diagnosed with AML will be determined by reverse transcription quantitative PCR (RT-qPCR).

To determine whether the E-selectin ligand expression is associated with clinical outcomes, descriptive statistics (i.e. mean, median, standard deviation, and range) and graphical methods (i.e. boxplots, jitter plots) will be used to summarize both pre- and post-treatment E-selection level to understand its distribution in each treatment arm. To evaluate its association to clinical outcomes, two-sample t-tests or Wilcoxon rank-sum tests will be conducted to compared the E-selection level between those who achieve remission versus not.

Suppose 80% of patients (n=536) enrolled will have a bone marrow sample available for E-selectin analysis. Assuming 375 patients (out of 536 patients) achieving a remission, we will have 88% power to detect an effect size of 0.3 (effect size defined as the difference in mean divided by the standard deviation, $\delta = |\mu_1 - \mu_1|/\sigma$) in baseline E-selectin expression levels between the responders and non-responders at the 0.05 two-sided alpha level; this assumes a remission rate of 70%. Furthermore, to analyze multiple factors related to the probability of achieving CR, logistic regression models will be constructed. For DFS, EFS, and OS, E-selection level along with other potentially prognostic factors will be examined in multivariable analyses, using Cox regression model, stratified by treatment arm. Similar analyses will be conducted for sE-selection. Secondary analysis will evaluate the sE-selectin expression level pre- vs. post-induction will be compared using two-sample t-tests or Wilcoxon rank-sum tests, as well as descriptive statistics and graphical methods. Exploratory analysis will be conducted to investigate the optimal cut-point of baseline E-selectin expression level through ROC analysis.

Flow cytometry will be used to assess for MRD by discriminating between normal regenerating hematopoietic cells in the bone marrow and any remaining acute myeloid leukemia (AML) which abnormally expresses cell surface antigens [27]. This technique, termed "Difference from Normal" is based on correlating the quantitative expression of multiple cell surface antigens (gene products) in the specimens using standardized antibody panels. The Difference from Normal approach identifies all the normal regenerating cells within the specimen first, subtracts them away and then detects clusters of abnormal cells within the remaining data set. Using this technique, it is possible to define the precise composition of the specimen, identifying cells of all lineages and maturational stages as well as assessing specimen quality in addition to detecting and quantifying any abnormal cell population [28].

Bone marrow specimens will be obtained at the end of induction and the end of consolidation. The quality of each specimen will be defined based on total cellularity, hemodilution, and viability. Collection of fewer than 100,000 cells in each of 8 tubes, significant hemodilution of >50%, lymphoid predominance of >50%, or significant cell death resulted in a specimen quality classification of suboptimal or inadequate [29].

14.3.4 Statistical Analysis Plan

A041701 is a randomized Phase II/III study. The study will open with accrual open to two arms (one experimental arm and one control arm). The total Phase II sample size is

expected to be approximately 262 eligible patients (131 patients per arm). The total Phase III sample size is expected to be 670 (335 patients per arm). In the event that the Alliance Data Safety and Monitoring Board (DSMB) releases the requested Phase II data, the hypothesis-generating analyses described here will be performed based on Phase II accrual. Otherwise, this proposal is mainly based on Phase III accrual. Because this substudy is being newly incorporated in a protocol amendment post-study activation (54 patients accrued as of 11/22/2019), the current accrual rate suggests that approximately 600 evaluable Phase III patients may participate in this substudy.

We assume that 60% patients treated on A041701 will achieve a CR/CRi. Of those achieving CR/CRi, we expect to have end-of-induction marrow samples for MRD assessment on 90% of patients (n=324), and blood samples on 95% of patients (n=342).

We note that the Cox regression models below will be stratified by treatment arm as appropriate. Multivariable analyses will be evaluated as a complement to each univariate analysis. Multivariable analyses will include baseline covariates age, gender, performance status, cytogenetic risk, white blood cell count, platelet count, bone marrow blast percentage, and number of induction courses (1 vs 2).

1. Primary integrated objective (To evaluate whether the presence of MRD will be a strong predictor of relapse-free survival (RFS) in patients achieving a CR/CRi following induction chemotherapy):

We expect that approximately 25% of patients who achieve a CR/CRi will have detectable MRD by flow cytometry using the current methodology. Log-rank test will be used to assess associations between MRD and RFS. And RFS will be estimated by the Kaplan-Meier method.

In the calculations below, the RFS is assumed to follow an exponential distribution with a median of 11.5 months (null hypothesis). For the RFS outcome (assuming 59 months of accrual and an additional one year of follow-up per protocol), the marrow results (n=324) will have 80% power to detect an absolute difference in median RFS of 5 months between MRD- and MRD+ patients (HR = 0.7), 13 months for MRD- versus 8 months for MRD+) with a two-sided alpha of 0.05, and the blood (n=342) results will have 83% power for the same effect size and alpha level. C-statistics will be calculated to quantify the model's ability to predict outcomes. We will also fit multivariable Cox regression models with both end-of-induction MRD (present vs absent) plus the covariates listed above.

In the event that the Alliance Data Safety and Monitoring Board (DSMB) releases the requested Phase II data, the hypothesis-generating analyses described here will be performed based on Phase II accrual. Similarly, because this substudy is being newly incorporated in a protocol amendment post-study activation (54 patients accrued as of 11/22/2019), the current accrual rate suggests that approximately 200 evaluable Phase II patients may participate in this substudy.

For the RFS outcome (assuming additional 18 months of accrual and an additional one year of follow-up per protocol), the marrow results (n=108) will have 63% power, and the blood (n=114) results will have 65% power for a HR of 0.6 and two-sided alpha of 0.05. C-statistics will be calculated to quantify the model's ability to predict outcomes. We will also fit multivariable Cox regression models with both end-of-induction MRD (present vs absent) plus the covariates listed above.

To analyze the association of MRD with overall survival (OS), time-to-relapse (TTR, defined as the time from randomization to relapse, with death without relapse censored at time of death), and relapse risk: OS and TTR will be estimated using the Kaplan–Meier

method, and compared using log-rank tests. Risk of relapse (RR) will be summarized using cumulative incidence estimates. Cox regression analyses will be used to assess the association between the outcomes of interest and the covariates listed above.

To compare whether evaluate whether MRD from the peripheral blood provides similar prognostic information compared to bone marrow: We will fit multivariate marginal Cox regression models (Wei, Lin, Weissfeld 1989) including either blood and marrow MRD results with covariates for sample type (blood versus marrow), and a second model both blood and marrow MRD, and a third model with the interaction between the two covariates. We will calculate C-statistics for each of these models.

To compare the presence of MRD at the end of induction versus end of consolidation time points to determine if either of these better predicts RFS: We will fit multivariate marginal Cox regression models (Wei, Lin, Weissfeld 1989) including either MRD results at the end of induction or at the end of consolidation. We will calculate C-statistics for each of these models.

To compare the rates of MRD by treatment arm: Two-way table and chi-square tests will be used to compare the MRD rates by treatment arm.

15.0 MONITORING PLAN AND REGULATORY CONSIDERATIONS

15.1 Central Data Monitoring and Source Data Verification

Centralized data monitoring activities will be performed for all patient cases enrolled at each site (as identified by a unique CTEP Institution Code). The cases selected for central data monitoring will be reviewed for completeness and consistency via source data verification (SDV) with source documents compared to the data reported via the electronic Case Report Forms in Rave. Central data monitoring with SDV will be performed for all patients for *key eligibility* and *response/disease outcomes.* The first two treatment cycles will be reviewed for all patients.

A source document is a document in which data collected for a clinical trial is first recorded. A subset of data is usually later entered in the Case Report Forms. The ICH-GCP guidelines define source documents as original documents, data, and records.

The following data and documents will be reviewed via centralized data monitoring and source documents should be uploaded within the two weeks after registration:

1) **Informed Consent Document (ICD):** De-identified last page of the signed and dated informed consent document as well as any pages with responses indicated by patient for optional studies. Patient's full signature should be redacted, but date should be retained.

2) **Key Eligibility Criteria:**

   a. Diagnosis of AML based on 2017 WHO criteria excluding acute promyelocytic leukemia with PML-RARA
   b. No activating mutation in Fms-like tyrosine kinase-3 (FLT3)
   c. No evidence of CNS involvement of AML.
   d. No prior chemotherapy for MDS or AML including hypomethylating agents or lenalidomide (see section 3.3.2 for exceptions).
   e. Age ≥60 years

3) **Treatment Verification/IP Administration:** Applicable drug administration and dosing records to document the first cycle of induction therapy and the first cycle of consolidation therapy.

4) **Disease Outcome/Response:** Verify the claimed response for the primary endpoint based on source data containing assessment or response per the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia.

See the *Data Submission Schedule*, available on the Alliance and CTSU websites, for additional details regarding source data verification requirements.

Sites should ensure that patient identifiers have been removed from all pages that will be uploaded and add study-specific identifying information (i.e. Alliance Patient ID) and then scan and upload all source documents to Rave. Please ensure that all pages are legible and correct.

In the event central monitoring or review of key performance indicators (KPIs) identify deficiencies, then additional central monitoring, an unscheduled on-site monitoring visit, or an audit visit may be triggered. Deficiencies or KPIs that may elicit one of these responses include, but are not limited to:

- Accrual rate
- Eligibility
- Early Termination
- Data submission timelines
- Outstanding forms
- Outstanding queries
- Query responsiveness
- Protocol deviations

15.2 On-site Monitoring

Member networks that accrue five or more patients will be monitored approximately every 12 months. Member networks that accrue 10 or more patients per year will be monitored approximately every 6 months. Member networks that accrue less than five patients will not be monitored on site, unless other deficiencies have been identified, and thus indicate the need for a monitoring visit.

The first on-site monitoring visit will occur after the fifth patient has been enrolled and within 6 months of the fifth enrollment. Thereafter, on-site monitoring visits will occur at approximately 12 month intervals during the treatment phase of the study.

At the end of each on-site monitoring visit, the monitor will debrief the site study team and highlight areas that need improvement (if applicable). Any deficiencies and related actions will be documented in a visit follow-up letter, and on-site monitoring visit follow-up letters will be distributed to the site Principal Investigator (PI) and Lead Clinical Research Professional within 30 days of the last day of the on-site monitoring visit.

All affiliate/component sites will be monitored at the main member site during scheduled on-site visits, unless a separate on-site visit is deemed necessary. All records from affiliate/component sites must be accessible to monitors. Institutions that utilize electronic medical records must provide monitors access to electronic records.

Routine monitoring visits will be scheduled at approximately 6 – 12 month intervals, depending on accrual and other KPIs to ensure proper oversight of trial execution. Frequency of monitoring visits may be adjusted and will be determined based upon factors such as enrollment rate, data

quality, protocol compliance, site performance, and the available amount of data to be monitored.

On-site monitoring visits will only be conducted during the treatment phase. Central data monitoring will continue during the follow-up phase. Institutions may also be audited per the Alliance auditing schedule.

Deficiencies impacting the protection of rights and safety of human patients, unreported or underreported safety information, or other non-compliance may result in an increase in the percentage of patient data monitored or monitoring visit frequency.

At selected sites, a minimum 25% of patients will be selected for on-site SDV of the following:

- Eligibility
- Primary endpoint

At selected sites, 100% of patients will be selected for on-site SDV of the following:

- Informed consent

15.3 Early Study Closure at Sites

Institutions may not close this trial without discussion and approval by the Alliance Regulatory team (regulatory@alliancenctn.org). Before contacting the Alliance regulatory team please confirm this study does not appear on the list of trials terminated by the Alliance or on a study-specific termination memo (located on the "Study Terminations of Patient Follow-up" page of the Alliance website or on the study specific page of the CTSU website).

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APPENDIX I LIST OF SPECIFIC ABNORMALITIES FOR WHICH KARYOTYPES MUST BE PROVIDED FOR SINGLE CELLS

1. Acute Myeloid Leukemia (AML) and Myelodysplastic Syndromes (MDS)

   a. any abnormality of 5q
   b. any abnormality of 7q
   c. any abnormality of 11q
   d. +8
   e. t(8;21)(q22;q22) + missing sex chromosomes
   f. t(15;17)(q22;q11-12)
   g. t(9;11)(p22;q23)
   h. t(6;9)(p23;q34)
   i. del(16)(q22), inv(16)(p13q22) or t(16;16)(p13;q22)
   j. Philadelphia chromosome
   k. ring chromosomes
   l. any abnormality involving 3q
   m. any abnormality of 12p
   n. der (1)t(1;7)(p11;p11)
   o. any abnormality of 9q
   p. any abnormality of 17p
   q. any abnormality of 20q
   r. any structural abnormality, other than the aforementioned, that is known to be recurrent in AML or MDS.

2. Acute Lymphocytic Leukemia (ALL)

   a. hyperdiploid cells, especially > 50 chromosomes
   b. t(4;11)(q21;q23)
   c. t(8;14)(q24;q32)
   d. t(2;8)(p11-13;q24)
   e. t(8;22)(q24;q11)
   f. Philadelphia chromosome
   g. t(1;19)(q23;p13) or der(19)t(1;19)(q23;p13)
   h. t(11;14)(p13;q13)
   i. t(11;14)(q13-23;q32)
   j. near-haploid cells
   k. any deletion of 6q
   l. any abnormality of 14q
   m. any abnormality of 9p
   n. any abnormality of 12p
   o. any abnormality of 11q
   p. any structural abnormality, other than the aforementioned, that is known to be recurrent in ALL.

APPENDIX II COLLABORATIVE AGREEMENTS LANGUAGE

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator"

(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). –Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX III PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Version #02

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **uproleselan**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

- Uproleselan does not cause direct or time-dependent inhibition of CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4.
- Uproleselan is a substrate for the efflux transporters P-gp and MRP2, may be a weak substrate for BCRP, and is not a substrate of the efflux transporter BSEP. These transport proteins may affect how much or how fast uproleselan is moved in and out of cells/organs.
- Uproleselan is not an inhibitor of the efflux transporters P-gp, BCRP, or BSEP.
- Uproleselan is not a substrate for or inhibitor of the following uptake transporters: OATP1B1, OATP1B3, OAT1, OAT3, OCT1 and OCT2.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Uproleselan may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Uproleselan must be used very carefully with other medicines that use certain transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates] of P-gp, MRP2,

and BCRP.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug uproleselan. This clinical trial is sponsored by the NCI. Uproleselan may interact with drugs that use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Uproleselan interacts with the transport proteins P-gp, MRP2, and BCRP, and must be used very carefully with other medicines that interact with these transporters.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of P-gp, MRP2, or BCRP.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

VOLANTE DE INFORMACIÓN SOBRE EL FÁRMACO PARA EL PACIENTE Y TARJETA PARA LA BILLETERA

Versión #02

Información para los pacientes, sus cuidadores y el equipo de atención médica ajeno al estudio sobre posibles interacciones con otros fármacos y suplementos herbales

El paciente _____ está inscrito en un ensayo clínico que usa el fármaco experimental en estudio, **uproleselan**. Este ensayo clínico está patrocinado por el Instituto Nacional del Cáncer. Este formulario está dirigido al paciente, pero incluye información importante para otras personas que atienden a este paciente.

Esto es lo que usted como proveedor de atención médica debe saber:

- Uproleselan no causa una inhibición directa o dependiente del tiempo de CYP1A, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 o CYP3A4.
- Uproleselan es un sustrato para los transportadores de eflujo P-gp y MRP2, puede ser un sustrato débil para BCRP y no es un sustrato del transportador de eflujo BSEP. Estas proteínas de transporte pueden afectar la cantidad o la rapidez con que se mueve uproleselan dentro y fuera de las células/órganos.
- Uproleselan no es un inhibidor de los transportadores de eflujo P-gp, BCRP o BSEP.
- Uproleselan no es un sustrato ni un inhibidor de los siguientes transportadores de captación: OATP1B1, OATP1B3, OAT1, OAT3, OCT1 y OCT2.

Al paciente: Lleve este papel a sus citas médicas y guarde la tarjeta de información adjunta en su billetera.

Uproleselan puede interactuar con otros fármacos que pueden causar efectos secundarios. Por esta razón, es muy importante que informe a los médicos del estudio sobre cualquier medicamento que esté tomando antes de inscribirse en este ensayo clínico. También es muy importante que informe a sus médicos si deja de tomar algún medicamento habitual o si comienza a tomar un nuevo medicamento mientras participa en este estudio. Cuando hable con sus médicos sobre sus medicamentos actuales, incluya los medicamentos que compra sin receta (remedio de venta libre) o cualquier suplemento herbal como la hierba de San Juan. Es útil llevar con usted los envases de los medicamentos o una lista actualizada de los medicamentos.

Muchos proveedores de atención médica pueden hacer recetas de medicamentos. Debe informar a todos sus proveedores de atención médica (médicos, asistentes médicos, enfermeras profesionales, farmacéuticos) que está participando en un ensayo clínico.

Esto es lo que usted y ellos deben saber:

Uproleselan debe usarse con mucho cuidado con otros medicamentos que usan ciertas proteínas transportadoras para que sea eficaz o se elimine de su sistema. Antes de inscribirse en el ensayo

clínico, el médico del estudio trabajará con sus proveedores de atención médica habituales para revisar los medicamentos y suplementos herbales que se consideren inductores/inhibidores potentes o sustratos de P-gp, MRP2 y BCRP.

- ¡Tenga mucho cuidado! Los medicamentos de venta libre (incluidos los suplementos herbales) pueden contener ingredientes que podrían interactuar con el fármaco del estudio. Hable con sus médicos o farmacéuticos para determinar si podría haber algún efecto secundario.
- Su proveedor de atención médica habitual debe consultar una fuente de consulta médica actualizada con frecuencia o llamar al médico del estudio antes de recetar cualquier medicamento nuevo o de suspender algún medicamento que esté tomando. El nombre de su médico del estudio es

_____ y se le puede contactar en

_____.

TARJETA PARA LA BILLETERA CON INFORMACIÓN SOBRE EL FÁRMACO DEL ESTUDIO

Está inscrito en un ensayo clínico que usa el fármaco experimental en estudio uproleselan. Este ensayo clínico está patrocinado por el NCI. Uproleselan puede interactuar con medicamentos que usan ciertas proteínas de transporte en su cuerpo. Por eso, es muy importante que:

- Informe a sus médicos si deja de tomar algún medicamento o si comienza a tomar algún medicamento nuevo.
- Informe a todos sus proveedores de atención médica (médicos, asistentes médicos, enfermeras profesionales o farmacéuticos) que está participando en un ensayo clínico.
- Consulte con su médico o farmacéutico siempre que necesite usar un medicamento de venta libre o un suplemento herbal.

Uproleselan interactúa con las proteínas de transporte P-gp, MRP2 y BCRP, y debe usarse con mucho cuidado con otros medicamentos que interactúan con estos transportadores.

- Antes de inscribirse en el ensayo clínico, su médico del estudio trabajará con sus proveedores de atención médica habituales para revisar los medicamentos y suplementos herbales que se consideren inductores/inhibidores potentes o sustratos de P-gp, MRP2 o BCRP.
- Antes de recetar nuevos medicamentos, sus proveedores de atención médica habituales deben consultar una referencia médica actualizada con frecuencia para obtener una lista de fármacos que deben evitarse o comunicarse con su médico del estudio.
- El nombre de su médico del estudio es

  _____ y se lo puede contactar en

  _____.