NCI Protocol #: 10434
Local Protocol #: *TBD*
Protocol Version Date: March 3, 2025

Protocol Title: Randomized Phase 2 Study of daunorubicin and cytarabine liposome + Pomalidomide versus daunorubicin and cytarabine liposome in Newly Diagnosed AML with MDS-Related Changes.

Protocol Version Date: March 3, 2025

The summary of changes table below provides a detailed summary and rationale for all changes to protocol #10434, from amendment 11 (Version 7/11/2023) to amendment 12 (Version 3/3/2025). Although this study is now closed for accrual, the amendment is being submitted to provide details of the change of Dr. Luznik laboratory.

SUMMARY OF CHANGES-PROTOCOL

Summary of changes for Amendment #12 version March 3, 2025		
#	**Section**	**Comment**
1	5.1	Updated the Table footnote to specify the location of Dr. Luznik laboratory
2	5.3.2.1	Revised the sub-section header to Scheduling of Specimen Collections from UNC to the Luznik Laboratory at JHU (only applicable to UNC, no other sites will ship samples to the Luznik Laboratory).
3	5.6.1	Revised the sub-section header to: Shipping of Specimens to the Luznik Laboratory at JHU.
4	5.7	Updated lab/lab PI/lab PI email information for Dr. Luznik's new lab
5	5.8.2	Revised this section to include updated information for Dr. Luznik
6	5.9.1	Revised this section to include updated information for Dr. Luznik
7	11	Updated footnotes to Luznik Laboratory at JHU.

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ClinicalTrials.gov Identifier: TBD

TITLE: Randomized Phase 2 Study of daunorubicin and cytarabine liposome + Pomalidomide versus daunorubicin and cytarabine liposome in Newly Diagnosed AML with MDS-Related Changes

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NCI-Supplied Agent: Pomalidomide (CC-4047) (NSC 767909)
Other Agent: daunorubicin and cytarabine liposome (NSC 775341), Commercial; Cytarabine (NSC 63878), Commercial

IND #: [redacted]
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Revision 7/June 27, 2022
Revision 8/ August 1, 2022
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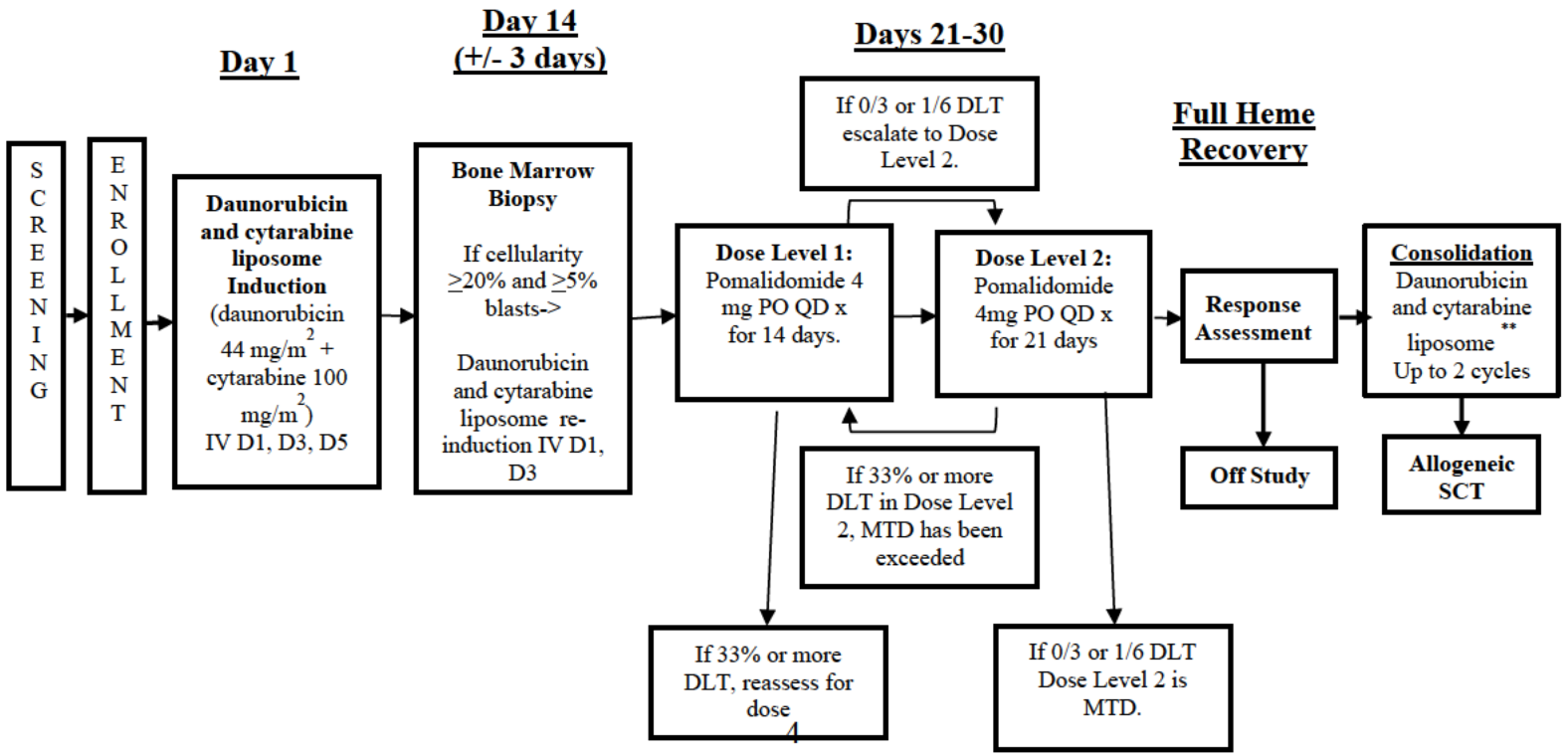
Revision 10/ October 5, 2022
Revision 11/ November 7, 2022
Revision 12/ January 11, 2023
Revision 13/July 11, 2023
Revision 14/March 3, 2025

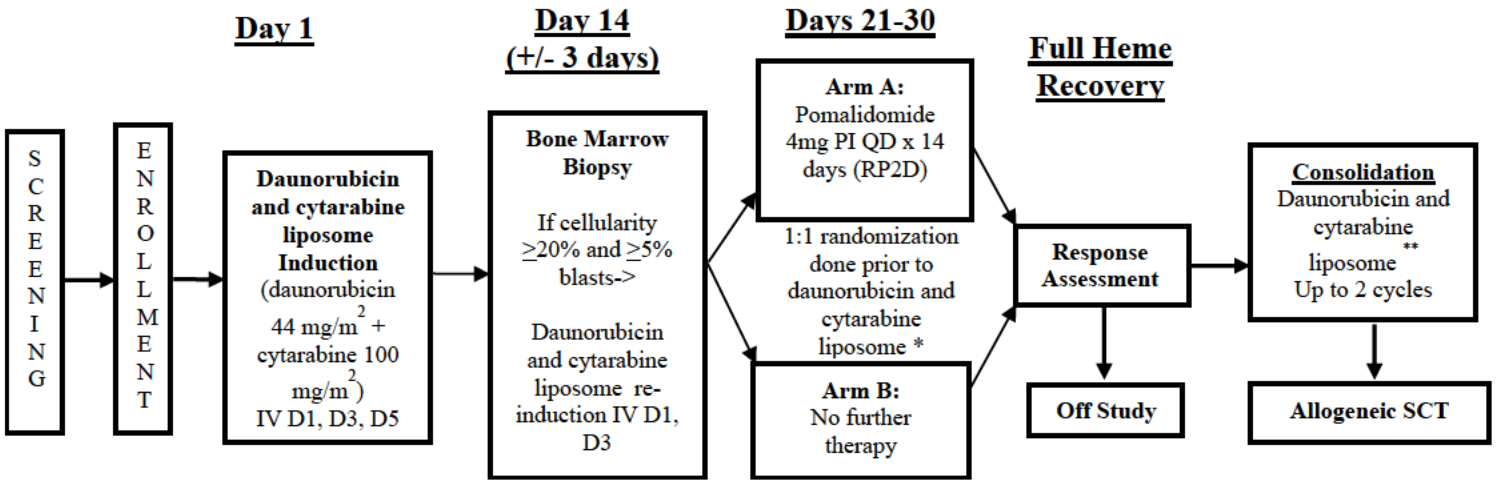
SCHEMA

A randomized, multicenter, phase 2 study utilizing a safety run-in exploring two dose levels of either 4 mg pomalidomide for 14 days or 4 mg pomalidomide for 21 days that will compare daunorubicin and cytarabine liposome (CPX-351) induction in combination with pomalidomide (Arm A) at the recommended phase 2 dose (RP2D) versus daunorubicin and cytarabine liposome alone (Arm B).

Safety Run-in Schema



Randomization Phase Schema



IV: intravenously; PO: orally; QD: once daily; D: Day; SCT: stem cell transplant; CR: complete response; CRi: complete response with incomplete hematologic recovery; RP2D: recommended phase 2 dose.
*Randomization stratified by age ≥60 *vs.* <60 years and in newly diagnosed AML with preexisting myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML) or myeloproliferative neoplasm (MPN) *vs.* therapy-related Acute Myeloid Leukemia (AML) *vs.* AML with myelodysplasia-related changes (MRC) based on cytogenetics or morphologic dysplasia without history of MDS/MPN.
**Consolidation will include up to 2 cycles of daunorubicin and cytarabine liposome 29 mg/m^2 and Cytarabine 65 mg/m^2 IV Days 1 and 3 every 5-8 weeks. Allogeneic SCT can occur directly after induction or after 1-2 cycles of consolidation.

Key Eligibility Criteria:

- Adult ≥18 and ≤75 years of age
- Newly diagnosed AML with 1) preexisting MDS, CMML or MPN; or 2) therapy-related AML; or 3) AML with MRC based on cytogenetics or morphologic dysplasia without history of MDS/MPN
- ECOG PS ≤2

Primary Endpoint:

Rate of complete response (CR) / complete response with incomplete hematologic recovery (CRi) after daunorubicin and cytarabine liposome + Pomalidomide *vs.* daunorubicin and cytarabine liposome

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1. OBJECTIVES

1.1 Primary Objective

1.1.1 To establish recommended phase 2 dose (RP2D) of Pomalidomide after daunorubicin and cytarabine liposome induction.

1.1.2 To compare the rate of overall complete response (CR)/complete response with incomplete hematologic recovery (CRi) with daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone in newly diagnosed Acute Myeloid Leukemia (AML) with preexisting myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or myeloproliferative neoplasm (MPN); therapy-related AML (t-AML); or AML with myelodysplasia-related changes (MRC) based on cytogenetics or morphologic dysplasia.

1.2 Secondary Objectives

1.2.1 To evaluate and compare rates of CR (full hematologic recovery) between daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone in newly diagnosed AML with preexisting MDS, CMML or MPN, t-AML or AML with MRC

1.2.2 To evaluate and compare toxicities (including treatment-related mortality) of daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone in newly diagnosed AML with preexisting MDS, CMML or MPN, t-AML, or AML with MRC based on cytogenetics or morphologic dysplasia.

1.2.3 To detect and compare the presence of minimal residual disease (MRD) by flow cytometry in those who achieve CR/CRi with daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone in newly diagnosed AML with preexisting MDS, CMML or MPN, t-AML, or AML with MRC based on cytogenetics or morphologic dysplasia.

1.2.4 To compare median event-free survival (EFS) of daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone in newly diagnosed AML with preexisting MDS, CMML or MPN, t-AML, or AML with MRC based on cytogenetics or morphologic dysplasia.

1.2.5 To compare median overall survival (OS) of daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone in newly diagnosed AML with preexisting MDS, CMML or MPN, t-AML, or AML with MRC based on cytogenetics or morphologic dysplasia.

1.2.6 To compare median and 2-year disease-free survival (DFS) after CR/CRi with daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone in newly diagnosed AML with preexisting MDS, CMML or

MPN, t-AML, or AML with MRC based on cytogenetics or morphologic dysplasia.

1.2.7 To compare rates of allogeneic stem cell transplant (SCT) after daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone in newly diagnosed AML with preexisting MDS, CMML or MPN, t-AML, or AML with MRC based on cytogenetics or morphologic dysplasia.

1.3 Exploratory Objectives

1.3.1 To assess for molecular biomarkers, Aiolos expression, and immune correlates of response with daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone in newly diagnosed AML with preexisting MDS, CMML or MPN, t-AML, or AML with MRC based on cytogenetics or morphologic dysplasia.

1.3.2 To assess for differences in MRD by molecular based platforms in daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone in newly diagnosed AML with preexisting MDS, CMML or MPN, t-AML, or AML with MRC based on cytogenetics or morphologic dysplasia.

2. BACKGROUND

2.1 Study Disease(s)

Acute Myeloid Leukemia (AML) patients have a poor prognosis with conventional chemotherapy agents. The prognosis and long-term outcomes of AML have been shown to be independently associated with cytogenetics and more recently molecular genomics. The European Leukemia Net (ELN) initially proposed stratification of patients to four different risk groups (favorable, intermediate-1, intermediate-2, and adverse) based on diagnostic cytogenetics and molecular mutations [1]. The ELN updated their proposed risk stratification in 2017 based on prognostic mutational status to reflect three different risk groups (favorable, intermediate and adverse)[2, 3]. Mrozek *et al*. retrospectively analyzed outcomes of 1,550 adult AML patients treated on Cancer and Leukemia Group B clinical trials from 1985-2006 based on ELN risk group and age (<60 and ≥60 years) [4]. There was a significant difference in outcomes (*i.e*. CR, OS, and DFS) between favorable, intermediate (including intermediate-1 and -2), and adverse-risk groups among both younger and older patients. Younger AML patients (<60 years) with adverse-risk were shown to have a CR rate of approximately 50% with induction chemotherapy, median OS and DFS=0.8 and 0.6 years, respectively; whereas older AML patients (≥60 years) with adverse-risk had dismal outcomes (39% CR rate, median OS and DFS=0.5 years). Thus, outcomes are extremely poor in patients with newly diagnosed adverse-risk AML.

Genomic risk assessment is typically performed as a panel in newly diagnosed AML patients and can take 1-2 weeks before final results are available. Fluorescence *in situ* hybridization (FISH) and cytogenetics can be more rapidly ascertained within 48-72 hours. The majority of newly diagnosed AML patients are treated with induction therapy prior to the results of their full genomic analyses with the exception of fms-like tyrosine kinase 3 (FLT3) mutations, which are

now available as a rapid assay to determine whether patients may benefit from the addition of Midostaurin, a FLT3 inhibitor, in newly diagnosed AML patients with FLT3 mutations.

Induction chemotherapy with infused cytarabine plus an anthracycline ('7+3') has been widely used as the standard of care for younger, fit AML patients despite suboptimal outcomes. However, outcomes are extremely poor in patients with secondary AML and/or adverse-risk cytogenetics. A randomized phase 3 trial comparing amonafide + cytarabine versus 7+3 induction in newly diagnosed secondary AML patients found no difference in response between either arm (CR rate=46% versus 45%, respectively) and dismal OS outcomes (median OS=7 months on both arms) [5]. A randomized phase 3 study compared daunorubicin and cytarabine liposome versus 7+3 in newly diagnosed AML patients 60-75 years with MRC. AML with MRC includes patients with secondary AML (*i.e*. therapy-related AML or AML from preexisting MDS/CMML) and those with MDS-related cytogenetics according to the World Health Organization (WHO) [6]. A total of 309 patients were randomized to receive daunorubicin and cytarabine liposome or 7+3. Daunorubicin and cytarabine liposome led to a significantly higher CR rate (47.7% versus 33.3%), median EFS (2.5 versus 1.3 months), and OS (9.6 versus 6.0 months) when compared with 7+3. Nonetheless, these findings highlight the dismal overall outcomes in this patient population despite the improvement seen with daunorubicin and cytarabine liposome. Based on these findings, daunorubicin and cytarabine liposome was Food and Drug Administration (FDA)-approved for the treatment of newly diagnosed therapy-related AML or AML with MRC, and represents a new standard of care for this patient population [7]. Optimal frontline management of AML with MRC represents an unmet need and novel therapies are urgently needed to improve clinical outcomes.

2.2 CTEP IND Agent

2.2.1 Pomalidomide (CC-4047) (NSC 767909)

Pomalidomide (CC-4047) is a member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiDs) that was approved on February 8, 2013 by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of patients with multiple myeloma (MM) who have received at least two prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy [8]. Other IMiD compounds include thalidomide and lenalidomide, which are approved for use in treatment of MM and myelodysplastic syndromes (MDS) and are under investigation for a number of other hematologic neoplasms. Pomalidomide shares a number of the beneficial pharmacologic properties of thalidomide and lenalidomide, but it is a more potent anti-proliferative immunomodulating agent than either drug. The pharmacodynamic properties of pomalidomide are of potential therapeutic benefit in the treatment of various hematologic neoplasms (MM, myelofibrosis with myeloid metaplasia [MMM]).

2.2.1.1 Mechanism of Action

IMiD compounds may affect the immune system in several ways, such as inducing immune responses, enhancing activity of immune cells, altering and modulating the induction of pro- and anti-inflammatory cytokines, and inhibiting inflammation [8]. IMiD compounds are also

antiangiogenic. Although their precise mechanism of action is currently under investigation, these agents offer promise for their anti-cancer and anti-inflammatory activities.

Pomalidomide has a dual mechanism of action; it is directly tumoricidal for MM cells, and it also has immunomodulatory activity with direct effects on T cell and natural killer (NK) cell-mediated immunity [8]. Pomalidomide's pleiotropic activities in a range of cell types including MM cells and immune effector cells suggests the existence of multiple molecular target molecules and downstream modulation of multiple molecular pathways. The possibility exists that a common molecular mediator present in various cell types that is proximal to the downstream modulation of multiple signaling pathways is involved in the inhibition of proliferation and induction of apoptosis in tumor cells and in the activation of immune effector cells. Cereblon (CRBN), a substrate receptor for the E3 ubiquitin ligase complex, is required for the teratogenic effects of thalidomide in zebrafish and chicken embryos; forms a ubiquitin E3 ligase complex with DNA damage-binding protein 1 (DDB1), cullin 4 (CUL4), and protein Roc1; and thalidomide treatment has been shown to inhibit the ubiquitin ligase activity of the complex [9]. Pomalidomide and lenalidomide are more potent structural analogs of thalidomide and it was demonstrated that both pomalidomide and lenalidomide interact with human cereblon [8]. Upon engagement with cereblon, the thalidomide analogs lenalidomide and pomalidomide induce ubiquitination and proteasomal degradation of two key transcription factors Ikaros (encoded by the gene IKZF1) and Aiolos (encoded by the gene IKZF3) that regulate immune cell development and homeostasis [10]. Pomalidomide and lenalidomide bind human cereblon and the expression of CRBN in myeloma cells is linked to both the efficacy of pomalidomide and lenalidomide and to the acquisition of resistance to lenalidomide [11]. In activated human T cells in which CRBN was transiently decreased, IL-2 and TNF-α induction by pomalidomide was markedly reduced. Since IL-2 and TNF-α are important for tumor surveillance by activated T cells, these results indicate that some of the immunomodulatory effects of pomalidomide are mediated via initial binding to CRBN.

An important aspect of the clinical use of lenalidomide is that tumors can acquire resistance to lenalidomide over time [12-14]. *In vitro* studies of long-term exposure to increasing concentrations of lenalidomide until the cells were resistant to its anti-proliferative effects indicated that CRBN expression decreased concurrently with the decrease in efficacy of lenalidomide [14]. However, pomalidomide maintained efficacy, although somewhat lower potency, in these lenalidomide resistant cells. It is not clear why pomalidomide was still efficacious in cells in which the concentration of CRBN was relatively decreased. It is possible that these molecules interact differentially with other proteins or induce a different conformational change in CRBN, resulting in differential effects within the context of the E3 ligase complex [11]. In a MM cell line made resistant to lenalidomide and pomalidomide, CRBN was undetectable, supporting the conclusion that CRBN is essential for the activity of these immunomodulatory compounds.

2.2.1.2 Non-Clinical Studies

The pleiotropic activities of pomalidomide on a range of cell types including MM cells and immune effector cells suggest modulation of multiple molecular pathways [8]. Indeed, activity of pomalidomide and lenalidomide are cell type- and context-dependent [15-20];;. Activities

include effects on the cell cycle such as G0/G1 arrest associated with the upregulation of the cyclin dependent kinase (CDK) inhibitor p21WAF-1 [19], downregulation of the expression of interferon regulatory factor 4 (IRF4) in MM cell lines,[21], and modulation of Rho guanosine-5'-triphosphate binding and hydrolyzing enzymes (GTPases) which are critical for actin hyperpolymerization and immune synapse formation [20].

Pomalidomide has potent anti-inflammatory activity *in vitro* [8]. Specifically, in lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMC), the pomalidomide tumor necrosis factor-α (TNF-α) 50% inhibitory concentration (IC50) is ~13 nM [22]. Pomalidomide also inhibits LPS-induced PBMC production of the pro-inflammatory cytokines and chemokines interleukin (IL)-1β, IL-6, IL-12, monocytes chemoattractant protein (MCP-1), macrophage inflammatory protein (MIP)-1α and elevates production of the anti-inflammatory cytokine IL-10. Pomalidomide augments T helper cell type 1 (Th1) (cell-mediated) and inhibits T helper cell type 2 (Th2) (humoral-mediated) T cell responses [8]. Pomalidomide enhances T cell proliferation and production of the Th1 cytokines IL-2 and interferon gamma (IFN-γ) by freshly isolated human peripheral T cells *in vitro* [23]. Moreover, the addition of pomalidomide to naive splenocytes stimulated *in vitro* with immobilized anti-CD3 antibody enhanced the production of IL-2, IFN-γ, and granulocyte macrophage colony stimulating factor (GM-CSF), while suppressing the production of the Th2 cytokines IL-4 and IL-10 [16].

Pomalidomide exerts multiple effects on the immune system and also demonstrates anti-fibrotic activity *in vivo [8]*. Therefore, in addition to its beneficial activities in relapsed/refractory MM, pomalidomide provides a potentially new treatment alternative for conditions that possess altered immunological parameters related to inflammation, fibrosis, and Th2 response, such as scleroderma. Pomalidomide also affects the regulation of fetal hemoglobin (hemoglobin F; [HbF]) expression by erythroid precursors from healthy adults as well as adults with sickle cell disease (SCD), making it a potential therapeutic agent for the treatment of nonmalignant hematologic disorders such as SCD and β-thalassemia.

Nonclinical safety pharmacology studies showed no major safety concerns on cardiac function in dogs and monkeys, central nervous system (CNS) functions in rats, or respiratory functions in rats and monkeys [8].

In rats and monkeys, pomalidomide exhibited low systemic clearance and a moderate volume of distribution [8]. The oral bioavailability was dose dependent. Following intravenous (IV) or oral administration of the enantiomers of pomalidomide, there was notable interconversion (18% to 32% based on area under the plasma concentration-time curve [AUC] ratios) between the enantiomers in monkeys.

[^{14}C]-pomalidomide-derived radioactivity was widely distributed into tissues in pigmented male rats, and moderate distribution of pomalidomide into the brain was observed in mice and rats [8]. Pomalidomide was detected in fetal blood following administration to pregnant rabbits. In lactating rats, pomalidomide was excreted into milk. In rats, monkeys, and humans, the urinary excretion of metabolites was a major route of clearance for the absorbed fraction of [^{14}C]-

pomalidomide, while urinary excretion of unchanged drug was minor. Intact pomalidomide represented a predominant portion of the circulating radioactivity in all species. In rats, monkeys, and humans *in vivo*, as well as *in vitro* in human and rabbit hepatocytes, pomalidomide was metabolized via hydrolysis of the glutarimide and phthalidmide rings and hydroxylation of phthalimide aryl ring (with subsequent glucuronidation). These data demonstrate similar metabolic pathways for pomalidomide in humans and animal species used in toxicity studies.

Pomalidomide is not a cytochrome P (CYP) isoenzyme inhibitor or inducer, and did not inhibit any of the drug transporters evaluated, including P-glycoprotein, breast cancer resistant protein (BCRP), organic anion transporter protein (OATP)1B1, OATP1B3, organic anion transporters (OAT)1 and OAT3, and organic cation transporter (OCT)2, at clinically relevant concentrations in vitro studies [8].

Pomalidomide has a low potential for acute toxicity in rodents [8]. The minimum lethal doses after oral administration was >2000 mg/kg, and >80 mg/kg and >50 mg/kg after IV dosing in mice and rats, respectively. Oral administration of pomalidomide to rats for 6 months was well-tolerated at doses up to 1000 mg/kg/day, and this dose was established as the no-observed-adverse-effect-level (NOAEL). Oral administration of pomalidomide to monkeys for 9 months was well tolerated at 0.05 and 0.1 mg/kg/day, and 0.1 mg/kg/day was established as the NOAEL corresponding to the AUC over 24 hours (AUC_{24h}) of 227, and 211 ng•hr/mL on Day 272 for males and females, respectively (approximately 0.5-fold exposure ratio relative to a 4 mg clinical dose). In the 1 mg/kg/day dose, test article-related morbidity and early euthanasia (3/sex) were observed and were attributed to immunomodulation/immunosuppression (decreased peripheral lymphocytes, histologic lymphoid depletion, and hypocellularity of bone marrow). These immunosuppressive effects were associated with staphylococcal infection and chronic inflammation of the large intestine. Villous atrophy of the small intestine and minimal and mild bile duct proliferation were also present. In addition, findings consistent with AML were observed in 1 of the females that was terminated early. Evaluation of recovery animals indicated that all treatment related findings were reversible after 8 weeks of dosing cessation, except for proliferation of intrahepatic bile ducts observed in 1 animal in the 1.0 mg/kg/day group.

In a fertility and early embryonic development study in rats, pomalidomide treatment of males and females resulted in a decrease mean number of viable embryos and an increase in post-implantation loss at dosages of 25 mg/kg/day or higher [8]. These effects were not observed when treated males were mated with untreated females. The NOAEL was <25 mg/kg/day (AUC_{24h} was 39960 ng•h/mL at this lowest dose tested, and the exposure ratio was 99-fold relative to a 4 mg clinical dose). Pomalidomide was found to be teratogenic in both rats and rabbits when administered during the period of major organogenesis. The NOAELs for developmental toxicity were <25 mg/kg/day for rat (AUC_{24h} was 34340 ng•h/mL on Gestation Day 17 at this lowest dose tested, and the exposure ratio was 85-fold relative to a 4 mg clinical dose) and <10 mg/kg/day for rabbit (AUC_{24h} was 418 ng•h/mL on Gestation Day 19 at this lowest dose tested, which was similar to that obtained from a 4 mg clinical dose).

Pomalidomide was also assessed for immunotoxicity in monkeys after treatment at 2 mg/kg/day for 28 days and had no impact on the innate immune system (granulocyte, monocyte, and NK cell function) [8]. However, effects on the adaptive immune system, including peripheral blood

lymphocyte depletion, alterations in humoral immune system, decreases in thymic weight, and general lymphoid depletion in lymphoid organs, were evident. Most of the observed effects recovered or partially recovered after a 30-day drug-free period.

Pomalidomide was not mutagenic in bacterial and mammalian cells and did not induce chromosomal aberrations in human peripheral blood lymphocytes or micronuclei formation in polychromatic erythrocytes in bone marrow of rats administered doses up to 2000 mg/kg/day [8]. Carcinogenicity studies have not been conducted.

2.2.1.3 Clinical Studies

The clinical program comprises safety and efficacy evaluations of pomalidomide for relapse or refractory MM, MMM, MPN-associated myelofibrosis, metastatic prostate cancer, advanced soft tissue sarcoma, small cell lung cancer, and non-oncology indication with SCD and SSc [8]. As of February 7, 2020, 26 studies using pomalidomide have been completed. Over 30 clinical trials have been conducted (started, completed, and/or ongoing) across these therapeutic indications. Across these studies, the pharmacokinetic (PK) profiles of single and multiple doses of pomalidomide from 0.5 mg to 50 mg, and 0.5 mg to 5 mg, respectively, have been evaluated in over 300 patients.

2.2.1.4 Clinical Pharmacology/Pharmacokinetic Studies

2.2.1.4.1 Human Pharmacokinetics (PK)

As of February 7, 2020, 13 clinical studies have characterized the clinical pharmacology and biopharmaceutics of pomalidomide [8]. Pharmacokinetic data have been collected from 306 patients who have received at least one dose of pomalidomide. PK profiles of single and multiple doses of pomalidomide from 0.5 mg up to 50 mg, and 0.5 mg up to 5 mg, respectively, have been evaluated. In general, the PK results were similar between healthy and MM patients.

2.2.1.4.2 Absorption

Pomalidomide was absorbed in healthy patients under fasting conditions at single, orally administered doses of 0.5 to 50 mg with a maximum plasma concentration (C_{max}) at a median time (t_{max}) of approximately 3 hours post dose [8]. The systemic exposure of single dose pomalidomide as determined from the AUC (AUC from time zero to the last measurable time point [AUC_{0-t}] and AUC from time zero extrapolated to infinity [$AUC_{0-\infty}$]) increased in an approximately dose proportional manner, whereas C_{max} increased in a proportional manner over 0.5 mg to 2 mg and in a less than dose proportional manner over the 1 mg to 50 mg dose range. Exploratory analysis suggests absorption rate decreases at doses greater than 10 mg. Multiple dose exposure over the 0.5 mg to 2 mg dose range was approximately dose proportional, with pomalidomide reaching steady state by Day 3.

2.2.1.4.3 Distribution

Mean (% coefficient of variation [CV]) apparent total volume of distribution when dosed orally (Vz/F) of pomalidomide in healthy patients after a single dose ranged from 74 L (20%) to 138 L

(30%) across a dose range of 1 mg to 10 mg daily [8]. Pomalidomide distributes into semen, with a geometric mean concentration of 16.4 ng/mL at 4 hours post-dose after 4 daily doses of 2 mg. This was approximately 67% of pomalidomide plasma concentration observed at the same time point on Day 5. *In vitro* data indicate that pomalidomide protein binding in human plasma was low to moderate (15.8% for R-enantiomer, 42.2% for S-enantiomer) and the binding was concentration independent in the concentration range of 30 and 1000 ng/mL.

2.2.1.4.4 Metabolism

A [^{14}C]-pomalidomide study showed that the majority of circulating total radioactivity was associated with pomalidomide (~70%) [8]. Pomalidomide is a racemic mixture of R- and S-enantiomers, CC-6016 and CC-5083, respectively. The mean C_{max} and AUC_{0-t} values for CC-6016 were approximately 49% and 50%, respectively, and for CC-5083 were approximately 52% and 49%, respectively, of those observed for pomalidomide in plasma, indicating that the R- and S-enantiomers were present in approximately equal amounts. Eight metabolites were detected in plasma, each at exposures <10% of the plasma pomalidomide. The metabolites observed were formed primarily via hydroxylation with subsequent glucuronidation, or hydrolysis of the parent compound. CYP-dependent metabolites accounted for approximately 43% of the excreted radioactivity, while non-CYP dependent hydrolytic metabolites accounted for 25%, and excretion of unchanged pomalidomide accounted for 10%. There were no unique or disproportionate metabolites observed in humans compared with *in vivo* data from rats and monkeys. These metabolites have shown no or weak activity in MM cell proliferation screens and the immunomodulatory assays and are unlikely to contribute significantly to these pharmacological activities of the parent compound.

2.2.1.4.5 Elimination

Pomalidomide is eliminated predominantly through renal excretion (~73% of the administered dose), with < 3% of the administered dose excreted in urine as unchanged pomalidomide across all dose levels, indicating extensive metabolism prior to excretion [8]. The radioactivity in feces (15.5% of the dose) contained parent compound (approximately 8% of the dose) and several metabolites. The metabolites in excreta were formed via similar pathways as those observed in plasma. Based on the *in vivo* rat, monkey and human metabolism data, there were no unique or disproportionate metabolites observed in humans. The geometric mean terminal elimination half-life ($t_{1/2}$) of pomalidomide was approximately 7.5 hours and the apparent total plasma clearance (CL/F) generally ranged from 6.5 to 10.8 L/hr. CL/F and $t_{1/2}$ in plasma appeared to be independent of dose and dosing duration.

2.2.1.4.6 Drug-Interactions

As a substrate, since pomalidomide is eliminated in humans via multiple pathways (CYP mediated metabolism, enzymatic and non-enzymatic hydrolysis, and excretion of unchanged drug), and several CYP enzymes are capable of metabolizing pomalidomide, namely CYP1A2, CYP3A4, and to a minor extent CYP2C19 and CYP2D6, it is not anticipated that coadministration of an inhibitor or inducer of any one of these CYPs will have a significant impact on pomalidomide pharmacokinetics [8]. Co-administration with dexamethasone (a weak

to moderate inducer of several CYP enzymes including CYP3A) did not affect the PK profile of pomalidomide in MM patients. Coadministration of a strong CYP1A2 inhibitor (fluvoxamine) with pomalidomide in the presence of a strong CYP3A4 inhibitor (ketoconazole) approximately doubled the mean exposure to pomalidomide compared to pomalidomide with ketoconazole alone. If strong inhibitors of CYP1A2 (*e.g.*, ciprofloxacin, enoxacin, and fluvoxamine) are coadministered with pomalidomide, patients should be closely monitored for the occurrence of side effects.
Pomalidomide is a substrate of P-glycoprotein (P-gp). P-gp in MDCK cells, although intestinal absorption did not appear to be limited by P-gp interaction (Investigator's Brochure, 2020). In the human absorption, metabolism and elimination (AME) study, at least 73% of the dose was absorbed, indicating good oral absorption. Additionally, parent drug is the major circulating entity, and any effect of P-gp inhibition on the minor metabolites is unlikely to have any clinical impact.

2.2.1.4.7 Food Effects

Two studies have assessed the effects of food on pomalidomide [8]. The median T_{max} observed in the fed state was approximately 3 hours later than that observed in the fasted state. Exposure to pomalidomide was slightly decreased with food. The mean ratio estimates for C_{max} and AUC_{0-t} were 75.6% and 91.5% in the fed state relative to the fasted state. The mean $t_{1/2}$ of pomalidomide was not affected by food administration. In summary, a high fat meal decreased the rate of absorption but had minimal effect on overall extent of absorption; therefore, pomalidomide can be administered without regard to food intake.

2.2.1.5 Safety and Efficacy Clinical Studies

Pomalidomide was safe at doses of up to 50 mg in a phase 1 single dose study in normal, healthy male volunteers and the maximum tolerated dose (MTD) was determined to be 5 mg every other day (QOD) or 2 mg daily (QD) in a phase 1 multidose clinical study in patients with relapsed or refractory multiple myeloma (RRMM) [8]. Dose-limiting toxicities (DLTs) seen in patients receiving higher doses were predominantly hematopoetic (*i.e.*, neutropenia), and lower grade, self-limited neutropenia was also seen in some of the 1 and 2 mg QD and 5 mg QOD recipients. In a multidose, phase 2 clinical study of patients with prostate cancer, 2 mg QD dosing was well tolerated and, unlike the MM patients who received 1 and 2 mg QD doses, only an overall shift to lower neutrophil counts was noted. No clinically relevant neutropenic adverse events (AEs) were observed, and no grade 3 or 4 neutropenic events occurred. It is, therefore, likely that patients with solid tumors that do not extensively involve the bone marrow will have a higher pomalidomide MTD than patients with hematologic malignancies.

At tolerated doses (MTD=2 mg QD and 5 mg QOD), pomalidomide has been shown to be active in patients with relapsed or refractory MM [8, 24, 25]. In 45 patients who received doses of pomalidomide ranging, by cohort, up to 10 mg daily, the most commonly occurring DLT was reversible neutropenia. As with other IMiDs administered to patients receiving concomitant systemic steroids, deep vein thrombosis (DVT) was seen (in one patient each in this study and in its subsequent named patient supply rollover program) [8, 26].

Preliminary efficacy and safety data from an ongoing phase 2 study, led by Martha Lacy *et al*. (Mayo Clinic), were published [27, 28]. Sixty patients with relapsed or refractory MM were enrolled. Pomalidomide was given orally at a dose of 2 mg daily on Days 1-28 of a 28-day cycle and dexamethasone was given orally at a dose of 40 mg daily on Days 1, 8, 15, 22 of each cycle. Patients also received aspirin 325 mg once daily for thromboprophylaxis. The study endpoints were the response rate in patients taking pomalidomide plus dexamethasone, including patients with lenalidomide resistant refractory MM, and safety of pomalidomide plus dexamethasone. Responses were recorded using the criteria of the International Myeloma Working Group. Thirty-eight patients achieved objective response (OR) (63%) including CR in 3 patients (5%), very good partial response (VGPR) in 17 patients (28%), and partial response (PR) in 18 patients (30%). The CR + VGPR rate was 33%. grade 3 or 4 hematologic toxicity occurred in 23 patients (38%) and consisted of anemia in three patients (5%), thrombocytopenia in two patients (3%) and neutropenia in 21 (35%). Among those that developed grade 3/4 neutropenia, all first experienced the neutropenia in Cycle 1-3; no new patients experienced grade 3/4 neutropenia in Cycle 4 or later. The most common non-hematological grade 3/4 toxicities were fatigue (17%) and pneumonia (8%). Other grade 3/4 non-hematological toxicities that occurred in less than 5% included diarrhea, constipation, hyperglycemia, and neuropathy. One patient (1.6%) had a thromboembolic event of deep vein thrombosis.

Lacy *et al*. have also demonstrated promising clinical activity of pomalidomide in myeloma patients with persistent disease following lenalidomide treatment [28]. A Celgene sponsored phase 1b/2 multi-center, randomized, open-label, dose escalation study evaluated the MTD, safety and efficacy of oral pomalidomide alone and in combination with low-dose dexamethasone in patients with relapsed and refractory MM. Eligible patients must have received at least 2 prior regimens and all patients must have received prior treatment that includes lenalidomide and bortezomib. This study consisted of a phase 1 single agent pomalidomide MTD segment and phase 2 randomized (pomalidomide plus low-dose dexamethasone versus pomalidomide alone) segment.

The MTD was 4 mg 21/28 days (there were 4 drug-related DLTs [grade 4 neutropenia] at 5 mg). Neutropenia and anemia were the most common grade 3/4 toxicities; there was a dose-dependent increase in grade 4 neutropenia. Based on the safety and response data, 4 mg 21/28 days was the dose for the phase 2 segment [29]. Phase 2 of the study was designed to evaluate the efficacy and safety of pomalidomide at the MTD alone and in combination with low dose dexamethasone and enrolled 221 patients. There were 113 pomalidomide + dexamethasone-treated patients and 108 pomalidomide treated patients. Median follow up was 14.2 months. Reported outcomes results for the pomalidomide and dexamethasone versus the pomalidomide only groups included the following: median PFS was 4.2 and 2.7 months (hazard ratio=0.68, P=.003), ORRs were 33% and 18% (P=.013), median response duration was 8.3 and 10.7 months, and median OS was 16.5 and 13.6 months, respectively. The most common grade 3-4 toxicity was neutropenia (41% in pomalidomide and dexamethasone and 48% in pomalidomide alone) [30].

Pre-clinical data and the prior experience with thalidomide and lenalidomide in the treatment of patients with MMM provide the rationale for the use of pomalidomide in patients with MMM. This is further supported by the results of a Celgene sponsored trial which indicated that pomalidomide therapy at 0.5 mg or 2 mg/day +/- an abbreviated course of prednisone 30 mg is

well tolerated in patients with myelofibrosis and active in the treatment of anemia [31]. After a median treatment period of 4.6 months, the anemia response rates in four arms were 23% (pomalidomide 2 mg/placebo), 16% (pomalidomide/prednisone), 36% (pomalidomide 0.5 mg/prednisone) and 19% (pomalidomide 0.5 mg/placebo). Response was durable and ranging from 3.2 to 16.9 + months.

Across the ongoing studies with available data, SAEs were reported by approximately 50% to 60% of patients. The safety profile in these studies may be expected in a population with advanced disease such as that participating in these studies and is consistent with that seen in the completed studies.

2.3 Other Agent

2.3.1 Daunorubicin and cytarabine liposome

Liposomal delivery systems for anthracyclines are a promising strategy to mitigate cardiotoxicity while maintaining efficacy [32-34]. The potential advantages of liposomal preparations include 1) prolonged time in the circulation due to protection of the drug from enzymatic inactivation; 2) altered bio-distribution of the liposome formulation with potential sparing of normal tissue to mitigate toxicity; and 3) circumvention of drug efflux transporters responsible for drug resistance [35-38]. Daunorubicin and cytarabine liposome liposome for intravenous administration is a fixed combination of daunorubicin (44 mg) and cytarabine (100 mg) in a 1:5 molar ratio encapsulated in liposomes. The liposome membrane is made of distearoylphosphatidylcholine (DSPC), distearoylphosphatidylglycerol (DSPG), and cholesterol in a 7:2:1 molar ratio.

The 1:5 molar ratio of daunorubicin:cytarabine has been shown to have synergistic effects at killing leukemia cells *in vitro* and in murine models. Daunorubicin has antimitotic and cytotoxic activity, which is achieved by forming complexes with DNA, inhibiting topoisomerase II activity, inhibiting DNA polymerase activity, affecting regulation of gene expression, and producing DNA-damaging free radicals. Cytarabine is a cell cycle phase-specific antineoplastic agent, affecting cells only during the S-phase of cell division. Cytarabine acts primarily through inhibition of DNA polymerase. Based on animal data, the liposomes enter and persist in the bone marrow, where they are taken up intact by bone marrow cells. In leukemia-bearing mice, the liposomes are taken up by leukemia cells to a greater extent than by normal bone marrow cells. After cellular internalization, liposomes undergo degradation releasing cytarabine and daunorubicin within the intracellular environment.

Based on positive phase 3 findings, daunorubicin and cytarabine liposome was approved by the FDA in August 2017 for the treatment of adults with newly diagnosed therapy-related AML or AML with MDS changes. Prior studies have demonstrated the importance of ratio-dependent synergy and antagonism for combinations of cytarabine and daunorubicin. Maintaining a fixed ratio is difficult when using combinations of free drugs given the different distribution, metabolism, and elimination properties of the individual drugs. In preclinical models, daunorubicin and cytarabine liposome provided elevated and prolonged drug concentrations that were orders of magnitude higher than free drug and also higher daunorubicin concentrations compared to Daunoxome (DNX), a liposomal anthracycline. When daunorubicin and cytarabine

liposome was given Days 1, 3, and 5 in the adult Phase 1 study, the clearance of cytarabine and daunorubicin was less than 120 mL/h/m2 across all dose levels. This is markedly less than the clearance of unencapsulated daunorubicin (38,600 mL/h/m2) and cytarabine (134,000 mL/h/m2) and results in striking differences in plasma elimination half-life when comparing daunorubicin and cytarabine liposome with free drug or with DNX [39, 40]. Of interest, there is almost no distribution phase of daunorubicin and cytarabine liposome, suggesting that virtually all detectable daunorubicin and cytarabine liposome in the plasma exists in the encapsulated form. In addition, these concentrations are maintained in the circulation at the synergistic daunorubicin to cytarabine 1:5 ratio [41-43]. Therefore, CPX 351 accumulates and persists in the bone marrow at drug concentrations many fold higher than free drugs and significantly higher than DNX. Further, liposome encapsulation may result in the drug being selectively taken up by the leukemia cells with subsequent release of cytarabine and daunorubicin from intracytoplasmic liposomes [41].

A number of studies of daunorubicin and cytarabine liposome have been conducted in both *de novo* and relapsed/refractory adult AML. The adult Phase 1 study of daunorubicin and cytarabine liposome reported DLT at 134 units/m^2. The DLTs were persistent cytopenia > 56 days (1 patient), congestive heart failure (CHF) (1 patient), and hypertensive crisis (1 patient) [44]. The episode of CHF occurred during a period of sepsis and was transient. Two phase 2 studies in adults demonstrated superior response rates and improved overall survival (OS) among patients with unfavorable risk features [7]. A randomized phase 3 study comparing daunorubicin and cytarabine liposome vs. 7+3 in older adults (60 to 75 years) with high-risk AML/MDS reported significantly improved complete response (CR) rates and OS in the daunorubicin and cytarabine liposome arm. Importantly, 60-day mortality due to progressive AML was significantly different between the daunorubicin and cytarabine liposome (3.3%) and 7+3 cohorts (11.3%). More patients treated with daunorubicin and cytarabine liposome received HSCT compared to those on the standard arm (34% daunorubicin and cytarabine liposome *vs*. 25% 7+3). An intent to treat OS analysis, landmarked at hematopoietic stem-cell transplantation (HSCT), demonstrated marked benefit for those randomized to the daunorubicin and cytarabine liposome arm (HR-0.46, p=0.0046). Although MRD data was not collected, this would suggest that patients with daunorubicin and cytarabine liposome had lower disease burden at time of HSCT compared to those who received standard 7+3 chemotherapy. The aforementioned clinical trial results in adults led to FDA approval of daunorubicin and cytarabine liposome for adult patients with newly diagnosed therapy-related AML or AML with MDS-related changes.

Standard dosing will be used for daunorubicin and cytarabine liposome. For induction, the dose is 44 mg/m^2 daunorubicin and 100 mg/m^2 cytarabine liposome IV infusion for 90 min on Days 1, 3, and 5. If needed, patients may undergo re-induction on Day 1 and 3 using the same dosing as the initial induction. Dosing for consolidation will be 29 mg/m^2 daunorubicin and 65 mg/m^2 cytarabine liposome IV infusion on days 1 and 3.

2.4 Rationale

2.4.1 Rationale for Current Study Design:

Multiple innate and adaptive immune system aberrations that promote leukemia immune escape

occur at diagnosis leading to immune suppression, exhaustion and senescence [45-47]. This immune dysfunction persists throughout disease progression in AML. We and others have shown that co-inhibitory molecules and senescence markers are expressed by $CD8^+$ T cells at diagnosis leading to T cell dysfunction [48-50]. Our recent analysis demonstrates that the dysfunctional phenotypic and transcriptional signatures of $CD8^+$ T cells are reversed in patients who achieve CR in contrast to non-responders, suggesting that immune modulation may provide benefit for patients who have not responded to intensive chemotherapy [48]. One of the predominant mechanisms of immune dysfunction in AML is related to the dysregulation of regulatory T cells (T_{regs}). T_{regs} are increased in the peripheral blood and bone marrow of AML patients [51-53], exhibit immunosuppressive effects on T effector cells [53], are minimally affected by chemotherapy [54], and are associated with worse outcomes in AML [52]. Our group demonstrated that early lymphocyte recovery (ELR), defined by the total white blood cell (WBC) count reaching $\geq 0.2 \times 10^9$/L above nadir, and customarily occurring between Days 14-21 of timed-sequential induction therapy (TST), is dominated by an expanded oligoclonal population of peripherally-derived T_{regs} [55]. These findings provided the impetus for a CTEP-sponsored phase 1 dose escalation study of pomalidomide, a potent immunomodulatory agent, administered at the time of ELR after induction TST in newly diagnosed AML and high-risk MDS. Through its interaction with cereblon, a substrate receptor for the E3 ubiquitin ligase complex, pomalidomide leads to the selective ubiquitination of transcription factors Ikaros and Aiolos thereby increasing IL-2 production [10].

In this phase 1 study, all patients received TST with AcDVP16 (cytarabine 667 mg/m^2/day continuous infusion [CI] IV Days 1-3, daunorubicin 45 mg/m^2 IV Days 1-3 [or idarubicin 8 mg/m^2 during daunorubicin shortage], and etoposide 400 mg/m^2 IV Days 8-10). Pomalidomide was administered orally at the time of ELR, after Day 14 of induction therapy and within 3 days of ELR, but no later than Day 30 of induction therapy (median Day 21) to 43 patients with newly diagnosed AML with non-favorable cytogenetics (n=39) and high-risk MDS (n=4). The MTD of pomalidomide was 4 mg for 21 days at ELR. Pomalidomide was well tolerated and drug-related grade ≥3 toxicities are shown in Table 1. Of those treated with AcDVP16 + pomalidomide, 33 (77%) patients achieved a CR/CRi (Table 2). Subset analyses revealed an encouraging CR rate in those with secondary AML (71% CR), AML with MDS-related changes (MRC: 85% CR), and those with unfavorable-risk cytogenetics (82% CR). Laboratory correlates from samples obtained from patients on this study revealed that pomalidomide significantly decreased Aiolos expression, induced T cell differentiation, proliferation and cytokine production, and led to distinct gene expression changes in immune function-related ontologies in $CD4^+$ and $CD8^+$ T cells [56].

Table 1: Non-hematologic grade ≥3 toxicities possibly related to pomalidomide

Adverse Event	**2 mg x 10 days (n=3)**	**4 mg x 10 days (n=3)**	**8 mg x 10 days (n=7)**	**4 mg x 21 days (n=25)**	**8 mg x 21 days (n=5)**
Infectious					
Febrile neutropenia		1	3	5	1
Lung infection				1	
Sepsis				1	

Electrolyte Abnormalities		
Hypokalemia	1	
Hepatic		
ALT elevation	1	1
AST elevation		1
Pulmonary		
Hypoxia	1	
Respiratory Failure		1
Renal		
Acute kidney injury	1	
General		
Fatigue	1	
Maculo-papular rash	5	1

Table 2: Summary of response characteristics

Response characteristics	**MDS (*n* = 4)**	**AML (*n* = 39)**	**Overall pom-treated (*n* = 43)**	**Not treated with pom (*n* = 8)**	**Overall evaluable (*n* = 51)**
CR	3 (75%)	28 (72%)	31 (72%)	4 (50%)	35 (69%)
CRi	0	2 (5%)	2 (5%)	1 (13%)	3 (6%)
Overall CR	3 (75%)	30 (77%)	33 (77%)	5 (63%)	38 (75%)
Overall CR subgroups					
Secondary AML	N/A	10/14 (71%)	10/14 (71%)	2/3 (67%)	12/17 (71%)
AML with MDS-related changes	N/A	11/13 (85%)	11/13 (85%)	2/4 (50%)	13/17 (76%)
<60 years	2/3 (67%)	21/28 (75%)	23/31 (74%)	2/3 (67%)	25/34 (74%)
>60 years	1/1 (100%)	9/11 (82%)	10/12 (83%)	3/5 (60%)	13/17 (76%)
ELN-risk (Dohner *et al.*,2017)					
Favorable	N/A	9/9 (100%)	9/9 (100%)	1/1 (100%)	10/10 (100%)
Intermediate	N/A	12/17 (71%)	12/17 (71%)	1/2 (50%)	13/19 (68%)
Adverse	N/A	9/13 (69%)	9/13 (69%)	3/4 (75%)	12/17 (71%)
SWOG cytogenetics risk [57]					
Favorable	N/A	N/A	N/A	N/A	N/A
Intermediate	1/1	16/23 (70%)	17/25 (68%)	3/3 (100%)	20/28 (71%)
Unfavorable	2/3 (67%)	12/14 (86%)	14/17 (82%)	2/4 (50%)	16/21 (76%)
Unknown	N/A	2/2 (100%)	2/2 (100%)	0/1 (0)	2/3 (67%)
4 mg × 21 days (MTD)	3/4 (75%)	15/21 (71%)	18/25 (72%)	N/A	18/25 (72%)

AML patient characteristics	**AcDVP16 historical controls *n* = 301 (6)**	**AcDVP16 + pomalidomide *n* = 39**
Median age (range)	52 (20–74)	54 (21–65)
Overall CR/CRi	205/301 (68%)	30/39 (77%)
Age ≥ 60 years	45/79 (57%)	9/11 (82%)
Secondary AML	51/96 (53%)	10/14 (71%)
Cytogenetic classification		
Intermediate	133/180 (74%)	16/23 (70%)

Unfavorable	49/94 (52%)	12/14 (86%)
Non-favorable	182/274 (66%)	28/37 (76%)a
Allogeneic SCT	98/301 (33%)	23/39 (59%)
Median OS	17.2 months	33.8 months
Median OS-unfavorable-risk cytogenetics	8.2 months	19.7 months
Median DFS	15.0 months	27.1 months
Median DFS-unfavorable-risk cytogenetics	9.2 months	8.2 months

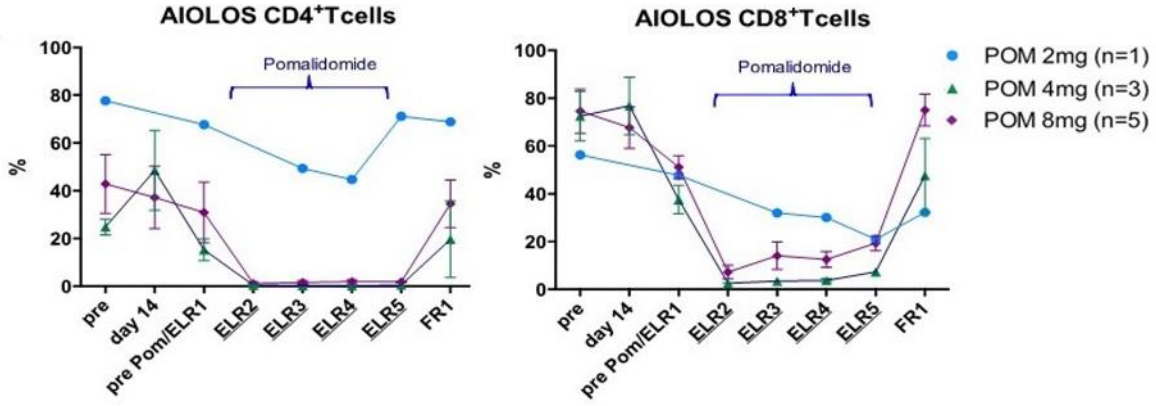
[a]Two patients had unknown cytogenetic risk per SWOG classification and were thus excluded for comparison to overall non-favorable risk.

Given the poor outcomes of patients with AML with MRC and the promising findings seen in this patient population in the phase 1 study, a randomized phase 2 study investigating the addition of pomalidomide to standard-of-care daunorubicin and cytarabine liposome in newly diagnosed AML with MRC is warranted to determine whether pomalidomide is an effective immunomodulatory adjunct after induction chemotherapy in patients with AML with MRC.

2.4.2 Justification of Pomalidomide Dose and Schedule

In the Phase 1 study of AcDVP16 followed by dose escalation of pomalidomide at ELR, pharmacodynamic (PD) analysis was performed by assessing pomalidomide's impact on Aiolos inhibition in $CD4^+$ and $CD8^+$ T cells by flow cytometry. In the initial cohort of pomalidomide dose escalation of 2 mg, 4 mg and 8 mg for 10 consecutive days at ELR, there was more robust Aiolos inhibition seen at the 4 mg and 8 mg doses when compared with 2 mg dose[58]. Additionally, there were no significant differences observed in Aiolos inhibition between the 4 mg and 8 mg doses (Figure 1).

Figure 1. Ailos Expression in CD4+ and CD8+ T cells with Increasing Pomalidomide Exposure.



Further, Aiolos expression was suppressed during pomalidomide administration only and returned to normal/baseline levels within 1 week after discontinuation of pomalidomide (Figure 2). These observations signified that the duration of pomalidomide exposure is most critical to achieve a PD effect. As such, pomalidomide dosing regimen of 4 mg for 21 consecutive days at ELR was established as the MTD and schedule after AcDVP16 induction (Table 1) [56]

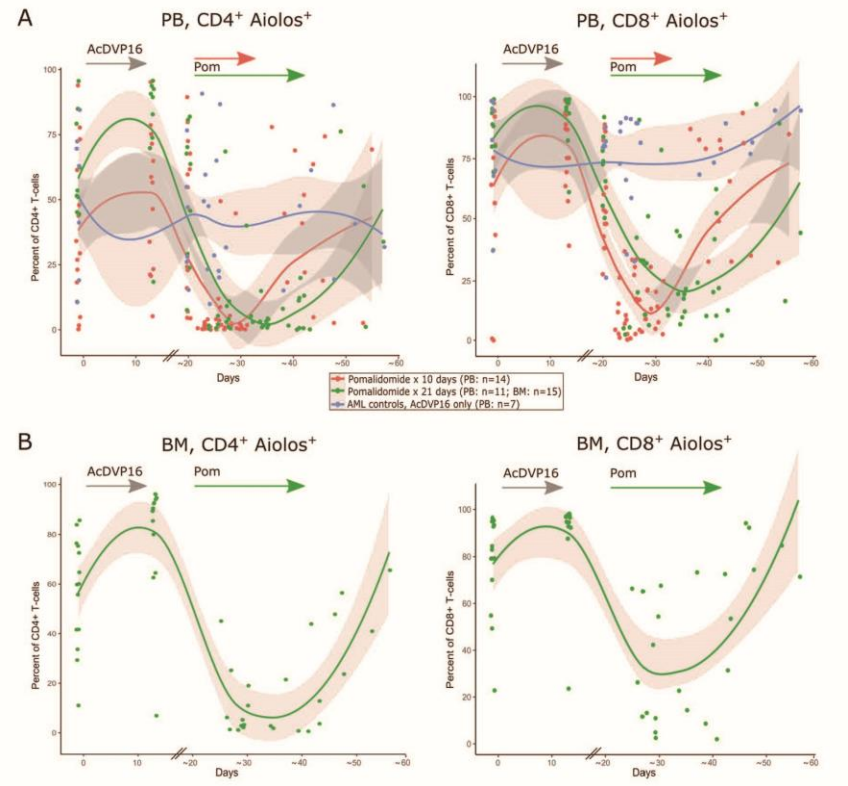
consistent with the FDA approved pomalidomide dose in multiple myeloma.

2.4.3 Rationale for Safety Run-In

The MTD of pomalidomide after AcDVP16 TST was 4 mg for 21 consecutive days at ELR. However, pomalidomide has not been investigated after daunorubicin and cytarabine liposome induction therapy. Thus, a safety run-in will be performed prior to randomization to determine the optimal schedule of pomalidomide after daunorubicin and cytarabine liposome induction. Two dosing schedules of pomalidomide will be explored in a safety run-in: 4 mg for 14 days versus 4 mg for 21 days. The recommended phase 2 dose/duration will then be used in the randomized phase 2 portion of the study after an evaluation of safety and tolerability data, efficacy, anti-tumor activity, exposure and PD effects, if available, in both cohorts.

Ultimately, we hypothesize that the addition of pomalidomide starting on day 21 of daunorubicin and cytarabine liposome induction therapy for patients with newly diagnosed AML with preexisting MDS, CMML or MPN, or AML with MRC based on cytogenetics or morphologic dysplasia without history of MDS/MPN, will lead to an improvement in CR/CRi rate compared with daunorubicin and cytarabine liposome alone.

Figure 2 Aiolos Expression Prior to, During and After Pomalidomide Administration



2.5 Correlative Studies Background

2.5.1 Integrated Correlative Studies

2.5.1.1 Foundation One Heme panel (Next Generation Sequencing Myeloid Mutational Panel)

It is standard-of-care to perform next generation sequencing (NGS) mutational panels on newly diagnosed AML patients to inform risk stratification and overall prognosis. Although there are a number of different laboratories and panels that are used for this assessment, it is critical to have a homogeneous and reproducible results with one uniform, comprehensive assay for a multicenter randomized trial. The Foundation One Heme NGS panel is a comprehensive genomic assay that interrogates 406 genes for four classes of alterations: single nucleotide variants, small insertions/deletions, copy number variants, and gene fusions. These results will be used to compare responders (*i.e*. CR/CRi) versus non-responders to determine if there is a molecular signature associated with response to pomalidomide. The NGS mutational panel is strongly recommended for all patients and bone marrow aspirates if NGS has not been performed prior to consent in order to have uniform results across all institutions. If NGS has been performed by an alternative laboratory within 30 days of consent, Foundation One Heme testing is still strongly recommended for uniform NGS testing but not required. Please notify the PI for discussion if Foundation One Heme Panel is not planning on being performed. Foundation One Heme will be collected prior to pre-treatment in both arms. Foundation One Heme Panel should be sent with clinical information and without study identification.

2.5.1.2 Aiolos Expression (Flow Cytometry)

Aiolos expression in T cells will be assessed by flow cytometry from bone marrow aspirate and peripheral blood samples prior to treatment with daunorubicin and cytarabine liposome +/- pomalidomide, during pomalidomide administration (Days 14 and 28), and at recovery. Determination of T cell expression of Aiolos is mandatory for all patients. The role of this assay is to determine whether Aiolos expression prior to treatment with daunorubicin and cytarabine liposome + pomalidomide and during pomalidomide administration is associated with response and clinical outcomes and will be compared with the Aiolos expression in the control arm samples collected at the same time points. The Aiolos expression will be examined in context with other T cell markers, to better delineate T cell differentiation and expression of co-signaling molecules and changes induced by pomalidomide administration.

Aiolos expression in T cells will be assessed in UNC and John Hopkins University (JHU) participants only. All other affiliate site participants are exempt.

2.5.1.3 Hematologics Measurable Residual Disease (MRD) Assay (Flow Cytometry and PCR-based)

In patients on both arms, MRD will be assessed by standardized flow cytometry assessment at the time of response by Hematologics, Inc. and PCR-based methodologies as standard of care. Neoplastic cells are distinguished from normal counterparts by multiparameter flow cytometry using a combination of difference from normal and leukemia-associated immunophenotype approaches, both of which allow sensitive detection of disease population based on abnormal expression of cellular antigens. Sensitivity is generally estimated at 0.5% or less of total

nucleated cells. This assay will be used uniformly to assess for MRD in patients receiving pomalidomide versus control group. Bone marrow aspirate collection is mandatory for all patients and will be collected pre-treatment and at response. Hematologics MRD should be sent with clinical information and without study identification.

2.5.2 Exploratory/Ancillary Correlative Studies

2.5.2.1 T-cell subsets (Flow Cytometry)

The purpose of the T-cell subsets assay is to assess whether pre-treatment expression of T-cell subsets (in blood *vs*. bone marrow) are associated with response to daunorubicin and cytarabine liposome + pomalidomide, as well as to assess whether pomalidomide can induce changes in T cell composition in responders versus non-responders. Bone marrow aspirate collection is mandatory for all patients and will be collected pre-treatment, Day 14, Day 28 and at response.

T-cell subsets will be assessed in UNC and JHU participants only. All other affiliate site participants are exempt.

2.5.2.2 RNA Sequencing of blasts (NGS)

mRNA-sequencing (mRNA-seq) of bulk bone marrow leukocyte samples from diagnostic samples and at response will be performed to assess for genetic subtypes and evaluation of gene expression signatures associated with immune activation and suppression in responders (*i.e*. CR/CRi) versus non-responders. mRNA-seq is mandatory for all patients and bone marrow aspirates will be collected prior to treatment and at the response assessment in both arms.

2.5.2.3 T cell receptor repertoire analysis

T cell receptor beta (TCRβ) will be amplified using mRNA isolated from CD8 + T cells in the peripheral blood. Following reverse transcription and cDNA amplification by PCR (using primers with unique sequence tags to minimize amplification bias), Illumina MiSeq sequencing libraries will be prepared by PCR ligation of barcoded sequencing adapters. Sequence data will be processed and TCRβ sequences analyzed. Each clonotype will be defined by a given variable gene (V), joining gene (J), and complementary determining region 3 (CDR3) usage. Repertoires will be evaluated V/J gene usage, CDR3 length, charge, hydrophobicity, and amino acid motifs, frequency of dominant clonotypes, shared clonotypes, and overall population diversity. Motif analysis will be done using the TEIRISIAS algorithm. Shannon entropy will be used as the index of diversity and estimated with confidence intervals for comparison of multiple populations as previously described. The Kruskal-Wallis test with Dunn's post-tests will be used to compare clonal diversity, sharing of specific sequence motifs, and IgHV mutation rate between responders vs. non-responders. Proportional hazards modeling and multivariate regression will be used to uncover relationships between continuous outcomes (DFS, OS) and repertoire characteristics.

T cell receptor repertoire analysis is mandatory for all patients and peripheral blood will be collected pre-treatment, Day 21 (for Arm A, this should be before pomalidomide) and at

response. The purpose of this assay is to determine whether pre-treatment TCR diversity is associated with response to daunorubicin and cytarabine liposome + pomalidomide *vs*. daunorubicin and cytarabine liposome alone.

2.5.3 DNA sequencing for mutation detection at complete remission

A DNA sequencing panel allowing detection of mutations present at pre-treatment will be used to assess for MRD by NGS to determine the proportion of patients who achieve an NGS MRD-negative CR after daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone. DNA isolated from bone marrow aspirates and/or blood collected at response assessment in both arms will be banked for this purpose. Patients for whom the Foundation One Heme panel (Section 2.5.1.1) on pre-treatment marrow aspirate does not identify appropriate mutations for such tracking may undergo additional sequencing on DNA stored from pre-treatment bone marrow aspirate. Sequencing will be performed in a single batch at the completion of the study, is for research purposes only and no results will be returned to patients.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Pathological confirmation of AML as defined by histologic, morphologic, or cytological evidence/confirmation of ≥20% blasts in bone marrow aspirate and/or biopsy.

3.1.2 Must meet criteria for t-AML or AML with MRC as defined by the 5th Edition of the World Health Organization (WHO) [59] Classification of Myeloid Neoplasms or the International Consensus Classification (ICC) of Myeloid Neoplasms [60]. Patients must meet one of the following criteria:

- 1) Therapy-related AML (AML derived from prior chemotherapy or radiation therapy)
- 2) AML originating from prior hematologic malignancy (MDS, CMML, or MPN)
- 3) AML with myelodysplasia-related cytogenetic abnormalities:
  - One of the following cytogenetic abnormalities:
    - Complex karyotype (3 or more unrelated chromosomal abnormalities in the absence of other class-defining recurrent genetic abnormalities as defined by WHO or ICC)
    - -7/del(7q)
    - Del(5q)/t(5q)/add(5q)
    - +8
    - i(17q)
    - -17/add(17p) or del(17p)
    - Del(20q)
    - -13/del(13q)
    - Del(11q)
    - Del(12p)/t(12p)/add(12p)
    - idicX(q13)

- 4) AML with Myelodysplasia-related mutations: Must have a mutation in one of the following genes:
  - ASXL1
  - BCOR
  - EZH2
  - RUNX1
  - SF3B1
  - SRSF2
  - STAG2
  - U2AF1
  - ZRSR2

3.1.3 No prior treatment for AML other than cytoreductive doses of hydroxyurea or leukapheresis.

3.1.4 Age ≥18 and ≤75 years on day of signing informed consent are eligible who are planned for intensive chemotherapy. Because no dosing or adverse event data are currently available on the use of pomalidomide in combination with daunorubicin and cytarabine liposome in patients <18 years of age, children are excluded from this study. Patients >75 years are not candidates for intensive chemotherapy with daunorubicin and cytarabine liposome.

3.1.5 ECOG Performance Status of 0-2 (Karnofsky ≥60%, see Appendix A).

3.1.6 Patients must have adequate organ and marrow function as defined below:

– total bilirubin	≤1.5 institutional upper limit of normal (ULN) unless due to leukemic infiltration, Gilbert's Syndrome, or hemolysis
– AST(SGOT)/ALT(SGPT)	≤5 × institutional ULN
– creatinine	≥30 ml/min creatinine clearance by cockroft-gault

3.1.7 Left Ventricular ejection fraction (LVEF) ≥50%

3.1.8 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.9 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.10 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured with undetectable HCV viral load. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.11 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac

function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

3.1.12 Females of childbearing potential (FCBP), defined as a female who: 1) has reached menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal for at least 24 consecutive months (*i.e.*, has had menses at any time in the preceding 24 consecutive months) must have a negative pregnancy test 72 hours prior to the start of study therapy. For FCBPs in Arm A, they must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting pomalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before starting pomalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix D Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix E: Pomalidomide Education and Counseling Guidance Document.

3.1.13 Ability to understand and the willingness to sign a written informed consent document. Participants with impaired decision-making capacity (IDMC) who have a legally-authorized representative (LAR) and/or family member available will also be eligible.

3.2 Exclusion Criteria

3.2.1 Patients with Wilson's Disease or Copper-related metabolic disorders.

3.2.2 Absolute blast count >30 x 10^9/L (cytoreduction with leukapheresis or hydroxyurea can be used to achieve absolute blast count <30 x 10^9/L prior to Day 1 of treatment).

3.2.3 Cumulative daunorubicin lifetime exposure >330 mg/m^2 and >180 mg/m^2 with prior mediastinal radiation therapy.

3.2.4 Patients with known active central nervous system leukemia should be excluded from this clinical trial because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. **Patients receiving intrathecal chemotherapy prophylaxis should receive pomalidomide ≥3 days after administration.**

3.2.5 Patients with uncontrolled intercurrent illness including, but not limited to, active and uncontrolled infection, symptomatic congestive heart failure, unstable angina pectoris, and cardiac arrhythmia. Patients with infection under active treatment and controlled with antibiotics are eligible.

3.2.6 Known additional malignancy (with the exception of prior hematologic malignancies that

have transformed to AML) that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, *in situ* cervical cancer or patients receiving maintenance treatments without active disease (for example, hormonal therapy for breast cancer or prostate cancer or other adjuvant chemotherapy approaches). Anti-cancer therapy as above should be discontinued >72 hours prior to Day 1 of treatment.

3.2.7 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Receipt of prior allogeneic stem cell transplant.

3.2.9 Administration of any therapy for MDS, CMML, or MPN (conventional or unconventional) must be completed by 2 weeks prior to treatment with daunorubicin and cytarabine liposome. Use of strong CYP1A2 inhibitors should be avoided.

3.2.10 Patients who are receiving any other investigational agents.

3.2.11 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pomalidomide (*e.g*. lenalidomide, thalidomide) or daunorubicin and cytarabine liposome or their excipients.

3.2.12 Development of erythema nodosum if characterized by a desquamating rash while taking thalidomide, lenalidomide, or similar drugs in the past.

3.2.13 Pregnant women are excluded from this study because pomalidomide is an immunomodulatory agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pomalidomide, breastfeeding should be discontinued if the mother is treated with pomalidomide. These potential risks may also apply to other agents used in this study. Women of childbearing potential must be willing to undergo pregnancy testing as outlined in the Time and Events Tables, Sections 11.1 and 11.2.

3.2.14 Any other medical condition that in the opinion of investigator would place patient at increased risk for toxicity during pomalidomide treatment (*i.e*. history of recurrent or serious thromboembolic events such as massive pulmonary embolism [see Section 6.2.7]).

3.3 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 patients 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.

4. REGISTRATION PROCEDURES

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 a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- 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,
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

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

An active CTEP-IAM user account and appropriate RCR registration is required to access all

CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

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

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

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

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRB Manager 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 or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status,
- 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, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile,
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

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

- An active Federalwide 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 protocol-specific requirements (PSRs).

4.2.1 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 its 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) using your CTEP-IAM username and password,
- 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 LAO-OH007, and protocol number 10434.
- Click on *Documents*, *Protocol Related Documents, and use the Document Type* filter and select *Site Registration*, download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

4.2.2 Protocol Specific Requirements for NCI Protocol 10434 Site Registration

- Completion of Site Initiation Visit to be completed before the first patient enrollment at a given site.
- Specimen Tracking System Training Requirement:
    - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
    - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
    - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
    - This training will need to be completed before the first patient enrollment at a given site.
    - Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580).

4.2.2.1 Site Registration Protocol Specific Requirement

Each site must have two trained counselors available for counseling all patients receiving pomalidomide supplied by the Division of Cancer Treatment and Diagnosis. Trained counselors must complete training using the online program provided free by Celgene, the Celgene Pregnancy Prevention Counseling Program (CPPCP). Registration for the program is done by completing the form found in Appendix G and following the directions provided in the email notification. After the training is complete, the counselors must generate a training certificate and provide it to the CTSU for documentation. Sites may not order pomalidomide until documentation for two trained counselors is provided to the appropriate office.

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 on 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 in order to receive further instruction and support.

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. 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 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 include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.4 Checking Site Registration Status

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

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 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.

4.3 Patient Registration

Prior to registering patients into Oncology Patient Enrollment Network (OPEN), participating sites are instructed to contact the Coordinating Center for the following:

• Subject Consent – Within 24 business hours of subject signing consent for the study, the Site Coordinator notifies the Project Manager by email (CPOMulticenter@med.unc.edu) with a completed new patient registration form and copies of consent.

• Eligibility Confirmation – After completion of all screening evaluations and if possible, within at least 48 business hours of anticipated study treatment start, the Site Coordinator notifies the Project Manager by email (CPOMulticenter@med.unc.edu) and includes the completed eligibility checklist and de-identified supporting source documentation. After

review of eligibility documents by the Lead Principal Investigator or designee(s), the Project Manager will email the Site Coordinator with confirmation or questions/comments regarding subject eligibility. If eligibility is confirmed, the Site Coordinator will be instructed by the Project Manager via email to proceed to patient registration in OPEN.

4.3.1 OPEN / IWRS

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 or IWRS will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- If a DTL is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site.
- 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, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in 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. IWRS system also sends an email confirmation of the registration. 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.

Patient enrollment for this study will be facilitated using the Slot Reservation System in

conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System or the IWRS Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

- Patients that have had a prescreening bone marrow biopsy will have a study slot reserved.
    - All prescreening clinical characteristics and cytogenetics from the bone marrow biopsy should be sent to the coordinating center for eligibility determination.

4.3.2 Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions on use of the STS can be found in Section 5.4.

4.3.3 OPEN/IWRS Questions?

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

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient

does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen	Send Specimens To:
Pre-treatment		
	2.5 mL Bone Marrow Aspirate (optional)- EDTA	Foundation Medicine, Inc.
	2.5 mL Bone Marrow Aspirate (mandatory)- EDTA 8 mL peripheral blood- EDTA (mandatory)	DNA sequencing- samples to be stored in Molecular Genetics Laboratory at University of North Carolina
	2 mL Bone Marrow Aspirate (Mandatory)- Sodium heparin	Hematologics
	20 mL Bone Marrow Aspirate Sodium Heparin (mandatory*) 20 mL Blood in Sodium Heparin Tube (mandatory*)	Luznik Laboratory*
	20 mL Bone Marrow Aspirate Acid Citrate Dextrose (ACD) or EDTA (mandatory) 20 mL Blood ACD or EDTA Tubes Tube (mandatory)	Tissue Procurement Facility, UNC-Chapel Hill
Day 14		
	40 mL Bone Marrow Aspirate Sodium Heparin (mandatory*)	Luznik Laboratory*
Day 21 (For Arm A, this should be before pomalidomide)		
	20 mL Blood in Sodium Heparin Tube (mandatory*)	Luznik Laboratory*
	20 mL Blood ACD or EDTA Tubes (mandatory)	Tissue Procurement Facility, UNC-Chapel Hill
Day 28 (+7 days)		
	40 mL Bone Marrow Aspirate Sodium Heparin (mandatory*) 40 mL Blood in Sodium Heparin Tube (mandatory*)	Luznik Laboratory*

Response (between Days 42 and 64)		
	2.5 mL Bone Marrow Aspirate Sodium Heparin (mandatory) 8 mL peripheral blood- EDTA (mandatory)	DNA Sequencing- samples to be stored in Molecular Genetics Laboratory at University of North Carolina
	20 mL Bone Marrow Aspirate (mandatory*) 20 mL Blood in Sodium Heparin Tube (mandatory*)	Luznik Laboratory*
	20 mL Bone Marrow Aspirate ACD or EDTA (mandatory) 20 mL Blood ACD)or EDTA Tubes (mandatory)	Tissue Procurement Facility, UNC-Chapel Hill
	2 mL Bone Marrow Aspirate (mandatory)- sodium heparin	Hematologics

**Specimens for Luznik Lab at JHU will be collected on UNC and JHU participants only.*

5.2 Summary Table(s) for Interventional Radiologist for Research Biopsies

N/A

5.3 Specimen Procurement Kits and Scheduling

5.3.1 Specimen Procurement Kits

N/A

5.3.2 Scheduling of Specimen Collections

5.3.2.1 Scheduling of Specimen Collections from UNC to the Luznik Laboratory at JHU (only applicable to UNC, no other sites will ship samples to the Luznik Laboratory).

- Blood and bone marrow should be processed on the same day of collection when possible or processed and stored locally and then sent in batches to Luznik Laboratory overnight Monday through Thursday. Do not send on Fridays.

- Processing of samples for the Luznik Laboratory should follow the Guideline in Appendix M.

5.3.2.2 Scheduling of Specimen Collections to the Tissue Procurement Facility.

- Bone marrow should be immediately ficolled to cryopreserve bone marrow mononuclear cells for shipment on dry ice to the UNC Tissue Procurement Facility for storage upon request. If unable to ficoll, bone marrow should be shipped the day of collection using

cold packs- please contact UNC TPF upon collection and shipment to alert for incoming samples.(unc_tpf@med.unc.edu). Do not send on Fridays. All specimens shipped to UNC TPF must contain appropriate labeling as outlined in section 5.4.2.1, and be accompanied by a shipping manifest.

- Blood should be immediately ficolled to cryopreserve peripheral blood mononuclear cells for shipment on dry ice to the UNC Tissue Procurement Facility for storage upon request. If unable to ficoll, bone marrow should be shipped the day of collection using cold packs- please contact UNC TPF upon collection and shipment to alert for incoming samples. (unc_tpf@med.unc.edu). Do not send on Fridays. All specimens shipped to UNC TPF must contain appropriate labeling as outlined in section 5.4.2.1, and be accompanied by a shipping manifest.

5.3.2.3 Scheduling of Specimen Collections to the UNC-Molecular Genetic Laboratory.

- Bone marrow should be shipped the day of collection when possible using cold packs. Do not send on Fridays.

- Blood should be shipped the day of collection when possible with cold packs. Do not send on Fridays.

5.3.2.4 Scheduling of Specimen Collections to Foundation Medicine

- If procuring samples on Friday, please FedEx priority overnight and specify Saturday delivery on the shipping label to ensure timely receipt.

5.3.2.5 Scheduling of Specimen Collections to Hematologics

- If shipping via FedEx for Saturday delivery, please use a Saturday delivery sticker (which Hematologics will provide) and check the Saturday delivery box on the address label. Both sticker and checked box are necessary to insure proper handling.

5.4 Specimen Tracking System Instructions

5.4.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

The Shipping List report **must** be included with all sample submissions.

5.4.2 Specimen Labeling

5.4.2.1 Blood and Bone Marrow Specimen Labels

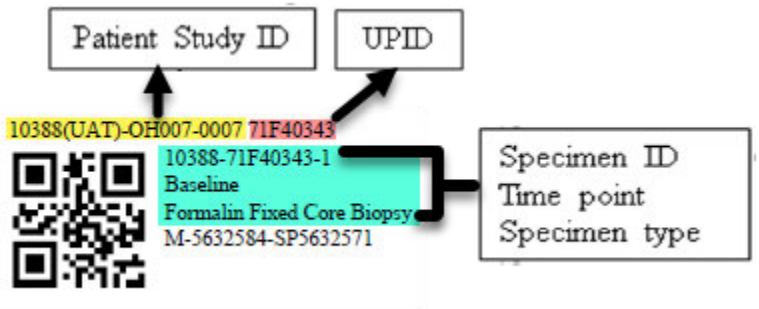
Include the following on research-only bone marrow and blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum, bone marrow)
- Laterality, if applicable (bone marrow only) (to be added by hand)
- Collection date (to be added by hand)
- This does not apply to standard-of-care testing with Foundation One Heme Panel prior to treatment and Hematologics MRD.

5.4.2.2 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5" high and 1.28" wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time. The last line on the example label is for the handwritten date and optional time.

5.4.3 Overview of Process at Treating Site

5.4.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization, and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration with eligibility specimen analysis:

1. Site enters first step data into OPEN.

2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends first step registration data, including the IDs and a TAC of "NOT REG" directly to Rave.
4. The specimen tracking system in Rave is utilized for the specimen that contributes to eligibility determination.
5. Site enters second and any subsequent step data into OPEN including results of specimen analysis.
6. IWRS receives all data from OPEN, then sends it onto Rave with either the treatment TAC or a TAC of "SCRN FAIL".
7. In addition to the specimen tracking forms completed to determine eligibility, data entry for screen failure patients should include Histology and Disease, all forms in the Baseline folder, any lab forms connected to eligibility determination, and Off Treatment/Off Study.

Any data entry errors made during enrollment should be corrected in Rave.

5.4.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date on each label. After collection, store labeled specimens as described in Section 5.4.2.
- Apply an extra specimen label to ***each*** report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Bone Marrow, Molecular Reports (up to 4), and Surgical (or Operative) reports. Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen) and/or Tissue Biopsy Verification form (when applicable). Uploaded reports should have protected health information (PHI) data, like name, date of birth, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number, diagnosis or relevant dates (such as collection date), and include the UPID and patient study ID on each document.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status.**

Step 5: Print shipping list report and prepare to ship.

- Shipping List report is available at the site level.
- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.5 Specimen Collection

5.5.1 Blood Collection

5.5.1.1 Collection of Blood in Sodium Heparin Tubes for Shipping Whole Blood

1. Peripheral blood samples will be obtained via phlebotomy.
2. Label green-top vacutainer tubes according to the instructions in Section 5.4.2.
3. Collect 10 mL blood in sodium heparin tube(s) and gently invert tube to mix.
4. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
5. If blood cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.

5.5.1.2 Collection of Blood in EDTA for Shipping Whole Blood

1. Peripheral blood samples will be obtained via phlebotomy.
2. Label lavender-top vacutainer tubes according to the instructions in Section 5.4.2.
3. Collect 10 mL blood in EDTA and gently invert tube to mix.
4. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
5. If blood cannot be shipped on the day of collection (e.g., a late scheduled collection),

then refrigerate until shipment.

5.5.2 Bone Marrow Collection

5.5.2.1 Collection of Bone Marrow aspirate in Sodium Heparin Tubes

1. Bone marrow will be collected through standard access to iliac crest.
2. Label green-top vacutainer tubes according to the instructions in Section 5.4.2.
3. Aspirate bone marrow in 4-10 mL sodium heparin tube(s) and gently invert tube to mix.
4. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
5. If bone marrow cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.

5.5.2.2 Collection of Bone Marrow aspirate in EDTA tubes (for Foundation One HEME Collections)

1. Bone marrow will be collected through standard access to iliac crest.
2. Label green-top vacutainer tubes with clinical information.
3. Aspirate bone marrow in 4-10 mL EDTA tube(s) and gently invert tube to mix.
4. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
5. If bone marrow cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.

5.5.2.3 Collection of Bone Marrow aspirate in EDTA tubes for DNA Sequencing

1. Bone marrow will be collected through standard access to iliac crest.
2. Label lavender-top vacutainer tubes according to the instructions in Section 5.4.2.
3. Aspirate bone marrow in 4-10 mL EDTA tube(s) and gently invert tube to mix.
4. Ship on day of collection (whenever possible) according to instructions in Section 5.6.
5. If bone marrow cannot be shipped on the day of collection (e.g., a late scheduled collection), then refrigerate until shipment.

5.5.2.4 Collection of Bone Marrow aspirate in EDTA tubes for RNA Sequencing (TPF)

1. Bone marrow will be collected through standard access to iliac crest.
2. Label lavender-top vacutainer tubes according to the instructions in Section 5.4.2.
3. Aspirate bone marrow in 10 mL EDTA tube and gently invest tube to mix.
4. Immediately transfer the sample to a tissue processing facility that will separate the mononuclear cells over ficoll, cryopreserve, and store in liquid nitrogen until transfer to the UNC Tissue Procurement Facility in a dry ice shipment according to instruction in Section 5.6.

5.6 Shipping of Specimens from Clinical Site to Other Laboratories

5.6.1 Shipping of Specimens to Luznik Laboratory at JHU

5.6.1.1 Specimen Shipping Instructions

Ship stored samples after processing in batches. Please coordinate shipment with PI and Luznik Laboratory at JHU. If processing not able to occur per guidelines in Appendix M, please send fresh specimens overnight to the Luznik Laboratory at JHU.

5.6.1.2 Shipping Address
Dr. Leo Luznik
Johns Hopkins Sidney Kimmel Comprehensive Cancer Center
1650 Orleans St.
Baltimore, MD 21287

5.6.1.3 Contact Information for Assistance
Dr. Leo Luznik
Leonido.luznik@bcm.edu

5.6.2 Shipping of Specimens to Tissue Procurement Facility.

5.6.2.1 Specimen Shipping Instructions

Ship cryopreserved peripheral blood mononuclear cell specimens on dry ice when requested by the PI/Project Manager. Ship overnight Monday-Thursday, excluding the day before a federal holiday. Several patients may be batched for shipment.

Ship cryopreserved bone marrow mononuclear cell specimens on dry ice when requested by the PI/Project Manager. Ship overnight Monday – Thursday, excluding the day before a federal holiday. Several patients may be batched for shipment.

5.6.2.2 Shipping Address
Tissue Procurement Facility
108 MacNider Building, CB7304
333 South Columbia St.
Chapel Hill, NC 27599

5.6.2.3 Contact Information for Assistance
Tissue Procurement Facility
Phone: 919-966-2620
unc_tpf@med.unc.edu

5.6.3 Shipping of Specimens to UNC-Molecular Genetic Laboratory

5.6.3.1 Shipping specimen Instructions

Ship fresh specimens overnight Monday-Thursday. Please send fresh samples. with cold packs.

5.6.3.2 Shipping Address

Molecular Genetics Lab
McLendon Clinical Laboratories
Outreach Services, 1st floor, East Wing
UNC Hospitals
Chapel Hill, NC - 27514

5.6.3.3 Contact Information for Assistance
Rachana Kshatriya
Phone: (984) 974-1825
Rachana.Kshatriya@unchealth.unc.edu

5.6.4 Shipping of Specimens to Foundation Medicine, Inc

5.6.4.1 Specimen Shipping Instructions

See the following link for the most up to date instructions.
https://assets.ctfassets.net/w98cd481qyp0/4qY3AxNKhJQF024FxoDmvU/cffb4094bc48e3badf125ccd5e43c645/FoundationOne_Heme_Specimen_Instructions__All_Sample_Types_.pdf

The kits for Foundation Medicine are not supplied by the study. Please follow the instructions listed on the website above for sample collection.

If procuring samples on Friday, please FedEx priority overnight and specify Saturday delivery on the shipping label to ensure timely receipt.

5.6.4.2 Shipping Address
Foundation Medicine, Inc.
7010 Kit Creek Road
Morrisville, NC 27560

5.6.4.3 Contact Information for Assistance
Phone: (888) 988-3639

5.6.5 Shipping of Specimens to Hematologics

Also see https://www.hematologics.com/shipping-instructions/hospital-shipping (cut and paste link in address bar)

5.6.5.1 Specimen Shipping Instructions

1. Complete Requisition Attach Billing & Diagnostic Information.
2. Seal Specimen in Biohazard Bag. Place Specimen in Shipping Container and Close.
3. Place Completed Requisition with Billing Information in Second Biohazard Bag & Seal.
4. Place Iceberg Cool Pack on Top of Sealed Biohazard Bag and Close Shipping Container.

5. Place Shipping Container in FedEx Diagnostic Pack & Seal. Complete and Attach Airbill. **If shipped on Friday, please mark for Saturday delivery and place Saturday delivery sticker on envelope.**
6. Call FedEx for Pick-Up (800-463-3339); Call Hematologics Client Services Dept. with Airbill Number (800-860-0934).

5.6.5.2 Shipping Address
3161 Elliott Ave. Suite 200
Seattle, WA 98121

5.6.5.3 Contact Information for Assistance
Phone: (800) 860-0934 or (206) 223-2700
FAX: (206) 223-5550

5.7 Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
1	Hematologics Flow cytometry measurable residual disease	Flow cytometry CLIA: :Y	Integrated Purpose: To assess for differences in measurable residual disease (MRD) based on flow cytometry between daunorubicin and cytarabine liposome + pomalidomide *vs* daunorubicin and cytarabine liposome	Bone Marrow	Pre-treatment Response (between Days 42 and 64)	M M	Hematologics
2	Foundation One Heme Panel	NGS/406 gene panel CLIA: Y	Integrated Purpose: To assess for genomic biomarkers of response to daunorubicin and cytarabine liposome + pomalidomide	Bone marrow	Pre-treatment	O	Foundation Medicine, Inc.
3	DNA Seq MRD	NGS CLIA: N	Exploratory Purpose: To assess for differences in measurable residual disease (MRD) based on NGS between daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome	Bone Marrow	Pre-treatment Response (between Days 42 and 64)	M M	Lab: Molecular Genetics Laboratory Contacts: Rachana Kshatriya Rachana.kshatriya@unchealth.unc.edu Wendy Thompson wendy.thompson@unchealth.unc.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
4	RNA-Seq	NGS CLIA: N	Exploratory Purpose: To compare transcriptome signatures of responders *vs* non-responders	Bone Marrow (Cryopreserved bone marrow mononuclear cells)	Pre-treatment Response (between Days 42 and 64)	M M	Lab: Tissue Procurement Facility Contact: TPF Lab unc_tpf@med.unc.edu
5	Aiolos Expression	Flow Cytometry CLIA: N	Integrated Purpose: To determine whether Aiolos expression (in blood *vs.* bone marrow) is associated with response to daunorubicin and cytarabine liposome + pomalidomide	Bone marrow	Pre-treatment Day 14 Day 28 Response (between Days 42 and 64)	M M M M	Luznik Laboratory, Baylor College of Medicine Leo Luznik leonido.luznik@bcm.edu
6	T-cell subsets	Flow cytometry CLIA: N	Exploratory Purpose: To assess whether pre-treatment expression of T-cell subsets (in blood *vs.* bone marrow) are associated with response to daunorubicin and cytarabine liposome + pomalidomide and to assess whether pomalidomide can induce changes in T cell composition in responders *vs.* non-responders	Bone Marrow (Collected as a part of Aiolos Expression)	Pre-treatment Day 14 Day 28 Response (between Days 42 and 64)	M M M M	Luznik Laboratory, Baylor College of Medicine Leo Luznik leonido.luznik@bcm.edu
Blood-based Biomarkers							

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
1	DNA-Seq MRD	NGS CLIA: N	Exploratory Purpose: To assess for differences in measurable residual disease (MRD) based on NGS between daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome	Blood (EDTA)	Pre-treatment Response (between Days 42 and 64)	M M	Lab: Molecular Genetics Laboratory Contacts: Rachana Kshatriya Rachana.kshatriya@unchealth.unc.edu Wendy Thompson wendy.thompson@unchealth.unc.edu
2	Aiolos expression	Flow cytometry CLIA: N	Integrated Purpose: To determine whether Aiolos expression (in blood *vs.* bone marrow) is associated with response to daunorubicin and cytarabine liposome + pomalidomide	Blood (PBMC)	Pre-treatment Day 21 - For Arm A should be before pomalidomide Day 28 (+7 days) Response (between Days 42 and 64)	M M M M	Luznik Laboratory, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Leo Luznik luznile@jhmi.edu
3	T-cell subsets	Flow cytometry CLIA: N	Exploratory Purpose: To assess whether pre-treatment expression of T-cell subsets (in blood vs. bone marrow) are associated with response to daunorubicin and cytarabine liposome + pomalidomide and to assess whether pomalidomide can induce changes in T cell composition in responders *vs* non-responders.	Blood (PBMC) (Collected as a part of Aiolos Expression)	Pre-treatment Day 21 - For Arm A should be before pomalidomide Day 28 (+7 days) Response (between Days 42 and 64)	M M M M	Luznik Laboratory, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Leo Luznik luznile@jhmi.edu

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
4	TCR diversity (TCRβ)	TCR repertoire/ RT-PCR and NGS Illumina MiSeq CLIA: N	Exploratory Purpose: To determine whether pre-treatment TCR diversity is associated with response to daunorubicin and cytarabine liposome + pomalidomide *vs.* daunorubicin and cytarabine liposome.	Blood	Pre-treatment Day 21 - For Arm A should be before pomalidomide Response (between Days 42 and 64)	M M M	Lab: Tissue Procurement Facility Contact: TPF Lab unc_tpf@med.unc.edu

5.8 Integrated Correlative Studies

5.8.1 Foundation One Heme Panel

5.8.1.1 Specimen(s) Receipt and Processing at Foundation Medicine, Inc.

Fresh bone marrow aspirate from pre-treatment should be sent to Foundation Medicine Inc. for NGS processing using the Foundation One Heme Panel. Samples should be received one day after collection for optimal analysis. Foundation One Heme Panel should be sent with clinical information and without study identification.

If a patient has already had NGS performed at a CLIA-certified laboratory within 30 days of consent, then Foundation One Heme testing is not mandatory to be performed, per standard-of-care and investigator discretion.

See also:
https://assets.ctfassets.net/w98cd481qyp0/4qY3AxNKhJQF024FxoDmvU/cffb4094bc48e3badf125ccd5e43c645/FoundationOne_Heme_Specimen_Instructions__All_Sample_Types_.pdf

5.8.1.2 Site Performing Correlative Study

Foundation Medicine Inc.

5.8.1.3 Contact information for notification of specimen shipment

Phone: (888) 988-3639

5.8.2 Aiolos Expression

5.8.2.1 Specimen(s) Receipt and Processing at Luznik Laboratory at JHU

Blood (sodium heparin tube) and bone marrow aspirate from pre-treatment, Day 14, Day 28 and at response will be shipped to the Luznik laboratory and processed according to laboratory SOPs for flow cytometry. Briefly, at each sampling interval, bone marrow and peripheral blood mononuclear cells (PBMC) will be processed by Ficoll density gradient centrifugation. Each sample is aliquoted in multiple vials of 10-15 x 10^6 cells/vial for bone marrow samples and 5-10 x 10^6 cells/vial for PBMC. Specimen for Aiolos expression will be collected from UNC and JHU participants only.

Frozen PBMCs will be transferred from the Luznik Lab at JHU to the Tissue Procurement Facility UNC-Chapel Hill for storage and then distributed to the Luznik Laboratory at Baylor College of Medicine for analysis.

5.8.2.2 Site Performing Correlative Study

Dr. Leo Luznik Laboratory; Baylor College of Medicine

5.8.2.3 Contact information for notification of specimen shipment

Leo Luznik (Leonido.Luznik@bcm.edu)

5.8.3 Hematologics Flow Cytometry Minimal Residual Disease

5.8.3.1 Specimen(s) Receipt and Processing at Hematologics

Fresh bone marrow aspirate in sodium heparin green top tubes at pre-treatment and response will be sent to Hematologics for processing. Hematologics MRD should be sent with clinical information and without study identification.

5.8.3.2 Site Performing Correlative Study

Hematologics

5.8.3.3 Contact information for notification of specimen shipment

Phone: (800) 860-0934 or (206) 223-2700

5.9 Exploratory/Ancillary Correlative Studies

5.9.1 T-Cell Subsets

5.9.1.1 Specimen(s) Receipt and Processing at Luznik Laboratory at JHU

Bone marrow aspirates (collected pre-treatment, Day 14, Day 28 and at response) and blood (collected at pre-treatment, Day 21, Day 28, and at response) in sodium heparin tubes may be processed locally per guidelines in Appendix M or fresh samples sent to Dr. Luznik's Laboratory (overnight). The samples will be processed according to laboratory SOPs. Briefly, at each sampling interval, bone marrow and PBMC will be processed by Ficoll density gradient centrifugation. Each sample is aliquoted in multiple vials of 10-15 x 10^6 cells/vial for bone marrow samples and 5-10 x 10^6 cells/vial for PBMC. Specimen for Aiolos expression will be collected from UNC and JHU participants only.

Frozen PBMCs will be transferred from Luznik Lab at JHU to the Tissue Procurement Facility UNC-Chapel Hill for storage and then distributed to the Luznik Laboratory at Baylor College of Medicine for analysis.

5.9.1.2 Site Performing Correlative Study

Dr. Leo Luznik Laboratory; Baylor College of Medicine

5.9.1.3 Contact information for notification of specimen shipment

Leo Luznik (Leonido.Luznik@bcm.edu)

5.9.2 DNA-Seq

5.9.2.1 Specimen(s) Receipt and Processing at Molecular Genetics Laboratory

Bone marrow aspirate and peripheral blood pre-treatment and at response will be shipped to University of North Carolina Molecular Genetics Laboratory overnight for processing and storage. DNA-Sequencing will be done at a later date to assess for MRD.

5.9.3 RNA-Seq and TCR Diversity

5.9.3.1 Specimen(s) Receipt and Processing at the Tissue Procurement Facility UNC-Chapel Hill.

Peripheral blood samples (10 ml EDTA x 2 or 8 ml ACD x 3) from Pre-Treatment, Day 21 (For Arm A should be before pomalidomide) and Response between days 42 and 64 will be processed locally if possible according to the laboratory SOPs to process by Ficoll density gradient centrifugation and cryopreserve in multiple vials of 5-10 x 10^6 cells/vial for PBMC. Multiple cryopreserved patient samples may be batched for overnight shipment on dry ice to the Tissue Procurement Facility UNC-Chapel Hill upon request.

5.9.3.2 Site Performing Correlative Study

RNA-Seq: Tissue Procurement Facility UNC-Chapel Hill (DNA-seq: TBD)

Bone marrow aspirates (collected pre-treatment and Response (between Days 42 and 64) in EDTA tubes should be processed **locally** according to prepare Bone Marrow Mononuclear Cells (BMMC) following ficol hypaque gradient centrifugation and cryopreservation in multiple vials that must exceed 5 x 10^6 cells/vial. After cryopreservation protocols are completed, samples must be stored under liquid nitrogen vapor phase until transfer to UNC Chapel Hill. Multiple patient samples may be batched for shipment overnight on dry ice to the Tissue Procurement Facility UNC-Chapel Hill.

5.9.3.3 Contact information for notification of specimen shipment

TPF Lab (unc_tpf@med.unc.edu)

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an inpatient or outpatient basis based on institutional standard until Day 6, and then all patients will be hospitalized starting on Day 6 of therapy until early hematologic recovery. Patients can be discharged once they achieve early hematologic recovery or per institutional standards. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the

intent to treat the patient's malignancy. To prevent hyperuricemia, all patients without known allergy will receive allopurinol 300 mg PO QD prior to beginning chemotherapy continuing through the period of maximal tumor lysis (at least through Day 5) or other antiuricemia regimen per institutional practice (refer to Section 6.2.6).

6.2 Safety Run-in

A safety run-in will be performed for pomalidomide dose finding purposes utilizing a standard 3 + 3 design. After daunorubicin and cytarabine liposome induction, up to 12 subjects will enter the safety run-in phase. There will be two dose levels (DLs). The dose for each dose level will remain the same (4 mg), while the duration of pomalidomide exposure will vary from 14 days to 21 days.

Pomalidomide Safety Run-in Dose Levels		
Dose Level	**Dose (mg)**	**Duration (Days)**
-1	4	10
1	4	14
2	4	21

6.3 Dose Escalation 3 + 3 Design

The safety run-in will follow a traditional 3 + 3 design. Three (3) subjects will be evaluated at each dose level for treatment-emergent toxicities. The maximum tolerated dose (MTD) will be defined as the highest dose tested in which more than 2 dose limiting toxicity (DLT; Section 6.4) occurred in evaluable subjects at that dose level using the following escalation procedure:

- If none of the first 3 subjects on DL1 experience a DLT, the dose may be escalated to the next level
- If 1 of the first 3 subjects on any DL experiences a DLT, then 3 additional subjects will be studied at the same dose level. If 1 or more of these 3 new subjects experience a DLT, then the MTD has been exceeded.
- If ≥ 2 subjects in a cohort of 3 experience a DLT, 3 additional subjects will be assigned to the lower dose level unless there have been 6 subjects already at that dose level, or this occurs in DL1. If needed, a dose level minus 1 incorporating 4 mg pomalidomide for 10 days will be employed.

The recommended phase 2 dose (RP2D) to be used in the randomized phase 2 portion of the study will be determined after evaluating safety, tolerability, efficacy, anti-tumor activity, exposure, and PD information (ie, Aiolos inhibition), if available, for both dose levels. Additionally, the RP2D will not exceed the estimated MTD and will be no greater than DL2.

6.4 Definition of a Dose Limiting Toxicity

DLTs related to pomalidomide will be graded per CTCAE v5.0 and be defined as the following: Grade ≥3 non-hematologic toxicity at least possibly related to pomalidomide and not related to underlying leukemia with the following exceptions:

A) Grade ≥3 isolated electrolyte abnormalities that last <72 hours with or without supportive care

B) Grade 3 anorexia, nausea, vomiting or diarrhea if it does not result in hospitalization or prolongation of hospitalization or parenteral nutrition via tube-feeds or central/total parenteral nutrition.

C) Infection, bleeding, or other direct complication of cytopenias due to underlying leukemia

D) Grade ≥3 tumor lysis syndrome if successfully managed clinically and resolving with 7 days without end-organ damage.

Furthermore, the following will be considered as DLTs if they are determined to be at least possibly related to treatment regimen:

- Grade 2 elevation of AST or ALT (>3x upper limit normal) and elevation of total bilirubin 2x upper limit normal without other known causes such as cholestasis
- Non-hematologic grade ≥ 4 toxicity (excluding infection)

Hematologic toxicity will be considered as a DLT if grade 4 neutropenia (ANC < 0.5x 10^9/L) and grade 4 thrombocytopenia (platelets < 25 x 10^9/L or transfusion-dependent) occur without evidence of persistent leukemia (*i.e.* <5% blasts in bone marrow) after ≥49 days from start of induction or re-induction for those receiving 1 or 2 induction cycles, respectively. This will apply until receipt of subsequent therapy but no more than 30 days after response assessment for each individual patient.

6.5 Randomization Phase

Randomization will occur prior to initiation of daunorubicin and cytarabine liposome and will be stratified by the following:

1) Age ≥60 *vs*. <60 years of age
2) Newly diagnosed AML with preexisting MDS, CMML, or MPN (or unexplained cytopenias >6 months) *vs*. 2) therapy-related AML *vs*. 3) AML with MRC based on cytogenetics or morphologic dysplasia without history of MDS/MPN.

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length - up to 64 (+/- 3 days)**
daunorubicin and cytarabine liposome (Arm A and Arm B)	In response to hypersensitivity reactions (See Section 7.2), antihistamines and/or corticosteroids may be administered. See Section 6.2	**Induction and second induction (if required):** Daunorubicin 44 mg/m^2 and cytarabine 100mg/m^2 **Consolidation:** For patients who	IV over 90 minutes (+/- 15 minutes)	**Induction:** Days 1, 3, and 5 during induction. **Second induction (if required):** Days 1 and 3 on the subsequent induction cycle.	Induction = 42+ days Consolidation = 5-8 weeks

	and 11 for additional premedications/precautions.	achieve CR/CRi, daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2		**Consolidation:** Days 1 and 3 for up to 2 cycles. Should start 5-8 weeks after the start of induction. If a second consolidation cycle is administered, it should be 5-8 weeks after the start of the first consolidation. cycle	
Pomalidomide (Arm A only)		4 mg	PO	Daily after induction, beginning Day 21 (+3 days) for one cycle for Arm A only	14 days (as determined in the run-in phase)

Arm A:
For induction, daunorubicin and cytarabine liposome (liposomal daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) is administered IV Days 1, 3 and 5. If patients require a second induction, they will receive daunorubicin and cytarabine liposome (liposomal daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) IV on Days 1 and 3. Daunorubicin and cytarabine liposome consolidation (liposomal daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) will occur >24 hours after completing pomalidomide and after achievement of CR/CRi.

Pomalidomide 4 mg daily is given for 14 days starting on Day 21 after induction or at least 48 hours after second induction has been completed, but may be delayed until Day 30. Patients may be discharged from the hospital once they achieve early hematologic recovery (*i.e.*, ANC ≥0.5 x 10^9/L and platelets >50 x 10^9/L) or per institutional standards.

All patients will be assessed for laboratory eligibility and patients in Arm A need to meet laboratory eligibility parameters in Criterion 3.1.6 prior to initiating pomalidomide. Pomalidomide initiation can be delayed (up to Day 30) in the following scenarios:

- Patients who receive re-induction with daunorubicin and cytarabine liposome (pomalidomide must be initiated no sooner than 48 hours after last dose of daunorubicin and cytarabine liposome)
- Patients who do not meet laboratory eligibility criteria on Day 21 but correct to eligibility criteria with supportive care by Day 30

- Patients with intercurrent illness whereby the investigator deems it unsafe to administer pomalidomide

Arm B:
Daunorubicin and cytarabine liposome (liposomal daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) is administered IV Days 1, 3 and 5. If patients require a second induction, they will receive daunorubicin and cytarabine liposome (liposomal daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2) IV on Days 1 and 3.

Arm A and B Consolidation:
Patients in both arms who achieve CR/CRi will receive consolidation therapy with daunorubicin and cytarabine liposome (29 mg/m^2 daunorubicin and 65 mg/m^2 cytarabine) IV infusion on Days 1 and 3 per standard-of-care for up to 2 cycles. In patients who develop cardiomyopathy or who exceed lifetime anthracycline dose of >430 mg/m^2 (or >280 mg/m^2 with prior mediastinal radiation) or have any other contraindications to daunorubicin and cytarabine liposome consolidation, moderate- to high-dose (1-3 g/m^2 IV Q12 hours Days 1, 3, and 5) cytarabine should be used in place of daunorubicin and cytarabine liposome for consolidation (See Appendix I). An allogeneic stem cell transplant will be performed for patients who are candidates for a transplant per investigator discretion in either arm after induction therapy, before or after consolidation therapy.

6.5.1 Pomalidomide

- Pomalidomide is administered by mouth (orally) without regards to food or other oral intake.
- Pomalidomide capsules should be swallowed whole, and should not be broken, chewed, or opened.
- If a dose of pomalidomide is missed, the dose may still be taken up to 12 hours after the time they normally would take it. If more than 12 hours have elapsed, the dose should be skipped. Take the next dose at the usual time. Patients should not take 2 doses to make up for the one they missed.
- If a patient vomits after taking pomalidomide, doses will not be made up and should be taken at the next scheduled dose.
- Patients who take more than the prescribed dose of pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Treatment compliance
At all times, when dispensing study drug, research center personnel will review the instructions, printed on the packaging, with patients. Patients will be asked to maintain a diary to record the drug administration (see Appendix H). Patients will be asked to bring any unused study drug and empty study drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules at each visit and reconcile with the patient diary.

6.5.2 Daunorubicin and cytarabine liposome

Daunorubicin and cytarabine liposome is a sterile, preservative-free, purple, lyophilized cake for reconstitution supplied in a single-dose clear glass vial as follows:

- For injection: 44 mg daunorubicin and 100 mg cytarabine in a 1:5 molar ratio encapsulated in liposomes for intravenous administration.

The use of daunorubicin and cytarabine liposome is contraindicated in patients with the following:

- History of serious hypersensitivity reaction to cytarabine, daunorubicin, or any component of the formulation

Please clarify or add a reference to section 6.1 about consolidation and allowed use of moderate to high dose cytarabine to replace daunorubicin and cytarabine liposome during consolidation.

Do not interchange with other daunorubicin-and/or cytarabine-containing products
Due to substantial differences in the pharmacokinetic parameters, the dose and schedule recommendations for daunorubicin and cytarabine liposome are different from those for daunorubicin hydrochloride injection, cytarabine injection, daunorubicin citrate liposome injection, and cytarabine liposome injection. Verify drug name and dose prior to preparation and administration to avoid dosing errors. Do not substitute other preparations of daunorubicin or cytarabine for daunorubicin and cytarabine liposome. Moderate- to high-dose (1-3 g/m^2 IV Q12 hours Days 1, 3, and 5) cytarabine can be used in place of daunorubicin and cytarabine liposome for consolidation (See Section 6.1, Arm A and B Consolidation).

6.6 General Concomitant Medication and Supportive Care Guidelines

Patients should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate.

Because there is a potential for interaction of pomalidomide with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix C (Patient Clinical Trial Wallet Card) should be provided to patients.

Pomalidomide is primarily metabolized by CYP1A2 and CYP3A4 and is a substrate for P-gp. Caution should be used with concomitant strong CYP1A2 inhibitors and alternative agents should be used if possible.

6.6.1 Antiemetics

Antiemetics will be used according to standard practices. Any 5-hydroxytryptamine (5-HT3) receptor inhibitor (*e.g.* ondansetron) combined with haloperidol or prochlorperazine as needed, will be used during chemotherapy infusions and during pomalidomide administration, as needed. A typical antiemetic regimen prior to daunorubicin and cytarabine liposome may be the following:

- Zofran 24 mg PO and dexamethasone 8 mg PO on D1, 3, and 5 administered 30 min prior to dose.

6.6.2 Menstrual Suppression

During the period of thrombocytopenia, to reduce the risk of bleeding, all premenopausal women should receive menstrual suppression. All premenopausal women who are in the pre-ovulatory half of the menstrual cycle will be placed on daily combination (estrogen + progesterone) oral contraceptive pills. All premenopausal women who are in the post-ovulatory phase (>14 days from last menstrual period) of the menstrual cycle will be given megestrol 40 mg QD x 2 days or institutional equivalent and then begun on combination oral contraceptive pills beginning 5 days after the onset of withdrawal bleeding. Combination pills will be continued throughout drug-induced aplasia if breakthrough bleeding does not occur. Breakthrough bleeding will be managed by increasing the progesterone content of the combination pills until bleeding is controlled. This increase can be achieved by doubling the dose of combination oral contraceptive. If bleeding is not controlled by 2 combination pills QD, a trial of megestrol (40-80 mg QD or equivalent) is indicated. Oral contraceptives or megestrol could be stopped after marrow recovery and achievement of platelet count of at least 30 x 10^9/L in order to permit endometrial sloughing unless used for ongoing pregnancy protection while taking pomalidomide. Similar menstrual suppression guidelines per institutional standard may be followed.

6.6.3 Antimicrobial Prophylaxis

Patients should receive prophylaxis directed against gram-negative gastrointestinal infections (GI), candidiasis, and/or herpes simplex virus (HSV), according to institutional standards.

6.6.4 Intrathecal prophylaxis

Intrathecal prophylaxis will be used according to institutional standard practice for those patients presenting with elevated WBCs. Any patient presenting with WBC >40 x 10^9/L or any monocytic phenotype should have screening lumbar puncture after clearance of peripheral blood blasts preferably by Day 14 of induction chemotherapy with prophylactic intrathecal chemotherapy instillation of cytarabine per institutional standards. Patients receiving intrathecal chemotherapy prophylaxis should not start pomalidomide for ≥3 days after chemotherapy administration.

6.6.5 Colony Stimulating Factors and Steroids

The routine use of colony stimulating factors is disallowed only during induction (e.g., this does not refer to consolidation). The use of colony stimulating factors in the presence of severe infection should be discussed with the study chair before implementation. Fever and rash are common side effects of pomalidomide. Low dose steroids (up to max 40 mg of prednisone per day or equivalent steroid dose) may be used as needed to control symptoms as long as infectious cause for fever has been excluded. This should be discussed with the study chair before implementation.

6.6.6 Management of Tumor Lysis Syndrome (TLS)

Tumor lysis occurs as part of initial cytoreductive therapy. The most extreme form, TLS, is characterized by hyperuricemia, hyperphosphatemia, increased lactate dehydrogenase (LDH) coagulopathy, and a potential cytokine release syndrome. Since the occurrence of TLS is magnified in the presence of high leukemia burden, we will not begin induction chemotherapy in any patient whose blood blast count is >30 x 10^9/L (see Eligibility 3.2.2). TLS also occurs with higher propensity in monoblastic phenotypes.

Tumor lysis labs consisting of basic metabolic panel, uric acid, LDH, and phosphate, must be drawn a minimum of twice daily at least through Day 5 of chemotherapy. Tumor lysis labs should be performed if clinically indicated after day 5 until maximum tumor lysis has abated. The following precautionary and prophylaxis regimens are suggested prior to and during initial chemotherapy administration:

- To prevent hyperuricemia, all patients without known allergy will receive allopurinol 300 mg PO QD prior to beginning chemotherapy and continuing through the period of maximal tumor lysis (at least through Day 5) or other antiuricemia regimen per institutional practice. Rasburicase may be used per institutional policy for hyperuricemia. Screening for G6PD deficiency should be obtained in susceptible populations before beginning Rasburicase.
- If there is an evidence of hyperphosphatemia prior or during administration of daunorubicin and cytarabine liposome, an oral phosphate binder per institutional practice (*i.e.*, sevelamer 400-800 mg) should be administered orally every 8 hours and continued as tolerated until hyperphosphatemia is resolved.
- Cytokine release syndrome can occur shortly after completion of drug infusion, accompany severe TLS, or after pomalidomide and present with fever, bronchospasm with dyspnea and/or respiratory distress, altered blood pressure, myalgias, arthralgias, tumor pain and/or urticarial rash. Any patient with cytokine release syndrome should receive 20 mg dexamethasone (or equivalent steroid) IV immediately.

6.6.7 Anticoagulation Consideration

Pomalidomide may increase the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. Anticoagulation is not necessary while on pomalidomide unless patients have a high-risk for thrombosis (*i.e.* prior history). Consideration should be given to the optional use of aspirin (81 or 325 mg) in patients with a high-risk of thrombosis while on pomalidomide and with platelet count >30 x 10^9/L. Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Routine use of warfarin is discouraged. Patients with AML will be allowed to start prophylactic antithrombotic therapy (if deemed high-risk) only when their platelet count is stable and >30 x 10^9/L unless they need therapeutic anticoagulation.

6.7 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for up to two consolidation cycles of daunorubicin and cytarabine liposome or until one of the following

criteria applies:

- Disease progression or 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
- Pregnancy
    - All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent
- Patients have treatment delays >2 weeks

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).

6.8 Duration of Follow-Up

Patients will be followed for 5 years after the start of induction therapy or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

In patients who complete consolidation chemotherapy and do not undergo an allogeneic stem cell transplant, patients should be followed approximately once every 1-2 months for the first year per institutional standard-of-care. Additionally, patients should receive surveillance bone marrow aspirate and biopsy while in remission approximately every 3 months for the first year after completing daunorubicin and cytarabine liposome consolidation.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Pomalidomide

Toxicities are graded using CTCAE v5.0. Grade ≥3 non-hematologic toxicities that are determined to be at least possibly related to pomalidomide and not related to underlying leukemia will require pomalidomide to be held until grade ≤1 and then restarted at 2 mg daily for the remainder of their treatment cycle (see Table below) with the following exceptions:

A) Grade ≥3 isolated electrolyte abnormalities that last <72 hours with or without supportive care

B) Grade 3 anorexia, nausea, vomiting or diarrhea if it does not result in hospitalization or parenteral nutrition via tube-feeds or central/total parenteral nutrition.

C) Infection, bleeding, or other direct complication of cytopenias due to underlying leukemia

D) Grade ≥3 tumor lysis syndrome if successfully managed clinically and resolving with 7 days without end-organ damage.

Additionally, subjects who develop grade 2 elevation of AST or ALT (>3x upper limit normal) and elevation of total bilirubin 2x upper limit normal without other known causes such as cholestasis will require pomalidomide to be held until improvement of AST/ALT and total bilirubin. Pomalidomide should be restarted at 2 mg daily after clinical improvement of these laboratory parameters.

Pomalidomide should be held if grade 4 neutropenia or thrombocytopenia occurs lasting >49 days from start of induction or reinduction in absence of active AML.

Pomalidomide should be held for grade 4 infectious toxicities and restarted at 2 mg daily once infection-related toxicity is ≤grade 3.

Missed doses of pomalidomide not taken within 12 hours of the time normally taken will not be made up. Patients with grade ≥3 maculopapular rash on pomalidomide should have drug held until improvement to ≤ grade 2. Patients who have symptoms and/or clinical sequelae of rash can receive concomitant prednisone and supportive care while remaining on pomalidomide. Patients with Stevens-Johnson Syndrome (SJS) or toxic epidermal necrolysis (TEN) should be taken permanently off pomalidomide. If tumor lysis syndrome develops on pomalidomide, subsequent doses should be held until tumor lysis syndrome resolves. Hematologic toxicity may occur after pomalidomide administration. Dose modifications will not occur during pomalidomide administration for hematologic toxicities.

Grade ≥3 venous or arterial thromboses will require pomalidomide to be discontinued permanently and subjects should be treated off study.

Subjects experiencing angioedema, skin exfoliation or any other severe dermatologic reaction should permanently discontinue pomalidomide and be treated off study.

For patients with mild or moderate hepatic impairment (Child-Pugh A or B), reduce the recommended dosage to 3 mg orally daily.

For patients with severe hepatic impairment (Child-Pugh C), reduce the recommended dosage to 2 mg.

Other Non-Hematologic Toxicity (with the exception of toxicities listed above)	**Management/Next Dose for Pomalidomide**
≤ Grade 1	No change in dose
Grade 2	No change in dose
Grade 3 or 4	Hold* until grade ≤1, and then restart at 2 mg. If grade 3 or 4 event occurs on lower dose (2 mg), then permanently discontinue pomalidomide. Missed doses should not be made up.
*Patients requiring a delay of >2 weeks should go off protocol therapy.	

Thromboembolic Events	**Management/Next Dose for Pomalidomide**
≤ Grade 2	No change in dose
Grade ≥3	Start anticoagulation as per standard-of-care. Pomalidomide should be discontinued.

Strong CYP1A2 Inhibitors
The use of strong CYP1A2 inhibitors (*e.g.* ciprofloxacin, fluvoxamine) should be avoided or used with caution. If a strong CYP1A2 inhibitor must be used, reduce the pomalidomide dose by 50%.

7.2 Daunorubicin and cytarabine liposome

Missed Doses of daunorubicin and cytarabine liposome
If a planned dose of daunorubicin and cytarabine liposome is missed, administer the dose as soon as possible and adjust the dosing schedule accordingly, maintaining the treatment interval.

Hypersensitivity Reactions
For hypersensitivity reactions of any grade/severity, interrupt daunorubicin and cytarabine liposome infusion immediately and manage symptoms. Reduce the rate of infusion or discontinue treatment as outlined below:

- Mild symptoms: Once symptoms resolve, reinitiate infusion at half the prior rate of infusion. Consider premedication with antihistamines and/or corticosteroids for subsequent doses of daunorubicin and cytarabine liposome.
- Moderate symptoms: Do not reinitiate infusion. For subsequent doses of daunorubicin and cytarabine liposome, premedicate with antihistamines and/or corticosteroids prior to initiating infusion at same rate.
- Severe/life-threatening symptoms: Permanently discontinue daunorubicin and cytarabine liposome treatment, treat according to the standard-of-care to manage symptoms, and monitor patient until symptoms resolve.

Cardiotoxicity
Discontinue daunorubicin and cytarabine liposome in patients who exhibit impaired cardiac function unless the benefit of continuing treatment outweighs the risk.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational and commercial agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agent(s)

8.1.1 Pomalidomide (NSC 767909)

NOTE:
Before pomalidomide is dispensed, patients must 1) have a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. Pharmacists may be trained counselors (see Celgene Pregnancy Prevention and Counselor Program Site Counselor Identification Form in the protocol). Only one cycle or a 28-day supply (whichever is shorter) may be dispensed to a patient at one time.

Chemical Name: 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione

Other names: CC-4047, Pomalyst

Classification: immunomodulatory agent

CAS Registry Number: 19171-19-8

Molecular Formula: $C_{13}H_{11}N_3O_4$ **M.W.:** 273.24

Mode of Action: Pomalidomide induces cell cycle arrest and apoptosis. *In vitro* studies show immunomodulatory activity on T cell and NK cell mediated immunity and inhibition of certain pro-inflammatory cytokines. Pomalidomide can overcome some instances of lenalidomide resistance which makes it an attractive agent for further drug development. Current investigations are underway to more precisely understand pomalidomide's multiple mechanisms of action.

Description: yellow solid with melting point of 319° C

How Supplied: Celgene supplies and CTEP, DCTD, NCI distributes pomalidomide hard gelatin capsules in the following strengths, sizes and descriptions: 2 mg (size 2, dark blue and orange), 3 mg (size 2, dark blue and green), and 4 mg (size 2, dark blue and blue). Excipients include mannitol, pregelatinized starch and sodium stearyl fumarate.

Pomalidomide capsules are supplied in high density polyethylene (HDPE) containers fitted with induction seals and child-resistant plastic closures. Each bottle contains 100 capsules.

Storage: Store at 20°C-25°C (68°F-77°F) [USP Controlled Room Temperature]

If a storage temperature excursion is identified, promptly return pomalidomide to controlled room temperature 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: Shelf life studies are ongoing for investigational supplies. Refer to the package labeling for commercially-labeled supplies.

Route of Administration: Take by mouth with or without food. Capsules should be swallowed whole and taken with water and not crushed, chewed or opened. If patients miss a dose, the dose may still be taken up to 12 hours after the time they normally would take it. If more than 12 hours have elapsed, the dose should be skipped. Take the next dose at the usual time. Patients should not take 2 doses to make up for the one they missed.

Dispensing: Dispense one cycle or up to a 28-day supply (whichever is shorter) at one time. Sites may not mail pomalidomide to patients.

Patient Care Implications and Counseling:

Risks Associated with Pregnancy

Pomalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that pomalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

Definition of female of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (*i.e.*, has had menses at any time in the preceding 24 consecutive months).

Before starting study drug:

Female Subjects:

- FCBP must have two negative pregnancy tests (minimum sensitivity of 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within

24 hours prior to the start of study drug. The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

- FCBP must agree to use two reliable forms of contraception simultaneously, or practice complete abstinence for 28 days before starting pomalidomide, while taking pomalidomide, during dose interruptions, and for at least 28 days after the last dose of pomalidomide.

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study, during dose interruptions, and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

All Subjects:

- Only enough pomalidomide for one cycle of therapy may be dispensed with each cycle of therapy.

- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, pomalidomide must be immediately discontinued.

Counseling

- In investigational studies where pomalidomide is supplied by the NCI, patients will be counseled by a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). Two healthcare professionals at each site will be trained by Celgene in requirements specific to counseling of subjects (investigators cannot counsel patients as part of this requirement). Refer to specific protocol sections for more information about training requirements.

- Once trained, these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with pomalidomide. This step will be documented with a completed Pomalidomide Education and Counseling Guidance Document (Appendix E) and no drug will be dispensed until this step occurs. Counseling includes verification with the patient that required pregnancy testing was performed and results were negative. A Pomalidomide Information Sheet (Appendix F) will be supplied with each medication dispense.

Potential Drug Interactions:

Pomalidomide is metabolized mostly by CYP 1A2 and 3A and is substrate for P-glycoprotein (P-gp). *In vitro* studies showed a significant plasma increase when strong CYP 1A2, 3A and P-gp inhibitors were given simultaneously. Avoid concomitant administration of strong inducers and inhibitors of CYP 1A2, 3A and P-gp in patients receiving

pomalidomide. Closely monitor INR when patients receive concomitant warfarin and dexamethasone. Refer to the protocol for pomalidomide dose modifications.

Pomalidomide does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, or 3A4/5 *in vitro*. It is also not an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, or OCT2.

Pomalidomide does not induce CYP1A2, 2B6, 2C9, 2C19, or 3A4/5 *in vitro*.

Special Handling:

Pomalidomide should not be handled by non-patient FCBP or non-patient partners of FCBP unless gloves are worn. If any contact with a broken pomalidomide capsule or the medicine in the capsule occurs, the exposed area should be washed immediately and thoroughly with soap and water.

Patient Care Implications:

Patients should be advised that smoking tobacco may reduce the efficacy of pomalidomide.

Pomalidomide can be removed by hemodialysis.

8.1.2 Availability

Pomalidomide is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Pomalidomide is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 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 can place orders for PMB-supplied agents only after enrollment and randomization onto the study. Please provide the participant ID# when placing an order.

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.

8.1.3.2 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.

8.1.4 Investigator Brochure Availability

The current versions of the IBs for the agents 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, 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 policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- 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 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)

8.2 Commercial Agent

8.2.1 Daunorubicin and cytarabine liposome

Product description: Daunorubicin and cytarabine liposome (CPX-351, Vyxeos™) for injection is a commercially available, sterile, preservative-free, purple, lyophilized cake for reconstitution supplied in a single-dose clear glass vial as follows:

- For injection: 44 mg daunorubicin and 100 mg cytarabine encapsulated in liposomes.

Each vial contains 44 mg daunorubicin and 100 mg cytarabine, and the following inactive ingredients: distearoylphosphatidylcholine 454 mg, distearoylphosphatidylglycerol 132 mg, cholesterol HP 32 mg, copper gluconate 100 mg, triethanolamine 4 mg, and sucrose 2054 mg.

Solution preparation: Daunorubicin and cytarabine liposome is a cytotoxic drug. Follow applicable special handling and disposal procedures (https://www.osha.gov/hazardous-drugs). Daunorubicin and cytarabine liposome is supplied as a single-dose vial and does not contain any preservatives. Do not save any unused portions for later administration.

Reconstitute and further dilute daunorubicin and cytarabine liposome prior to intravenous infusion.

Reconstitution:

- Calculate the daunorubicin and cytarabine liposome dose based on daunorubicin and individual patient's BSA.
- Calculate the number of vials of daunorubicin and cytarabine liposome based on the daunorubicin dose.
- Remove the appropriate number of vials of daunorubicin and cytarabine liposome from the refrigerator and equilibrate to the room temperature for 30 minutes.
- Then, reconstitute each vial with 19 mL of Sterile Water for Injection using a sterile syringe and immediately thereafter start a 5-minute timer.
- **Carefully swirl the contents of the vial for 5 minutes** while gently inverting the vial every 30 seconds.
- Do not heat, vortex, or shake vigorously.
- After reconstitution, let rest for 15 minutes.
- The reconstituted product should be an opaque, purple, homogeneous dispersion, essentially free from visible particulates. After reconstitution (but before final dilution), each mL will contain 2.2 mg of daunorubicin and 5 mg of cytarabine.
- Use the reconstituted solution immediately. If needed, store the reconstituted solution in the vial refrigerated at 2ºC to 8ºC (36°F to 46°F) for up to 4 hours. Note that the reconstituted product in the vial and the reconstituted product which has been diluted into an infusion solution are stable for a total of 4 hours (not 4 hours each) when stored at 2°C to 8°C.

Dilution:

- Calculate the volume of reconstituted daunorubicin and cytarabine liposome required using the following formula:
  [volume required (mL) = dose of daunorubicin (mg/m^2) X patient's BSA (m^2) ÷ 2.2 (mg/mL)]
- Gently invert each vial 5 times prior to withdrawing the reconstituted product for further dilution.
- Aseptically withdraw the calculated volume of the reconstituted product from the vial(s) with a sterile syringe and transfer it to an infusion bag containing 500 mL of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. There may be residual product remaining in the vial. Discard unused portion.

- Gently invert the bag to mix the solution. The dilution of the reconstituted product results in a deep purple, translucent, homogeneous dispersion, free from visible particulates.
- If the diluted infusion solution is not used immediately, store in a refrigerator at 2ºC to 8ºC (36°F to 46°F) for up to 4 hours. If the reconstituted solution in the vial was stored for 4 hours, the diluted infusion solution must be used immediately and cannot be stored for an additional 4 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Only solutions without visible particles should be used.

Route of administration:

- For intravenous use only.
- Do not mix daunorubicin and cytarabine liposome with or administer as an infusion with other drugs.
- Administer daunorubicin and cytarabine liposome by constant intravenous infusion over 90 minutes via an infusion pump through a central venous catheter or a peripherally inserted central catheter. An in-line membrane filter may be used for the intravenous infusion of Vyxeos, provided the minimum pore diameter of the filter is greater than or equal to 15 µm.
- Flush the line after administration with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.

Agent Ordering: Daunorubicin and cytarabine liposome is commercially available. Refer to the daunorubicin and cytarabine liposome package insert for more information.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This is a randomized two-arm study of daunorubicin and cytarabine liposome + pomalidomide versus daunorubicin and cytarabine liposome alone in newly diagnosed AML with preexisting MDS, CMML or MPN; t-AML; or AML with MRC based on cytogenetics or morphologic dysplasia without history of MDS/MPN. We will test the null hypothesis that the CR/CRi rates in the two arms are the same. We will enroll 39 patients in each arm. We will test for futility after responses from the first 16 patients accrued to each arm are available. The trial may be stopped for futility if the one-sided Fisher's p-value is higher than 0.52.

If the trial is not stopped for futility, 39 patients will be enrolled to each arm. We will conclude that the combination therapy is better than daunorubicin and cytarabine liposome alone if the one-sided Fisher's p-value at the end of the trial is lower than 0.05. This design yields 80% power with the one-sided type I error rate of 0.05 assuming 48% CR/CRi rate in daunorubicin and cytarabine liposome alone arm and 77.3% CR/CRi rate in daunorubicin and cytarabine liposome + pomalidomide arm (alternative hypothesis). The probability to stop for futility under the alternative hypothesis is 0.07. The probability to stop for futility under the null hypothesis

(same CR/CRi rates of 48% in both arms) is 0.57.

An Intent-to-Treat analysis will be used for this study.

9.1.1 Feasibility Analysis:

We will assess the feasibility of adding pomalidomide for both arms between Day 21-30. Patients on Arm A (pomalidomide arm) will need to meet laboratory-based eligibility criteria to receive pomalidomide which could be delayed up until Day 30. Patients on Arm B (no pomalidomide) will also be assessed for "eligibility" to receive pomalidomide, even though this arm will not receive pomalidomide, to further assess the feasibility of this approach in a larger patient population. We have incorporated a feasibility stopping rule if >25% of enrolled patients do not receive pomalidomide (Arm A) or are not eligible to receive pomalidomide (Arm B) by Day 30 as shown below.

9.1.2 Feasibility stopping rule:

Feasibility of patients being able to start pomalidomide will be assessed based on the table below. We will assess patients in both arms and patients will be combined for this analysis. The study is not feasible if more than 25% of the patients cannot start pomalidomide. To assess feasibility, we will test the hypothesis that the probability for a patient not to start pomalidomide is 25% versus lower than 25%. We will look at the data in approximately 10 patient intervals (*e.g.* after data are available from the first 10 patients, 20 patients, 30 patients, *etc.*). At an interim analysis, we will conclude that the study is not feasible if the p-value for testing the one-sided feasibility hypothesis is less than 0.10. The table below gives the stopping boundary in terms of the number of patients not being able to receive pomalidomide. The study is deemed not feasible if the number of patients not being able to receive pomalidomide is $\geq b_n$.

Number of Patients, n	10	20	30	40	50	60	70	78
Boundary, b_n	5	9	12	17	17	20	23	25
Number of Patients, n	10	20	30	40	50	60	70	78
Boundary, b_n	5	9	12	17	17	20	23	25

9.1.3 Continuous Monitoring for Toxicity

Sequential boundaries will be used to monitor dose-limiting toxicity (DLT). DLT is defined in Section 6.4.

The accrual will be halted if excessive numbers of dose-limiting toxicities are seen, that is, if the number of dose-limiting toxicities is equal to or exceeds b_n out of n patients with full follow-up (see table). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.2 when the rate of dose-limiting toxicity is equal to the acceptable rate 0.2.

The trial will be stopped if the number of patients with dose-limiting toxicity is equal to or exceeds b_n out of n patients with complete follow-up.

Number of Patients, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	2	3	3	3	4	4	4	5	5	5	6	6	6	6	7	7	7	7	8
Number of Patients, *n*	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	8	8	8	9	9	9	10	10	10	10	11	11	11	11	12	12	12	12	13	

9.1.4 Feasibility Analysis for Completion of 21 Days of Pomalidomide

We will test for futility after responses from the first 16 patients accrued to each arm are available. During the futility interim analysis, we will compute the proportion of patients on Arm A who received less than 14 days of pomalidomide out of patients who are past 21 days from the first dose of pomalidomide, and compute the corresponding 50% CI. The dose of pomalidomide might be re-evaluated if the upper bound of the CI is below 50%. For example, if 12 or more out of 16 patients received less than 14 days of pomalidomide, then pomalidomide dose and schedule will be re-evaluated.

9.2 Sample Size/Accrual Rate

We anticipate enrollment in up to 5 different institutions (including the lead site University of North Carolina). AML with MRC is present in 20-30% of newly diagnosed AML patients and we thus anticipate approximately 3-5 patients to be enrolled on this study monthly. We anticipate accrual of 78 patients to take approximately 2 years to accrue.

PLANNED ENROLLMENT REPORT

DOMESTIC PLANNED ENROLLMENT REPORT (SCREENING)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	3	0	0	3
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	12	10	0	0	22
White	35	62	3	3	103
More Than One Race	0	3	0	0	3
Total	47	78	3	3	131

DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0

DOMESTIC PLANNED ENROLLMENT REPORT (TREATMENT)					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Asian	0	2	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	7	6	0	0	13
White	21	37	2	2	62
More Than One Race	0	1	0	0	1
Total	28	46	2	2	78

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9.3 Stratification Factors

Patients will be stratified by age (≥60 *vs.* <60 years) and newly diagnosed AML with preexisting MDS, CMML or MPN, *vs.* therapy-related AML, *vs.* AML with MRC based on cytogenetics or mutations without history of MDS/MPN.

9.4 Analysis of Secondary Endpoints

1) CR with full hematologic recovery (ANC >$1x10^9$/L and platelets >$100x10^9$/L) will be assessed and compared with both arms A and B
2) Toxicities will be assessed by CTCAE v. 5.0 and compared descriptively between Arms A and B
3) Patients who achieve CR without MRD by flow cytometry via Hematologics, Inc. will be compared descriptively between Arms A and B
4) Event-Free Survival (EFS), defined as time from Day 1 of daunorubicin and cytarabine liposome until no response is achieved, relapse or death will be compared between Arms A and B
5) Disease-Free Survival (DFS) and 2-year DFS, defined as time from CR/CRi until relapse or death, will be compared between Arms A and B
6) Overall Survival (OS), defined as time from randomization until death or last follow-up, will be compared between Arms A and B
7) Rate of allogeneic stem cell transplantation will be compared between Arms A and B

9.5 Reporting and Exclusions

9.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment.

9.5.2 Evaluation of Response

Response Criteria in AML in Appendix J.

All patients included in the study must be assessed for response to treatment, even if there are

major protocol treatment deviations. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, *etc.*). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

9.6 Data Safety Monitoring Board

The conduct of this study will be overseen by the ETCTN DSMB. The DSMB will be responsible for recommendations to the Principal Investigator and NCI regarding possible trial closure and/or early reporting of the study. The study team (with the exception of the study statistician) will not have access to the summary outcome data until released by the DSMB.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

10.1.1 CAEPR for Pomalidomide (CC-4047, NSC 767909)

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 2133 patients.* Below is the CAEPR for Pomalidomide (CC-4047).

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 2.4, May 22, 2022[1]

Adverse Events with Possible Relationship to Pomalidomide (CC-4047)[2] (CTCAE 5.0 Term) [n= 2133]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia[3]			***Anemia[3] (Gr 2)***
CARDIAC DISORDERS			
		Myocardial infarction[4]	
GASTROINTESTINAL DISORDERS			
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
		Nausea	***Nausea (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
		Sudden death NOS	
HEPATOBILIARY DISORDERS			
		Hepatic failure	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[5]		***Infection[5] (Gr 2)***
\INVESTIGATIONS			
	Alanine aminotransferase increased		
	Blood bilirubin increased		
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
		Anorexia	***Anorexia (Gr 2)***
	Hyperkalemia		
	Hyponatremia		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Back pain		
		Bone pain	***Bone pain (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			

Adverse Events with Possible Relationship to Pomalidomide (CC-4047)[2] (CTCAE 5.0 Term) [n= 2133]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (second primary malignancies)[2]	
		Treatment related secondary malignancy[2]	
NERVOUS SYSTEM DISORDERS			
	Depressed level of consciousness		
		Dizziness	***Dizziness (Gr 2)***
		Dysesthesia	
		Paresthesia	
	Peripheral sensory neuropathy		
		Nervous system disorders - Other (progressive multifocal leukoencephalopathy)	
		Stroke[4]	
PSYCHIATRIC DISORDERS			
	Confusion		
		Hallucinations	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Urinary retention		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Cough	***Cough (Gr 2)***
		Dyspnea	***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Rash maculo-papular	***Rash maculo-papular (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (DRESS syndrome)	
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
VASCULAR DISORDERS			
		Thromboembolic event[4]	

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

[2]While not observed in human trials of pomalidomide, teratogenic effects (birth defects), thromboembolic events increases in secondary malignancy, tumor lysis syndrome, Stevens-Johnson syndrome, and thyroiditis/hypothyroidism are known events for this class of agents that include thalidomide and lenalidomide.

[3]Sickle cell crises in patients with SCD is a rare but serious event.

[4]Venous thromboembolic events (e.g., deep vein thrombosis and pulmonary embolism) and arterial thromboembolic events (e.g., myocardial infarction and stroke) have been observed to occur more frequently in multiple myeloma patients treated with pomalidomide and dexamethasone.

[5]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Pomalidomide (CC-4047) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Pomalidomide (CC-4047) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (sickle cell anemia with crisis)[3]; Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Heart failure; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision; Eye disorders - Other (eyelid swelling)
GASTROINTESTINAL DISORDERS - Abdominal pain; Colonic perforation; Dry mouth; Dyspepsia; Enterocolitis; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Disease progression; Malaise
IMMUNE SYSTEM DISORDERS - Allergic reaction
INVESTIGATIONS - CD4 lymphocytes decreased; CPK increased; Creatinine increased; Weight gain; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperuricemia; Hypocalcemia; Hypokalemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Chest wall pain; Generalized muscle weakness; Muscle cramp; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (multiple myeloma, myelofibrosis, progression of MM); Tumor pain
NERVOUS SYSTEM DISORDERS - Dysphasia; Headache; Intracranial hemorrhage; Ischemia cerebrovascular; Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Depression; Insomnia
RENAL AND URINARY DISORDERS - Hematuria
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Epistaxis; Nasal congestion; Oropharyngeal pain; Postnasal drip; Productive cough; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (sputum discolored)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Erythema multiforme; Hyperhidrosis; Pruritus
VASCULAR DISORDERS - Vascular disorders - Other (hyperviscosity syndrome)

Note: Pomalidomide (CC-4047) 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.

10.1.2 CAEPR for Daunorubicin and cytarabine liposome (CPX-351, Vyxeos, NSC 775341)

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. Frequency is provided based on 375 patients. Below is the CAEPR for (Daunorubicin and Cytarabine) Liposome (CPX-351; Vyxeos).

Version 2.1, August 18, 2022[1]

Adverse Events with Possible Relationship to (Daunorubicin and Cytarabine) Liposome (CPX-351; Vyxeos) (CTCAE 5.0 Term) [n= 375]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
Febrile neutropenia		
CARDIAC DISORDERS		
	Atrial fibrillation	
		Cardiac disorders - Other (arrhythmia)[2]
		Restrictive cardiomyopathy
	Sinus tachycardia	
GASTROINTESTINAL DISORDERS		
	Abdominal distension	
	Abdominal pain	
Constipation Diarrhea		
	Dyspepsia	
	Mucositis oral	
Nausea		
	Periodontal disease	
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Chills		
Edema limbs		
Fatigue		
Fever		
	Generalized edema	
INFECTIONS AND INFESTATIONS		
Infection[3]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Bruising	
	Infusion related reaction	
INVESTIGATIONS		
	Neutrophil count decreased	
	Platelet count decreased	
METABOLISM AND NUTRITION DISORDERS		

Adverse Events with Possible Relationship to (Daunorubicin and Cytarabine) Liposome (CPX-351; Vyxeos) (CTCAE 5.0 Term) [n= 375]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
Anorexia		
	Hypokalemia	
	Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Dysgeusia	
Headache		
PSYCHIATRIC DISORDERS		
	Anxiety	
	Confusion	
Insomnia		
RENAL AND URINARY DISORDERS		
	Acute kidney injury	
	Hematuria	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough		
Dyspnea		
Epistaxis		
	Hypoxia	
	Oropharyngeal pain	
	Pleural effusion	
	Respiratory failure	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Hyperhidrosis	
	Pruritus	
Purpura		
Rash maculo-papular		
VASCULAR DISORDERS		
	Hematoma	
	Hypertension	
Hypotension		
Vascular disorders - Other (hemorrhage)[4]		

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

[2]Arrhythmia may include Sinus and Ventricular arrhythmias.

[3]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[4]The majority of hemorrhage events were mild. Major events, defined as symptomatic bleeding in a critical area or organ (e.g., eye, GI hemorrhage, GU hemorrhage, respiratory hemorrhage, reproductive hemorrhage), and nervous system [including fatal intracranial hemorrhage and cerebrovascular accident] have been reported.

Adverse events reported on (Daunorubicin and Cytarabine) Liposome (CPX-351; Vyxeos) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that (Daunorubicin and Cytarabine) Liposome (CPX-351; Vyxeos) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Heart failure
INVESTIGATIONS - Ejection fraction decreased
METABOLISM AND NUTRITION DISORDERS - Hyponatremia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy
NERVOUS SYSTEM DISORDERS - Seizure; Syncope
PSYCHIATRIC DISORDERS - Delirium
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pulmonary edema

Note: (Daunorubicin and Cytarabine) Liposome (CPX-351; Vyxeos) 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.

Refer to the Package insert for daunorubicin and cytarabine liposome for more information.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 Rave-CTEP-AERS Integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of Adverse Events (AEs) 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.

Adverse Events that occur after informed consent is signed and prior to start of treatment are collected in Medidata Rave using either the Adverse Baseline Symptoms form (SAE) or the Pre-treatment Biopsy Adverse Event form (AE and SAE that occur as a result of tissue biopsy specimen collection).

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 event should be reported 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 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. 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.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

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

Note: A death on study requires both routine and expedited reporting, regardless of causality as long as the death occurred within 30 days after the last administration of the investigational agent. Attribution to treatment or other cause must be provided.

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.

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

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 patient 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 electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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 submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 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 within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 10.4):

CTCAE SOC	Adverse Event	Grade
Skin And Subcutaneous Tissue Disorders	Infusion Reactions	3
Skin And Subcutaneous Tissue Disorders	Rash	3
General Disorders And Administration Site Conditions	Fever	3
Blood And Lymphatic System Disorders	Febrile neutropenia	3
Infections And Infestations	Infection	3
Gastrointestinal Disorders	Nausea	3
General Disorders And Administration Site Conditions	Fatigue	3
Metabolism And Nutrition Disorders	Anorexia	2
Investigations	Lymphocyte count decreased	3
Investigations	Neutrophil count decreased	3
Investigations	Platelet count decreased	3
Investigations	White blood cell count decreased	3

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must <u>also</u> be reported in routine study data submissions.**

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

- Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of

age or disease state) of a female patient or the partner of a male patient occurring while the patient is on pomalidomide or within 28 days after the patient's last dose, are considered immediately reportable events. Pomalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported via CTEP-AERS as a grade 4 event under: SOC pregnancy, puerperium and perinatal conditions; adverse event: pregnancy, puerperium and perinatal conditions-other, fetal exposure.
    - The female patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

- The Investigator will follow the female patient until completion of the pregnancy, and must make an amendment to the initial pregnancy report immediately regarding the outcome of the pregnancy and neonatal status (either normal or abnormal outcome).

- If the outcome of the pregnancy was abnormal (including spontaneous or therapeutic abortion, fetal demise and congenital abnormalities), the Investigator should report the abnormal outcome as an amendment to the initial pregnancy report as soon as the as the Investigator has knowledge of the outcome.

- All neonatal deaths and neonatal complications that occur within 28 days of birth should be reported, without regard to causality, as an amendment to the initial pregnancy report. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the pomalidomide should also be reported as an amendment within 24 hours of the Investigator's knowledge of the event.

<u>Male Patients</u>

- If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking pomalidomide should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

10.6 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 expeditiously 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.

10.7 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 AE reporting unless otherwise specified.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy unless otherwise indicated in the Time and Events Tables. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

11.1 Time and Events Table: Induction

Assessments		Treatment Schedule (INDUCTION Therapy daunorubicin and cytarabine liposome with or without re-induction)[1,2]										Day 28 (+7 days)	RECOVERY PERIOD (30-45 DAYS)[2]	Full Heme Recovery or on Day 49 +/- 3 days[2]		EOT[3]	Follow- up[4]
	Pre-study[1]	Day 1	Day 2	Day 3	Day 4	Day 5	Days 6-13	Day 14 (+/-3 days)	Days 15-21	Day 21 (+3 days)	After starting pomalidomide (Arm A) or eligibility for pomalidomide						
Informed Consent	X													Patients with CR/CRi post recovery receive Consolidation +/- SCT see T&E Table 11.3 If No CR complete EOT visit			
Medical History	X																
Physical exam, vital signs, and weight	X	X	X	X	X	X				X			X			X	
ECOG Performance Status	X	X								X			X			X	
Echocardiogram	X																
Pregnancy Test	X[1]						X[5]			X[5]	X[5]	X					
Hematology labs[6]	X	X	X	X	X	X	X[8]	X	X[8]	X	X	X	X			X	
Complete Metabolic Panel (CMP)	X	X[7]	X[7]	X[7]	X[7]	X[7]	X[8]	X	X[8]	X	X[8]	X[8]	X			X	
Tumor lysis labs	X	X[7]	X[7]	X[7]	X[7]	X[7]											
Basic Metabolic Panel (BMP)		X[7]	X[7]	X[7]	X[7]	X[7]											
Coagulation labs	Performed per investigator's discretion																
Concomitant meds	X	X----------X											X			X	
Toxicity		X----------X											X			X	

Assessment (CTCAE v5.0)																	
Bone marrow biopsy	X[9]							X[9]				X[9]		X[9]			
Blood sample for biomarkers	X[10]									X[10]		X[10]		X[10]			
daunorubicin and cytarabine liposome		X		X		X											
Allopurinol[11]		X	X	X	X	X											
Pomalidomide 4 mg (ARM A only)										X[5]	X	X					
Pomalidomide Education and Counseling (Arm A only)										X[12]				X[12]			
Pomalidomide Dispensing (Arm A only)										X[13]							
Survival analysis																	X

1. Screening Windows for pre-study assessments are as follows:
    a. Complete history, physical exam, ECOG performance status, echocardiogram (does not need to be repeated after consent if done within 14 days of study treatment), bone marrow biopsy for disease assessment, and blood samples for biomarkers should be performed within 14 days prior to Day 1 of study treatment (daunorubicin and cytarabine liposome induction).
    b. All other screening evaluations including hematology and chemistry labs, and serum β-HCG pregnancy test (only applies to FCBP) must be performed within 3 days prior to Day 1 of study treatment (daunorubicin and cytarabine liposome induction).

2. Study visits should occur as scheduled in the time and events table unless otherwise specified. If pomalidomide is not administered on Day 21 in Induction Phase, please follow scheduled assessments aligned with Days 15-20 (to be continued Days 22-28) in the induction table. After pomalidomide is administered, please follow the assessments listed in the Induction Time and Events Table under "Daily after pomalidomide (Arm A) or eligibility for pomalidomide until discharge from hospital." Full hematologic recover is defined as (absolute neutrophil count [ANC] $\geq 1x10^9$/L and platelet count $\geq 100 \times 10^9$/L).

3. The end of treatment visit should only occur when patients permanently stop study treatment and should be performed within 30 days (+/-7 days) after the last dose of study medication. Patients who have an ongoing ≥grade 2 or SAE at this visit will continue to be followed until the event is resolved or deemed irreversible by the investigator.

4. See Section 6.4 for long-term follow up plan for this study.

5. An FCBP is a female who: 1) has reached menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (*i.e.*, has had menses at any time in the preceding 24 consecutive months).

a. For patients in Arm A: When starting pomalidomide, serum β-HCG pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of pomalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days; at discontinuation of pomalidomide and at Day 28 post the last dose of pomalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on study treatment (including breaks in treatment), at discontinuation of pomalidomide and at Day 14 and Day 28 post the last dose of pomalidomide (see Appendix D: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods). Pregnancy test during recovery should occur 3-4 weeks after the last dose of pomalidomide.

6. Hematology labs: CBC with differential

7. During induction therapy hematology and serum chemistry labs will be performed twice daily on study Days 1-5 as outlined below.
   - Once daily labs
     - CBC with differential
     - CMP
     - BMP (obtained approximately 12 hrs [+/- 2h] after CMP on the same day)

   - Twice daily labs
     - Tumor lysis labs twice daily for Days 1-5. After day 5, tumor lysis labs should be performed only if clinically indicated. Tumor lysis labs consist of basic metabolic panel, uric acid, LDH, and phosphate.

8. Starting on Day 6, CBC with differential and CMP should be collected three times a week at minimum until completion of pomalidomide or hematologic recovery (whichever occurs later). If patients are hospitalized, it is recommended to check a CBC and CMP daily while hospitalized.

9. Bone marrow aspirate will be collected as follows(for additional information see Section 5):
   a. **Prescreening**:
      i. Bone marrow aspirate sample- 2.5 mL to be sent for next generation sequencing at Foundation Medicine, Inc.
      ii. Bone marrow aspirate sample- 2 mL to be sent for MRD analysis at Hematologics.
      iii. Bone marrow aspirate sample- 2.5 mL to be sent to University of North Carolina Molecular Genetics Laboratory
      iv. Correlative samples- 20 mL to the Tissue Procurement Facility UNC-Chapel Hill, 20 mL stored for future research
      v. Correlative samples- 20 mL to Luznik Laboratory at JHU, 20 mL stored for future research (from UNC and JHU participants only)
   b. Day 14:
      i. 40 ml bone marrow aspirate for correlative research to Luznik Laboratory at JHU (from UNC and JHU participants only)
   c. Day 28(+7 days):
      i. 40 ml bone marrow aspirate for correlative research to Luznik Laboratory at JHU (from UNC and JHU participants only)
   d. Response (between Days 30 and 64):
      i. A Bone marrow biopsy should be performed at full hematologic recovery or by day 49 (+/-3 days) if ANC $<0.5x10^9$/L and Platelets $<25x10^9$/L. Pomalidomide should be discontinued for at least 3 days prior to response assessment.
      ii. 2.5 ml bone marrow aspirate to University of North Carolina Molecular Genetics Laboratory
      iii. 20 ml bone marrow aspirate to Luznik Laboratory at JHU for correlative studies (from UNC and JHU participants only)
      iv. 20 ml bone marrow aspirate to the Tissue Procurement Facility for correlative studies
      v. 2 ml bone marrow aspirate to Hematologics for MRD analysis

10. Correlative blood samples will be collected as described below (for additional information see Section 5.0):
    a. **Pretreatment:**
       i. 8-10 mL EDTA to be sent to University of North Carolina Molecular Genetics Laboratory
       ii. 20 ml sodium heparin tubes for correlative research to Luznik Laboratory at JHU (from UNC and JHU participants only)
       iii. 20 ml sodium heparin tubes for correlative research to the Tissue Procurement Facility UNC-Chapel Hill

b. **Day 21 (For Arm A this should be before pomalidomide):**
   i. 20 ml sodium heparin tubes for correlative research to Luznik Laboratory at JHU (from UNC and JHU participants only)
   ii. 20 ml sodium heparin tubes for correlative research to the Tissue Procurement Facility UNC-Chapel Hill

c. **Day 28 (+ 7 days):**
   i. 40 ml sodium heparin tube for correlative research to Luznik Laboratory at JHU (from UNC and JHU participants only)

d. At Response (between Days 30 and 64):
   i. A Bone marrow biopsy should be performed at full hematologic recovery or by day 49 (+/-3 days) if ANC $<0.5x10^9$/L and Platelets $<25x10^9$/L. Pomalidomide should be discontinued for at least 3 days prior to response assessment.
   ii. 8-10 mL EDTA to be sent to University of North Carolina Molecular Genetics Laboratory
   iii. 20 ml sodium heparin tubes for correlative research to Luznik Laboratory at JHU (from UNC and JHU participants only)
   iv. 20 ml sodium heparin tubes for correlative research to the Tissue Procurement Facility UNC-Chapel Hill

11. To prevent hyperuricemia, all patients without known allergy will receive allopurinol 300 mg PO QD prior to beginning chemotherapy continuing through the period of maximal tumor lysis (at least through Day 5) or other antiuricemia regimen per institutional practice. Refer to Section 6.2.

12. For patients in Arm A: The Pomalidomide Education and Counseling Guidance Document (Appendix E) must be completed and signed by a trained counselor at the participating site prior to each dispensing of Pomalidomide treatment. A copy of this document must be maintained in the patient records. The Pomalidomide Information Sheet (Appendix F) will be given to each patient receiving pomalidomide treatment. The patient must read this document prior to starting pomalidomide study treatment and each time they receive a new supply of study drug.

13. Only enough pomalidomide for the one cycle of study treatment may be provided to the patient each cycle.

11.2 Time and Events Table: Reinduction

Assessments	*Reinduction[1]				Day 21-30 (at least 48 hours after completion of re-induction)	After starting pomalidomide (Arm A) or eligibility for pomalidomide	Day 28 (+7 days)	RECOVERY PERIOD (30-45 DAYS)[2]	Full Heme Recovery or on Day 64 +/- 3 days[2]	Patients with CR/CRi post recovery receive Consolidation +/- SCT see T&E Table 11.3	EOT[2]	Follow-up[3]
	Day 15-21 (Day 1 of reinduction)	Day 15-21 (Day 2 of reinduction)	Day 15-21 (Day 3 of reinduction)	Day 15-21 (after reinduction)								
Physical exam, vital signs, and weight	X		X		X				X		X	
ECOG Performance Status					X				X		X	
Pregnancy Test	X			X^4	X^4		X^4			If No CR complete EOT visit		
Hematology labs[5]	X^5	X^5	X^5	X^6	X^6	X^6	X				X	
Complete Metabolic Panel (CMP)	X^5	X^5	X^5	X^6	X^5	X^6	X^6				X	
Tumor lysis labs	X	X	X									

Concomitant meds	X----------X								X				
Toxicity Assessment (CTCAE v5.0)	X----------X								X			X	
Bone marrow biopsy							X[7]		X[7]				
Blood sample for biomarkers					X[8]		X[8]		X[8]				
daunorubicin and cytarabine liposome Re-induction[9]	X		X										
Pomalidomide 4 mg PO (at least 48 hours after reinduction) Arm A only					X	X	X						
Pomalidomide Education and Counseling (Arm A only)					X[10]				X[10]				
Pomalidomide Dispensing (Arm A only)					X[11]								
Survival analysis													X

*Reinduction with daunorubicin and cytarabine liposome must be initiated by Day 21.
( ) denotes other possible start days for daunorubicin and cytarabine liposome re-induction chemotherapy and subsequent assessments performed as shown above taking into account the delayed start.

1. Study visits should occur as scheduled in the time and events table unless otherwise specified. If pomalidomide is not administered on Day 21 in Induction Phase, please follow scheduled assessments aligned with Days 15-20 (to be continued Days 22-28) in the induction table. After pomalidomide is administered, please follow the assessments listed in the Induction Time and Events Table under "Daily after pomalidomide (Arm A) or eligibility for pomalidomide until discharge from hospital." Full hematologic recover is defined as (absolute neutrophil count [ANC] $\geq 1x10^9$/L and platelet count $\geq 100 \times 10^9$/L).

2. The end of treatment visit should only occur when patients permanently stop study treatment and should be performed within 30 days (+/-7 days) after the last dose of study medication. Patients who have an ongoing ≥grade 2 or SAE at this visit will continue to be followed until the event is resolved or deemed irreversible by the investigator. A response bone marrow aspirate/biopsy should be performed by day 49 +/- 3 days from day 1 of re-induction daunorubicin and cytarabine liposome if ANC $<0.5x10^9$/L and platelets $<25x10^9$/L

3. See Section 6.4 for long-term follow up plan for this study.

4. An FCBP is a female who: 1) has reached menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (*i.e.*, has had menses at any time in the preceding 24 consecutive months).
    a. For patients in Arm A: When starting pomalidomide, serum β-HCG pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of pomalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days; at discontinuation of pomalidomide and at Day 28 post the last dose of pomalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on study treatment (including breaks in treatment), at discontinuation of pomalidomide and at Day 14 and Day 28 post the last dose of pomalidomide (see Appendix D: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods). Pregnancy test during recovery should occur 3-4 weeks after the last dose of pomalidomide.

5. During re-induction therapy hematology and serum chemistry labs will be performed once daily on study Days 1-3 as outlined below.
   - Once daily labs
     - CBC with differential
     - CMP

6. After completion of daunorubicin and cytarabine liposome reinduction and prior to pomalidomide administration, BMP should be done every other day and CMP should be done every other day on alternating days.

7. Bone marrow aspirate will be collected as follows(for additional information see Section 5):
   a. Prescreening:
      i. Bone marrow aspirate sample- 2.5 mL to be sent for next generation sequencing at Foundation Medicine, Inc.
      ii. Bone marrow aspirate sample- 2 mL to be sent for MRD analysis at Hematologics.
      iii. Bone marrow aspirate sample- 2.5 mL to be sent to University of North Carolina Molecular Genetics Laboratory
      iv. Correlative samples- 20 mL to Tissue Procurement Facility UNC-Chapel Hill, 20 mL stored for future research
      v. Correlative samples- 20 mL to Luznik Laboratory, 20 mL stored for future research (from UNC and JHU participants only)
   b. Day 14:
      i. 40 ml bone marrow aspirate for correlative research to Luznik Laboratory (from UNC and JHU participants only)
   c. Day 28(+7 days):
      i. 40 ml bone marrow aspirate for correlative research to Luznik Laboratory (from UNC and JHU participants only)
   d. Response (between Days 30 and 64):
      i. 2.5 ml bone marrow aspirate to University of North Carolina Molecular Genetics Laboratory
      ii. 20 ml bone marrow aspirate to Luznik Laboratory for correlative studies (from UNC and JHU participants only)
      iii. 20 ml bone marrow aspirate to the Tissue Procurement Facility UNC-Chapel Hill for correlative studies
      iv. 2 ml bone marrow aspirate to Hematologics for MRD analysis

8. Correlative blood samples will be collected as described below (for additional information see Section 5.0):
   a. Pretreatment:
      i. 8-10 mL EDTA to be sent to University of North Carolina Molecular Genetics Laboratory
      ii. 20 ml sodium heparin tubes for correlative research to Luznik Laboratory (from UNC and JHU participants only)
      iii. 20 ml sodium heparin tubes for correlative research to the Tissue Procurement Facility UNC-Chapel Hill
   b. Day 21 (For Arm A, this should be before pomalidomide):
      i. 20 ml sodium heparin tubes for correlative research to Luznik Laboratory (from UNC and JHU participants only)
      ii. 20 ml sodium heparin tubes for correlative research to the Tissue Procurement Facility UNC-Chapel Hill
   c. Day 28 (+ 7 days):
      i. 40 ml sodium heparin tube for correlative research to Luznik Laboratory (from UNC and JHU participants only)
   d. At Response (between Days 30 and 64):
      i. 8-10 mL EDTA to be sent to University of North Carolina Molecular Genetics Laboratory
      ii. 20 ml sodium heparin tubes for correlative research to Luznik Laboratory (from UNC and JHU participants only)
      iii. 20 ml sodium heparin tubes for correlative research to the Tissue Procurement Facility UNC-Chapel Hill

9. Daunorubicin and cytarabine liposome re-induction = liposomal daunorubicin 44 mg/m^2 and cytarabine 100 mg/m^2 IV Days 1 and 3 of re-induction.

10. For patients in Arm A: The Pomalidomide Education and Counseling Guidance Document (Appendix E) must be completed and signed by a trained counselor at the

participating site prior to each dispensing of Pomalidomide treatment. A copy of this document must be maintained in the patient records. The Pomalidomide Information Sheet (Appendix F) will be given to each patient receiving pomalidomide treatment. The patient must read this document prior to starting pomalidomide study treatment and each time they receive a new supply of study drug.

11. Only enough pomalidomide for the one cycle of study treatment may be provided to the patient each cycle.

11.3 Time and Events for Consolidation

Patients with CR/CRi may receive up to two cycles of consolidation therapy. Each cycle is 5-8 weeks.

Assessments	Prior to consolidation	Consolidation[2] Day 1 of each cycle	Day 3 of consolidation	Recovery period[3]	Day 21 (+/- 7 days) of each consolidation cycle	End of Consolidation Day 35 (+21 days) from last cycle of consolidation	EOT Visit	Follow Up[9]
Informed Consent							X	
Physical exam, vital signs, weight[1]		X			X	X	X	
Performance Status[1]		X			X			
Echocardiogram	X[4]						X	
Hematology labs[5]		X	X	X[6]	X	X	X	
Complete Metabolic Panel (CMP)		X	X	X[6]	X	X		
Concomitant meds[1]		X	X	X[7]	X	X	X	
Toxicity Assessment[1]		X	X	X[7]	X	X	X	
Bone marrow biopsy						X	X	
Daunorubicin and cytarabine liposome[2]		X	X					
Cytarabine[8]		X	X					
Allogeneic Stem Cell Transplant	May happen before or after consolidation							
Survival analysis								X

1. Pre-consolidation cycle visits and assessment should occur within 3 days as scheduled unless otherwise specified. Other scheduled assessments should occur on days specified in T&E Table unless otherwise specified.
2. Consolidation will include daunorubicin and cytarabine liposome (daunorubicin 29 mg/m^2 and cytarabine 65 mg/m^2) liposome IV Days 1 and 3 for up to 2 Cycles, please see Section 6.1.
3. Recovery period of each consolidation cycle (*i.e.*, Day 4 until Day 1 of subsequent cycle)- refer to Section 6.1.

4. Echocardiogram should be performed within 7 days prior to 1st cycle of consolidation and if clinically indicated.
5. Hematology labs: CBC with differential.
6. Hematology labs (CBC with differential) and CMP to be drawn at a minimum twice weekly during recovery period (*i.e.*, Day 6 until Day 1 of subsequent cycle) of each consolidation phase.
7. Concomitant Medications and Toxicity Assessments should occur once weekly during recovery period (*i.e.*, Day 6 until Day 1 of subsequent cycle) of consolidation
8. In patients who develop cardiomyopathy, have an LEVF <50 prior to starting consolidation, who exceed lifetime anthracycline dose of > 430 mg/m^2 (or >280 mg/m^2 with prior mediastinal radiation) or have any other contraindications to daunorubicin and cytarabine liposome consolidation, moderate to high dose (1-3 g/m^2 IV Q12 hours Days 1, 3 and 5) cytarabine can be used in place of daunorubicin and cytarabine liposome for consolidation.
9. See Section 6.4 for long-term follow up plan for this study.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Hematologic Tumors

Patients will be evaluated using ELN AML Response Criteria (2017) [2]. See Appendix J.

12.1.1 Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with daunorubicin and cytarabine liposome.

Evaluable for Objective Response. Only those patients who have measurable disease present at baseline, have received at least one cycle of induction therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions in Appendix J.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

Medidata Rave is a 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:

- A valid account, 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 an Non-Physician Investigator (NPIVR) or Investigator (IVR), and
    - Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

If the study has a DTL, individuals 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 Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to accept the invitation in the Tasks pane located in the upper right-corner of the iMedidata screen. 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.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at:

http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.3 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. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

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

This study does not use the Rave Calendaring functionality and therefore the DQP Delinquent Forms module will not include details for this study, and the DQP Summary table on the Rave Home page will display *N/A* for the Total Delinquencies summary count.

13.4 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 patient 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 patients, 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.

13.5 Incidental/Secondary Findings Disclosure Procedure

Results will be placed in the patient's medical record if confirmed by a CLIA-certified laboratory and signed off by the MTB. Notification of results of reportable genetic profiling will be provided to the patient's treating physician who will be responsible for sharing results with their patient. Negative reports (*i.e*. no alteration found) will also be reported. If an incidental germline mutation is discovered that has clinical implications with respect to hereditary cancer predisposition, for example, this information will be conveyed through formal genetic counseling. Along with the results, the participant's physician will explain the implications of the testing, including whether their genetic profile renders them eligible for a specific therapy or clinical trial, and/or if their genetic profile carries any prognostic significance for their disease. Participants will be informed that researchers may contact them in the future, to request their participation in new research or in the event new discoveries or therapies become available that may be applicable to their specific genetic profile.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al.*, 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg\ /\ dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

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APPENDIX C PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: 10434

Study Drug(S): Pomalidomide

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX D POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

1.1 Risks Associated with Pregnancy

Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it can cause birth defects or death to an unborn baby.

The teratogenic effect of pomalidomide in humans cannot be ruled out. Therefore, a pregnancy prevention program must be followed.

1.1.1 Definition of Females of Childbearing Potential (FCBP)

A FCBP is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

1.1.2 Definition of Females Not of Childbearing Potential (FNCBP)

Females who do not meet the above definition of FCBP should be classified as FNCBP.

1.2 Counseling

1.2.1 Females of Childbearing Potential

For a FCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting pomalidomide, throughout the entire duration of pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide
- She understands and agrees to inform the Investigator if a change or stop of method of contraception is needed
- She must be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence pomalidomide as soon as it is dispensed following a negative pregnancy test

- She understands and accepts the need to undergo pregnancy testing based on the frequency outlined in this plan (Section 0) and in the Informed Consent
- She acknowledges that she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

The Investigator must ensure that a FCBP:

- Complies with the conditions of the pregnancy prevention plan, including confirmation that she has an adequate level of understanding
- Acknowledges the aforementioned requirements.

1.2.2 Females Not of Childbearing Potential

For a FNCBP, pomalidomide is contraindicated unless all of the following are met (ie, all FNCBP must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- She acknowledges she understands the hazards pomalidomide can cause to an unborn fetus and the necessary precautions associated with the use of pomalidomide.

1.2.3 Males

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time. Therefore, male subjects taking pomalidomide must meet the following conditions (ie, all males must be counseled concerning the following risks and requirements prior to the start of pomalidomide):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a FCBP
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a FCBP
- Understand the potential teratogenic risk if the subject donates semen or sperm.

1.3 Contraception

1.3.1 Female Subjects of Childbearing Potential

Females of childbearing potential enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting pomalidomide; 2) while taking pomalidomide; 3) during dose interruptions; and 4) for at least 28 days after the last dose of pomalidomide.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. If the below contraception methods are not appropriate for the FCBP, she must be referred to a qualified provider of contraception methods to determine the medically effective contraception method appropriate to the subject. The following are examples of highly effective and additional effective methods of contraception:

- Examples of highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])
  - Tubal ligation
  - Partner's vasectomy
- Examples of additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

1.3.2 Male Subjects

Male subjects must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

1.4 Pregnancy Testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for FCBP.

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation, at study discontinuation, and at Day 28 following the last dose of pomalidomide.

Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.

1.5 Pregnancy Precautions for Pomalidomide Use

1.5.1 Before Starting Pomalidomide

1.5.1.1 Female Subjects of Childbearing Potential

Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting pomalidomide. The first pregnancy test must be performed within 10 to 14 days prior to the start of pomalidomide and the second pregnancy test must be performed within 24 hours prior to the start of pomalidomide. The subject may not receive pomalidomide until the study doctor has verified that the results of these pregnancy tests are negative.

Females of childbearing potential must use two reliable forms of contraception simultaneously, or practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact for at least 28 days before starting pomalidomide.

1.5.1.2 Male Subjects

Male subjects must agree to practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or agree to use a condom during sexual contact with a pregnant female or a FCBP while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.

1.5.2 During and After Study Participation

1.5.2.1 Female Subjects

- Females of childbearing potential with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation, at study discontinuation, and at Day 28 following the last dose of pomalidomide.
- Females of childbearing potential with irregular menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every

14 days while taking pomalidomide, at study discontinuation, and at Days 14 and 28 following the last dose of pomalidomide.

- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control if not committing to complete abstinence, or confirm commitment to complete abstinence.
- If a FCBP considers the need to change or to stop a method of contraception, the Investigator must be notified immediately.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a subject, pomalidomide must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Pomalidomide must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

1.5.2.2 Male Subjects

- Must practice complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or use a condom during sexual contact with a pregnant female or a FCBP while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide, even if he has undergone a successful vasectomy.
- Must not donate semen or sperm while receiving pomalidomide, during dose interruptions or for at least 28 days after the last dose of pomalidomide.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male subject while taking pomalidomide, the Investigator must be notified immediately.

1.5.3 Additional Precautions

- Subjects should be instructed to never give pomalidomide to another person.
- Subjects should be instructed to return any unused capsules to the study doctor.
- Subjects should not donate blood while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.

- No more than a 28-day pomalidomide supply may be dispensed with each cycle of pomalidomide.

APPENDIX E POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT

1. Pomalidomide Education and Counseling Guidance Document for Female Subjects

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

Check one risk category:

- ☐ FCBP (Female of childbearing potential): a female who: 1) has achieved menarche (first menstrual cycle) at some point, 2) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)
- ☐ NOT FCBP

1.1 Female of Childbearing Potential:

1. I have verified and counseled the subject regarding the following:

- ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. Females of childbearing potential must agree not to become pregnant while taking pomalidomide.
- ☐ That the required pregnancy tests performed are negative.
- ☐ The subject confirmed that she is using TWO reliable methods of birth control at the same time, or complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) from heterosexual contact (at least 28 days prior to receiving pomalidomide, while receiving pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide).

  One highly effective method and one additional method of birth control must be used AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

  – Examples of highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants, levonorgestrel-releasing intrauterine system [IUS], medroxyprogesterone acetate depot injections, ovulation inhibitory progesterone-only pills [e.g. desogestrel])

- Tubal ligation
- Partner's vasectomy

– Examples of additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

☐ The subject confirmed that even if she has amenorrhea she must comply with advice on contraception.

☐ Pregnancy tests before, during administration of pomalidomide and at the last dose of pomalidomide, even if the subject agrees not to have reproductive heterosexual contact.

☐ Frequency of pregnancy tests to be done:

– Two pregnancy tests will be performed prior to receiving pomalidomide, one within 10 to 14 days, and a second within 24 hours of the start of pomalidomide.

– Every week during the first 28 days of this study and a pregnancy test every 28 days while the subject is taking pomalidomide if menstrual cycles are regular.

– Every week during the first 28 days of this study and a pregnancy test every 14 days while the subject is taking pomalidomide if menstrual cycles are irregular.

– If the subject missed a period or has unusual menstrual bleeding.

– When the subject is discontinued from the study and at Day 28 after the last dose of pomalidomide if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at Days 14 and 28 after the last dose of pomalidomide.

☐ The subject confirmed that she will stop taking pomalidomide immediately in the event of becoming pregnant and to call her study doctor as soon as possible.

☐ The subject confirmed that she has not and will not breastfeed a baby while taking pomalidomide and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will never share pomalidomide with anyone else.

☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.

☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.

☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.

2. I have provided the Pomalidomide Information Sheet to the subject.

1.2 Female Not of Childbearing Potential (Natural Menopause for at Least 24 Consecutive Months, a Hysterectomy, or Bilateral Oophorectomy):

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject has not and will never share pomalidomide with anyone else.
   - ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The subject confirmed that she will return unused pomalidomide capsules to the study doctor.
2. I have provided the Pomalidomide Information Sheet to the subject.

Do Not Dispense Pomalidomide if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence from heterosexual contact) at least 28 days prior to receiving pomalidomide, while receiving pomalidomide and during dose interruptions.**
- **The subject stated that she has or does not want to adhere to pregnancy precautions outlined within this Pregnancy Prevention Plan (PPP).**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

2. Pomalidomide Education and Counseling Guidance Document for Male Subjects

To be completed prior to each dispensing of pomalidomide.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (dd/mmm/yyyy)

1. I have verified and counseled the subject regarding the following:
   - ☐ Potential risk of fetal exposure to pomalidomide: A teratogenic potential of pomalidomide in humans cannot be ruled out. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby.
   - ☐ The subject confirmed that he has practiced complete abstinence (True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence [eg calendar, ovulation, symptothermal or post-ovulation methods] and withdrawal are not acceptable methods of contraception.) or used a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or FCBP, while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject confirmed that he has not impregnated his female partner while in the study.
   - ☐ The subject confirmed that he will notify his study doctor if his female partner becomes pregnant and the female partner of a male subject taking pomalidomide confirmed that she will call her healthcare provider immediately if she becomes pregnant.
   - ☐ The subject has not and will never share pomalidomide with anyone else.
   - ☐ The subject confirmed that he has not donated and will not donate semen or sperm while taking pomalidomide or during dose interruptions and that he will not donate semen or sperm for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not donate blood while taking pomalidomide, during dose interruptions and for at least 28 days after the last dose of pomalidomide.
   - ☐ The subject has not and will not break, chew, or open pomalidomide capsules at any point.
   - ☐ The subject confirmed that he will return unused pomalidomide capsules to the study doctor.
2. I have provided the Pomalidomide Information Sheet to the subject.

<u>Do Not Dispense Pomalidomide if:</u>

- **The subject stated that he has or does not want to adhere to pregnancy precautions outlined within this PPP.**

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____(dd/mmm/yyyy)

Maintain a copy of the Education and Counseling Guidance Document in the subject's records.

APPENDIX F POMALIDOMIDE INFORMATION SHEET

For subjects enrolled in clinical research studies

Please read this Pomalidomide Information Sheet before you start taking pomalidomide and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rats and rabbits.

   If you are a female who is able to become pregnant:

   - **Do not take pomalidomide if you are pregnant or plan to become pregnant**
   - **You must practice complete abstinence from sexual contact with a male or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting pomalidomide
     - while taking pomalidomide
     - during breaks (dose interruptions) of pomalidomide
     - for at least 28 days after the last dose of pomalidomide
   - **You must have pregnancy testing done at the following times:**
     - within 10 to 14 days prior to the first dose of pomalidomide
     - 24 hours prior to the first dose of pomalidomide
     - weekly until completion of pomalidomide
     - if you have regular menstrual periods: every 28 days after the first month until completion of pomalidomide
     - if you have irregular menstrual periods: every 14 days after the first month until completion of pomalidomide
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of pomalidomide (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking pomalidomide if you become pregnant while taking pomalidomide**
     - If you suspect you are pregnant at any time during the study, you must stop pomalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to the National Cancer Institute

who will report the cases to the pharmaceutical collaborator, Celgene Corporation.

- **Do not breastfeed while taking pomalidomide and for at least 28 days after the last dose of pomalidomide**
- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not able to become pregnant:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to an unborn baby in females whose male partner is receiving pomalidomide is unknown at this time.

- Male subjects (including those who have had a vasectomy) must practice complete abstinence or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
  - While you are taking pomalidomide
  - During breaks (dose interruptions) of pomalidomide
  - For at least 28 days after the last dose of pomalidomide
- **Male subjects should not donate sperm or semen** while taking pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
- **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to the National Cancer Institute who will report the cases to the pharmaceutical collaborator, Celgene Corporation. Your partner should call their healthcare provider immediately if they become pregnant.**

2. All subjects:

- **Do not share pomalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.**
- **Do not donate blood** while you take pomalidomide, during breaks (dose interruptions) and for at least 28 days after the last dose of pomalidomide.
- **Do not break, chew, or open pomalidomide capsules at any point.**
- You will get no more than a 28-day supply of pomalidomide at one time.
- Return unused pomalidomide capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

APPENDIX G CELGENE PREGNANCY PREVENTION AND COUNSELING PROGRAM SITE COUNSELOR IDENTIFICATION FORM

Celgene Corporation	**Celgene Pregnancy Prevention & Counseling Program Site Counselor Identification Form** **NCI Protocol #:**

- **Please identify at least two (2) counselors and fax back to 888-314-2392**
- **Use one form per counselor.**
- **Identified counselors must be licensed healthcare professionals (e.g. RN, PA, RPh, PhD, LPN, CNP, or MD) and must not be the principal investigator.**
- **If you have any questions, please email (coop_ma@celgene.com)**

General Information

Principal Investigator: _____ Institution Name: _____

Counselor Information

CTEP person ID: _____ CTEP site ID: _____

First Name: _____ Middle Initial: _____ Last Name: _____

License Type: (circle one) MD PhD PA CNP RN LPN RPh Other: _____

Email Address: _____

Phone: _____ Fax: _____

Institution Street Address: _____

City: _____ State/Region: _____

Zip/Post Code: _____ Country: _____

Which training will you require? ☐ **Adult** ☐ **Pediatric**

Were you previously approved as a Counselor? ☐ **No** ☐ **Yes (Previous training)** ☐ **Adult** ☐ **Pediatric**

If no, please list all the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) that you *plan to provide* counseling for:

If yes, please list the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) *for protocols Celgene has already associated you with*:

Protocol#:	CTEPsiteID	Institution

APPENDIX H PATIENT'S MEDICATION DIARY FOR POMALIDOMIDE

(See next page)

CTEP-assigned Protocol #_10434_____
Local Protocol # _____

PATIENT'S MEDICATION DIARY – POMALIDOMIDE

Today's date _____ **Agent**_____**Pomalidomide**_____

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month.
2. You will take your dose of pomalidomide each day. You will take one ___ capsule every day. You should swallow the capsule whole. **Do not chew**. Do not break or open the capsules.
3. If a dose of pomalidomide is missed, take the dose within 12 hours of when it is due. If more than 12 hours have passed, the dose should be skipped. Take the next dose at the usual time. Do not take 2 doses to make up for the one missed. If a patient vomits after taking pomalidomide, doses will not be made up and should be taken at the next scheduled dose.
4. Record the date, the number of capsules of each size you took, and when you took them.
5. If you have any comments or notice any side effects, please record them in the Comments column.
6. Please return the forms to your physician when you go for your next appointment.

Day	Date	What time was dose taken?	# of capsules taken _ mg	Comments
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____ _____
4. Total number of capsules taken this month (each size)_____
5. Physician/Nurse/Data Manager's Signature _____

Patient's signature:_____

APPENDIX I CYTARABINE DRUG INFORMATION FOR HIGH DOSE CYTARABINE (HiDAC) CONSOLIDATION

Below is a summary of information for cytarabine. For additional information, please refer to the prescribing information.
https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=681b5dc4-4fcf-4fab-ad78-02cb9a4a5dd0&type=display

Product description:
Cytarabine Injection, an antineoplastic, is a sterile isotonic solution for intravenous and subcutaneous use. Cytarabine is cytotoxic to a wide variety of proliferating mammalian cells in culture. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G_1 phase to the S-phase. Although the mechanism of action is not completely understood, it appears that cytarabine acts through the inhibition of DNA polymerase.

Cytarabine Injection, an antineoplastic, is a sterile isotonic solution for intravenous and subcutaneous use, which contains no preservative and is available in 20 mg/mL (1000 mg/50 mL) Pharmacy Bulk Package.

A Pharmacy Bulk Package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for intravenous infusion.

Each mL contains 20 mg cytarabine, USP and the following inactive ingredients: sodium chloride 0.68% and Water for Injection q.s. When necessary, the pH is adjusted with hydrochloric acid and/or sodium hydroxide to a target pH of 7.4. Each vial contains approximately 5.82 mEq sodium.

Agent Supply:
Cytarabine will be commercially supplied.

Solution preparation
Please refer to the package insert.

Route of administration:
IV

Dosage and Administration
In patients who develop cardiomyopathy or who exceed lifetime anthracycline dose of > 430 mg/m^2 (or >280 mg/m^2 with prior mediastinal radiation) or have any other contraindications to daunorubicin and cytarabine liposome consolidation, moderate-high dose (1-3 g/m^2 IV Q12 hours days 1, 3 and 5) cytarabine can be used in place of daunorubicin and cytarabine liposome for consolidation.

Storage
Store at 20°C to 25°C (68°F to 77°F) [USP Controlled Room Temperature].

Stability
Chemical stability studies were performed by a stability indicating HPLC assay on cytarabine injection in infusion solutions. These studies showed that when cytarabine injection was diluted with Water for Injection, 5% Dextrose Injection or Sodium Chloride Injection, in both glass and plastic infusion bags, 97-100% of the cytarabine was present after 8 days storage at room temperature.

Adverse Events:
Expected Reactions: Because cytarabine is a bone marrow suppressant, anemia, leukopenia, thrombocytopenia, megaloblastosis and reduced reticulocytes can be expected as a result of administration with cytarabine. The severity of these reactions are dose and schedule dependent. Cellular changes in the morphology of bone marrow and peripheral smears can be expected.

Infectious Complications: Infection: Viral, bacterial, fungal, parasitic, or saprophytic infections, in any location in the body may be associated with the use of cytarabine alone or in combination with other immunosuppressive agents following immunosuppressant doses that affect cellular or humoral immunity. These infections may be mild, but can be severe and at times fatal.

The Cytarabine (Ara-C) Syndrome: A cytarabine syndrome has been described by Castleberry. It is characterized by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6-12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are deemed treatable, corticosteroids should be contemplated as well as continuation of therapy with Cytarabine Injection.

Most Frequent Adverse Reactions: Anorexia, hepatic dysfunction, nausea, fever, vomiting, rash, diarrhea, thrombophlebitis, oral and anal inflammation or ulceration, bleeding (all sites). Nausea and vomiting are most frequent following rapid intravenous injection.

Less Frequent Adverse Reactions: Sepsis, abdominal pain, pneumonia, freckling, cellulitis at injection site, jaundice, skin ulceration, conjunctivitis (may occur with rash), urinary retention, dizziness, renal dysfunction, alopecia, neuritis, anaphylaxis, neural toxicity, allergic edema, sore throat, pruritus, esophageal ulceration, shortness of breath, esophagitis, urticaria, chest pain, pericarditis, headache, bowel necrosis, pancreatitis, sinus bradycardia**.**

Handling and Disposal:
Procedures for proper handling and disposal of anti-cancer drugs should be considered. Several guidelines on this patient have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Dispose of remaining drug per institutional guidelines.

APPENDIX J RESPONSE CRITERIA FOR AML

Category	Definition
Response	
CR without minimal residual(CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC
Complete remission (CR)	Bone marrow blasts ,< 5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 x 10^9/L (1000/mL); platelet count ≥100 x 10^9/L (100 000/mL)
CR with incomplete hematologic recovery (CRi)	All CR criteria except for residual neutropenia (< 1.0 x 10^9/L [1000/mL]) or thrombocytopenia (< 100 x 10^9/L
Morphologic leukemia-free state (MLFS)	Bone marrow blasts < 5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%
Treatment failure	
Primary refractory disease	No CR or CRi after 1-2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause
Relapsed Disease (after CR, CRh, or CRi)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood in at least 2 peripheral blood samples at least 1 week apart; or development of extramedullary disease

(Dohner *et al*., 2022)

APPENDIX K REQUISITION FORM: MOLECULAR GENETICS LABORATORY, UNC HOSPITALS

Use only for: NCI 10434: Randomized Phase 2 Study of daunorubicin and cytarabine liposome + Pomalidomide versus daunorubicin and cytarabine liposome in Newly Diagnosed AML with MDS-Related Changes.
Facility Name (Sending Site):_____

Facility Address: _____ City/State/Zip:_____

Phone number: _____

Form Completed By: _____

Specimen ID: _____ *(Write the ID or place labels with specimen ID only)*

Specimen Type:

1. *Peripheral Blood – EDTA ; Number of Tubes: _____*
2. *Bone marrow Aspirate – EDTA; Number of Tubes: _____*
3. *Bone marrow Aspirate – Sodium Heparin; Number of Tubes: _____*

Collection Date & Time_____

1. Label each sample with the following information:
   - Specimen ID
   - Date and time of sample collection; and
   - Initials of person responsible for collection

2. Packaging the sample:

a. Place absorbent material around the labeled specimen container, and insert into a watertight container. Paperwork should be enclosed in a separate plastic bag accompanying the specimen.

b. Place the container and the paperwork (this requisition) in a sturdy outer container along with a cold pack. Add enough cold packs to the container for the tubes to arrive cold at UNC. **DO NOT SHIP ON DRY ICE**

c. **Total number of EDTA Tubes shipped: _____ Date Shipped: _____**

d. Seal the shipping container with waterproof tape. Mail the package promptly by an express service (preferably FedEx) to the following address.

Attn: Molecular Genetics Lab
McLendon Clinical Laboratories

Outreach Services, 1st floor, East Wing
UNC Hospitals
Chapel Hill, NC - 27514
Phone: (984) 974-1825

e. The specimens must be shipped for arrival to the laboratory on **Monday through Friday**. Molecular Genetics laboratory is closed over the weekends, and specimens cannot be accepted on weekends.

a. Please send a 'heads-up' email with the NCI 10434 Specimen ID, and shipment tracking to the UNC staff email addresses below to ensure receipt: Rachana.kshatriya@unchealth.unc.edu and wendy.thompson@unchealth.unc.edu

Questions? Call *UNC Molecular Genetics Laboratory* at (984) 974-1825
UNC use only: receipt date_____
time_____MLM#_____initials_____

APPENDIX L TUMOR PROCUREMENT FACILITY SPECIMENT SHIPPING INSTRUCTIONS

Shipping instructions for AMBIENT samples:

- Include the appropriate submission form with each sample.
- For tissue slides please also include the corresponding pathology report(s). Remove name, MRN or any other PHI from the report. Write the initials, study number (NCI10434) and sequence number on the pathology report.
- Ship overnight. These samples must NOT be shipped on dry ice.
- Samples may only be sent Monday through Thursday. DO NOT ship on Friday, Saturday, Sunday, or the day before a holiday. Allow ample time for delivery. Any questions regarding holiday schedules may be addressed to the appropriate lab contact(s) on the specimen submission forms.
- Please notify CPO PM and UNC-TPF of an incoming shipment by e-mailing a copy of the submission form.

Shipping instructions for Refrigerated (2–8^{o}C) samples:

- Include the appropriate submission form with each sample.
- For fresh tissue please also include the corresponding pathology report(s). Remove name, MRN or any other PHI from the report. Write the initials, study number (NCI10434) and sequence number on the pathology report.
- Ship overnight. These samples must NOT be shipped on dry ice; send with gel packs that will maintain the fresh tissue sample at refrigerator temperatures (2 – 8^{0}C)
- Samples may only be sent Monday through Thursday. DO NOT ship on Friday, Saturday, Sunday, or the day before a holiday. Allow ample time for delivery.
- Please notify CPO PM and UNC-TPF of an incoming shipment by e-mailing a copy of the appropriate submission form.

Shipping instructions for FROZEN samples:

- Please ship frozen PBMC, plasma, and tissue as they are collected and processed. Do not wait to batch ship.
- Samples may only be sent Monday through Wednesday. DO NOT ship on Thursday, Friday, Saturday, Sunday, or the day before a holiday. Allow ample time for delivery.
- Package samples in an insulated Styrofoam box with plenty of dry ice.
- Place Styrofoam box within another box (e.g., cardboard, wooden, plastic).
- Complete and affix Dry Ice label to the outside of the package.
- Please send samples by courier that guarantees overnight service.
- Please notify the CPO PM and UNC-TPF of an incoming shipment by e-mailing a copy of the appropriate submission form.

IATA PACKING INSTRUCTIONS

Packing Instructions — Class 6 — Toxic and Infectious Substances

- http://www.iata.org/whatwedo/cargo/dangerous_goods/Documents/DGR52_PI650_EN.pdf

Multicenter Site Shipping of Specimens

- Multicenter Sites will ship all specimens to:

Tissue Procurement Facility
108 MacNider Building
333 South Columbia St
Chapel Hill, NC 27599

(All specimens will be shipped as appropriate to the specimen type as outlined above.)

UNC-TPF Receipt of Specimens

- Upon Receipt, UNC-TPF will notify the sending site and UNC project manager of the receipt and condition of all specimens.
- UNC-TPF Storage and Distribution of Specimens
- UNC-TPF will store all frozen specimens at -70 or below.
- All whole blood shipped ambient will be processed to PBMC/Plasma and stored as above.
- All tissue specimens will be stored in a desiccator.
- All specimens will be stored at the UNC-TPF biorepository until requested for release to the lab(s) of analysis.

APPENDIX M CRYOPRESERVATION OF PBMC'S FROM FRESH PB AND BM SAMPLES

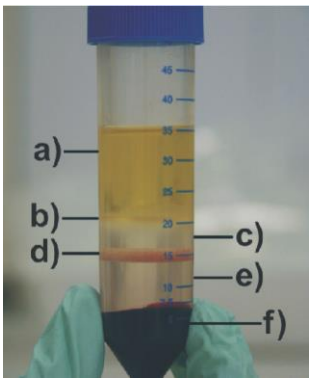
Purpose:
PBMCs (peripheral blood mononuclear cells) are cryopreserved for later separation for Aiolos expression and lymphocyte subsets analysis.

Supplies:
- (2) 10mL green top Heparin tubes
- Ficoll Plaque Premium GE ficoll-paque 17-5442-03
- FBS (Fetal Bovine Serum) SH3008803HI Heat Inactivated FBS
- PBS Hyclone DPBS Modified w/o calcium w/o magnesium
- Wide 1000ul Pipette tips – Finntip 9405163
- Conical Tubes 50ml
- Cryovial for storing isolated mononuclear cells (For sample quality and quantity please use externally threaded cryovials, such as Fisherbrand 10-500-26)
- Mr. Frosty ™ freezing chamber

Specimen Process:

1. Warm-up the Ficoll medium to room temperature (RT) protected from light, and mix the medium by inverting the bottle gently.
2. Aseptically transfer 15-20ml of Ficoll medium to a 50ml conical tube
3. Carefully layer the blood (max 25 ml per tube) on top of the Ficoll, using a serological pipette. Close the tubes with the screw-cap.
4. Centrifuge 30 minutes at 400 x g at 20°C in a swinging bucket rotor without brake.
5. After centrifugation, the sequence of layers occurs as follows (from top to bottom):

    a. Plasma
    b. Enriched fraction (interphase of lymphocytes or mononuclear cells)
    c. Ficoll medium
    d. Ficoll medium
    e. Pellet (erythrocytes and granulocytes)



6. Remove the plasma layer fraction up to a minimum remnant of 5 to 10 mm above the interphase. This helps to prevent contamination of the enriched cells with platelets.
7. Harvest the enriched cell fraction (lymphocytes or mononuclear cells) by means of a Pasteur pipette and transfer into a new 50mL Falcon tube.
8. Add PBS to the cells in the conical tube tube to a total volume of 50mL, and centrifuge for 10 minutes at room temperature (18-25°C) at a speed sufficient to

sediment the cells without damaging cells. i.e. 400 x g. (Washing removes Ficoll medium and reduces the percentage of platelets).

9. Remove supernatant, and add enough PBS to the tube for cell count.
10. Count cell numbers. Expect 1 x 10^6 cells/ml of whole blood.
11. Prepare a **minimum** of 5-10 million cells in each cryovial in 1.8 mls final volume.
12. Spin down the specimens at 400 x g and add freezing medium (90% FBS and 10% DMSO) to the cells. Mix it with pipet up and down 4 times gently. Avoid making bubbles.
13. Each cryovial tube should be marked on a temperature-resistant label with the following mandatory information:
    - Study Number, Study Site, and Subject Number (1522UNC-101, 1522JH-102)
    - Time Point
    - Date Sample Drawn and Processed
    - Sample Type (PBMC)
    - Cell Number (PBMC)
    - Freezing Volume (PBMC)
14. The vials should be put in a pre-chilled slow freezing container Mr. Frosty™ to guarantee that the temperature drops 1 degree/minute, and put it in -80°C freezer for 18-72 hours prior to storing them in LN2 unit.
15. All vials should be transferred to liquid nitrogen.
16. TPF should use their database to track the aliquots.

Tissue Procurement Facility BMMNC from Bone Marrow Specimens

Supplies:

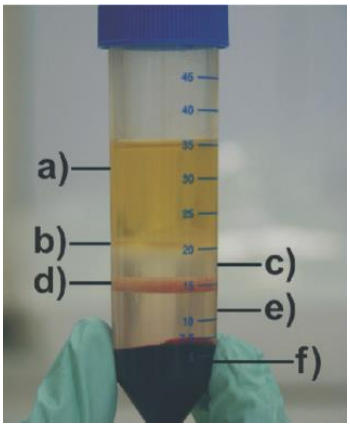
- 100 u strainer
- (2-4) 10MmL green top Heparin tubes
- Ficoll Plaque Premium GE ficoll-paque 17-5442-03
- FBS (Fetal Bovine Serum) SH3008803HI Heat Inactivated FBS
- PBS Hyclone DPBS Modified w/o calcium w/o magnesium
- Wide 1000ul Pipette tips – Finntip 9405163
- Conical Tubes 50ml
- 100 uM filter BD Falcon Cell Strainer 352360
- Cryovial for storing isolated mononuclear cells (For sample quality and quantity please use externally threaded cryovials, such as Fisherbrand 10-500-26)
- Mr. Frosty ™ freezing chamber

Specimen Process:

1. Warm-up the Ficoll medium to room temperature (RT) protected from light, and mix the medium by inverting the bottle gently.
2. Aseptically transfer 15-20ml of Ficoll medium to a 50ml conical tube

3. Carefully layer the bone marrow aspirate (max 25 ml per tube) on top of the Ficoll, using a serological pipette. Close the tubes with the screw-cap.
4. Centrifuge 30 minutes at 400 x g at 20°C in a swinging bucket rotor without brake.
5. After centrifugation, the sequence of layers occurs as follows (from top to bottom):

    a. Plasma
    b. Enriched fraction (interphase of lymphocytes or mononuclear cells)
    c. Ficoll medium
    d. Ficoll medium
    e. Pellet (erythrocytes and granulocytes)



6. Remove the plasma layer fraction up to a minimum remnant of 5 to 10 mm above the interphase. This helps to prevent contamination of the enriched cells with platelets.
7. Harvest the enriched cell fraction (lymphocytes or mononuclear cells) by means of a Pasteur pipette and filter it through a 100u cell strainer into a new 50mL conical tube.
8. Add PBS to the cells in the centrifuge tube to a total volume of 50mL, and centrifuge for 10 minutes at room temperature (18-25°C) at a speed sufficient to sediment the cells without damaging cells. i.e. 400 x g. (Washing removes Ficoll medium and reduces the percentage of platelets).
9. Remove supernatant, and add enough PBS to the tube for cell count.
10. Count cell numbers. Expect a large number of cells that are AML tumor blasts, nucleated red blood cells, myeloid cells, and lymphocytes.
11. Prepare a **minimum** of 10 - 15 million cells in each cryovial in 1.8 mls final volume.
12. Spin down the specimens at 400 x g and add freezing medium (90% FBS and 10% DMSO) to the cells. Mix it with pipet up and down 4 times gently. Avoid making bubbles.
13. Each cryovial tube should be marked on a temperature-resistant label with the following mandatory information:
    - Study Number, Study Site, and Subject Number (1522UNC-101, 1522JH-102)
    - Time Point
    - Date Sample Drawn and Processed
    - Sample Type (BMMNC)
    - Cell Number (BMMNC)
14. The vials should be put in a pre-chilled slow freezing container Mr. Frosty ™to guarantee that the temperature drops 1 degree/minute, and put it in -80°C freezer for 18-72 hours prior to storing them in LN2 unit.
15. All vials should be transferred to liquid nitrogen.
16. TPF should use their database to track the aliquots.