Activated: 1/14/19
Closed: 5/21/21

Version Date: 01/23/20
Amendment #: 1

CHILDREN'S ONCOLOGY GROUP

AINV18P1

A PHASE 1 STUDY OF PALBOCICLIB [redacted], A CDK 4/6 INHIBITOR, IN COMBINATION WITH CHEMOTHERAPY IN CHILDREN WITH RELAPSED ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) OR LYMPHOBLASTIC LYMPHOMA (LL)

Participation Limited to the 21 COG sites that constituted the Phase 1 Consortium and the following institutions:
CA078: Loma Linda University Medical Center
CA139: Lucile Packard Children's Hospital Stanford University
MD017: Johns Hopkins University/Sidney Kimmel Cancer Center
NC007: UNC Lineberger Comprehensive Cancer Center
NY011: Laura and Isaac Perlmutter Cancer Center at NYU Langone
OK003: University of Oklahoma Health Sciences Center
TX020: Cook Children's Medical Center
UT002: Primary Children's Hospital

[redacted]

For COG Operations Contacts see: http://members.childrensoncologygroup.org

TABLE OF CONTENTS

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

AGENT NSC#72256 AND [redacted]
Palbociclib

For COG Phase 1/Pilot Consortium Operations
Contacts see: https://members.childrensoncologygroup.org

IND Sponsor: COG [redacted]

SEE Section 8.2.6, AND Section 8.3.6 FOR SPECIMEN SHIPPING ADDRESSES

The Children's Oncology Group has received a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

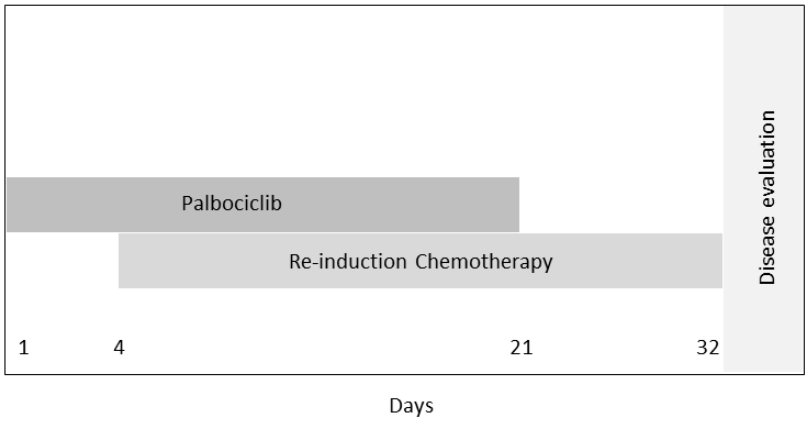
ABSTRACT

AINV18P1 is a pilot study evaluating safety and feasibility of palbociclib in combination with an established re-induction platform for children, adolescents and young adults with relapsed/refractory ALL and lymphoblastic lymphoma. Targeting cell cycle progression has been an effective therapeutic strategy in a spectrum of malignancies. Prior studies have shown that deregulation of the physiological cell cycle machinery is essential for both the induction and progression of ALL. Additionally, molecular targeting of the interaction of D type cyclins with cell cycle dependent kinases (CDK4 and 6) efficiently suppressed ALL growth and disease progression *in vivo* and this effect was augmented by concomitant delivery of cytotoxic agents.

Palbociclib is an orally active, potent, selective inhibitor of CDK4 and CDK6. CDK6 is highly homologous to CDK4 and can perform the same function by phosphorylating retinoblastoma protein (Rb), thus potentially creating a redundant mechanism to promote cell cycle progression. Inhibition of both enzymes is therefore necessary to ensure the greatest possible antitumor activity. Palbociclib inhibits DNA synthesis by preventing progression from the G1 to S phase of the cell cycle. Treatment of tumor cells with palbociclib inhibits Rb phosphorylation and induces growth arrest. Accordingly, a reduction in Rb phosphorylation serves as a biomarker of CDK4/6 inhibition by palbociclib.

Eligible patients will receive a single cycle of re-induction therapy. Palbociclib will be administered once daily for 21 days in combination with an established 4-drug re-induction platform. After completion of the feasibility portion of the study an expanded cohort will be enrolled at the MTD and/or recommended phase 2 dose (RP2D) of palbociclib to further assess the safety and feasibility of this regimen and to preliminarily explore the biological and clinical activity within the confines of a phase 1 study.

EXPERIMENTAL DESIGN SCHEMA



Therapy will be interrupted if there is evidence of progressive disease or drug related dose-limiting toxicity. Each patient will receive a single cycle of therapy.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of palbociclib administered in combination with re-induction chemotherapy in pediatric patients with relapsed B- or T-lineage ALL/LL.

1.1.2 To define and describe the toxicities of palbociclib administered on this schedule.

1.1.3 To characterize the pharmacokinetics of palbociclib in pediatric patients with relapsed B- or T-lineage ALL/LL.

1.2 Secondary Aims

1.2.1 To preliminarily define the antitumor activity of palbociclib in combination with chemotherapy for children with relapsed ALL/LL within the confines of a Phase 1 study.

1.2.2 To assess the biologic activity of palbociclib in this patient population.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Disrupted cell cycle regulation is a hallmark of cancer and targeting the cell cycle machinery has been an approach taken to treat a broad spectrum of malignancies. The cell cycle is divided into G1 (pre-DNA synthesis), S (DNA synthesis), G2 (pre-division) and M (cell division) phases and the transition through these phases is regulated by cyclins and cyclin-dependent kinases (CDKs). Upon mitogenic stimulation, cyclins

engage CDKs, leading to their activation. D-type cyclins are input-sensing proteins that directly receive mitogenic signals. Cyclin D molecules, like all canonical cyclins, feature a cyclin box motif that contains important residues for directly engaging CDKs, and it is through this interaction that catalytic activity is conferred to the CDK.

D-type cyclins associate with either CDK4 or CDK6, which share extensive homology. CDK4 is the key regulator of the G1-S transition. In complex with Cyclin D, CDK4 phosphorylates retinoblastoma protein (Rb) and drives cell cycle progression, a process inhibited by p16INK4A (CDKN2A).[1] With this background and rationale, a number of CDK inhibitors have been developed for the treatment of cancers that show activation of the cyclin D–CDK4/6–INK4–Rb pathway. Palbociclib (formerly PD-0332991) is an orally active small molecule produced by Pfizer that potently and specifically inhibits CDK4 and CDK6 leading to cell cycle arrest and this agent is currently used to treat wide range of cancers in adults.

Acute lymphoblastic leukemia (ALL) survival now approaches 90% for children using conventional cytotoxic agents, but at a cost of cumulative toxicities and late effects. Despite improvements in outcomes for children with B- and T lymphoblastic leukemia (B-ALL and T-ALL) in recent years, the outcome of patients with primary resistant or relapsed disease remains very poor, particularly for children with second or greater relapses, refractory disease or T-cell disease. [2] Remission re-induction rates for this population are less than 40% and very few children survive long term. [3,4] Therefore, current research efforts are focused on a better understanding of the molecular pathogenesis of these diseases in order to identify drug targets that may facilitate the development of more effective and less toxic tumor-specific therapies.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

Preclinical studies in ALL summarized below describe the essential role of cyclin D3 in T-ALL initiation and progression. These studies have also demonstrated that targeting of the CDK4/6 complex using palbociclib, can suppress ALL proliferation and lead to efficient cell death and disease remission in animal models of the disease and in human disease transplant settings.

***CCND3* is over-expressed in T-ALL and is essential for disease initiation and progression.** Sicinska et al. have previously shown that Ccnd2 (Cyclin D2) and Ccnd3 (Cyclin D3) are expressed during lymphocyte differentiation and that they play different roles in this process. [5] To prove the functional connection between Ccnd3 overexpression and T-ALL growth, its expression has been silenced in a large number of human T-ALL cell lines, the majority of which carry *NOTCH1* mutations. Ccnd3 silencing impacted tumor cell growth due to significant inhibition of cell cycle progression (S phase entry). Further, in a transplantation model of NOTCH-driven T ALL deletion of Ccnd3 ($Ccnd3^{-/-}$) failed to induce leukemia whereas Ccnd3 expressing progenitors led to induction of disease that rapidly progressed and killed all recipients by week 10-post transplantation. Normal peripheral T-cells lacking Ccnd3 could be detected but these cells showed no signs of transformation. These studies were the first to identify an essential role for Ccnd3 function in T-ALL. [5]

Targeting Ccnd3:CDK4/6 complexes using a small molecule inhibitor. To determine whether pharmacological inhibition of cyclin D3:CDK4/6 complexes could prove beneficial for the targeting of T-ALL, Aifantis and colleagues treated 15 human and mouse T-ALL cell lines (Fig. 1A), as well as primary T-ALL cells (not shown) with PD-0332991, an orally active small molecule that potently and specifically inhibits CDK4 and CDK6. [6] They demonstrated that PD-0332991 is active at low concentrations (0.5μM) and has the ability to very efficiently suppress S-phase entry, leading to proliferation defects. All lines, including those in which T-ALL was driven by both *NOTCH1* and *TAL1* oncogenes, were sensitive to PD-0332991 treatment. Further biochemical studies were consistent with the cell cycle effects demonstrating specific loss of phosphorylated Rb (pRb) and hyper-phosphorylation and accumulation of the CDK inhibitor p27 (Fig. 1B). Furthermore, mixing of PD-0332991 treated and untreated T-ALL cells *in vitro* proved the cytostatic effects of the treatment. Gene expression analysis of T-ALL lines treated with the inhibitor further supported the specific targeting of the S phase entry machinery in these cells (Fig. 1C). In addition to these *in vitro* studies, Aifantis and colleagues also treated T-ALL animal models with PD-0332991. There was a dramatic response to the drug treatment (Fig. 1D-G) *in vivo* as demonstrated initially by the prolongation of life for the treated animals. Drug treatment led to a significant drop in blood counts, splenomegaly, tissue infiltration and overall disease regression. Surprisingly, PD-0332991 treatment appeared to induce apoptosis of leukemic cells (Figure 1G), explaining the rapid response to the treatment. These were exciting and promising findings and suggested strongly that anti-CDK4/6 treatment could be a very promising way to target T-ALL. [6]

CDK4/6 pharmacologic inhibition in B and T-lineage ALL and in combination with chemotherapy. To determine the effects of CDK4/6 pharmacologic inhibition more broadly in ALL, we expanded studies to include B-lineage ALL and also investigated CDK4/6 inhibition in combination with chemotherapy. B leukemic cell lines (Reh, RS4, UOCB1, Nalm-6) were each treated with 1 μM PD-0332991 for 24 hours. Cell cycle changes were determined by proliferation assays with bromodeoxyuridine (BrdU). Cells were labeled with propidium iodide and anti-BrdU antibody, then evaluated by fluorescence-activated cell sorting (FACS) using a FACScan flow cytometer (BD Scientific). Treatment with PD-0332991 induced G1 phase cell cycle arrest with the percentage of cells in S phase decreased by more than 80% in all B-ALL cell lines evaluated (Fig.2).

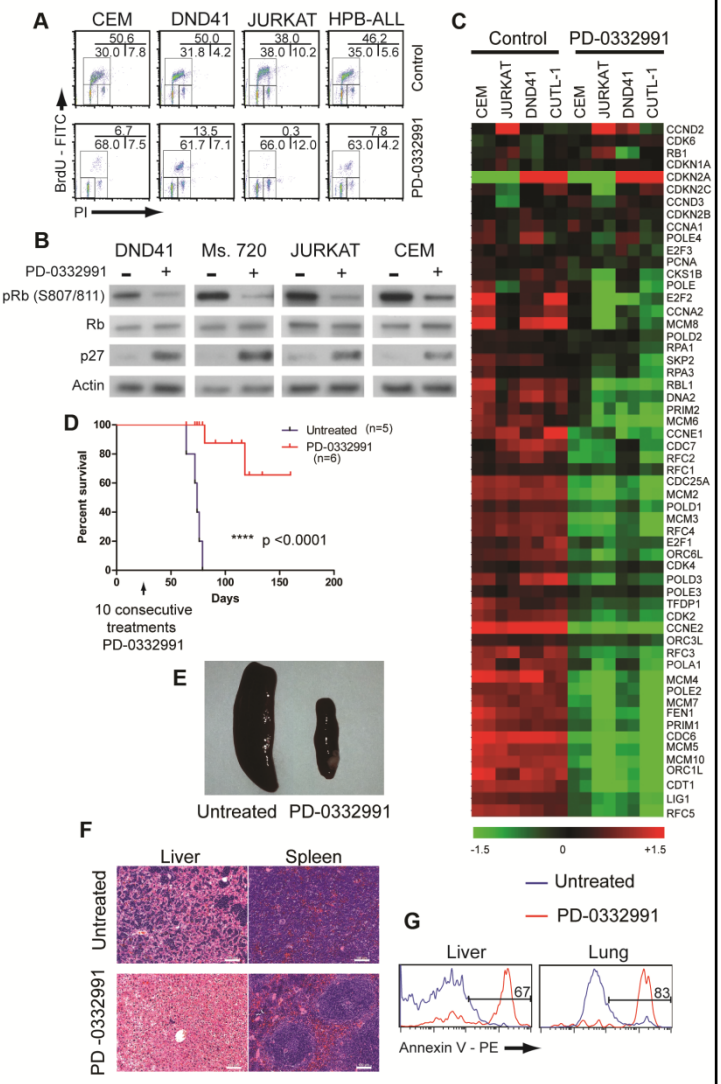


Figure 1. The PD-0332991 inhibitor suppresses T-ALL growth. PD-0332991 efficiently suppresses cell cycle entry in human T-ALL cell lines **(A)**. **B)** PD-0332991 blocks S phase entry by affecting Rb phosphorylation and p27 (Cdkn1b) degradation. **C)** Molecular response to PD-0332991 in human T-ALL cells, demonstrating effects on cell cycle regulators. **D)** Overall survival of different animal cohorts after 10 consecutive days of treatment. Significant effects on spleen size **(E)** and tissue infiltration **(F)** are shown, 2 weeks post treatment. **(G)** Induction of cell death in leukemia cells in response to inhibitor treatment. Annexin staining in liver and lung T-ALL cells is shown.

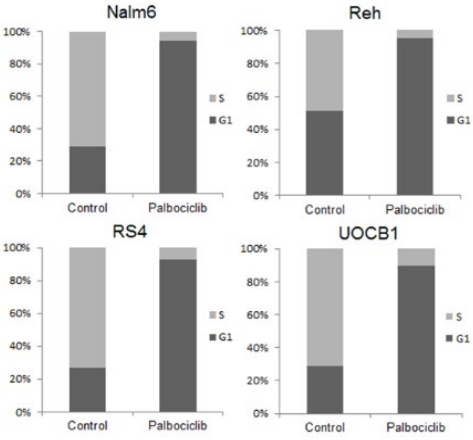


Figure 2. Cell cycle changes after 24 hours of treatment with PD-0332991.

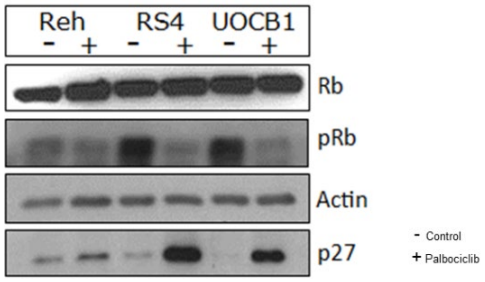


Figure 3. pRb and p27 expression after 24 hours of treatment with PD-0332991.

Cell lines also consistently showed a decrease in pRb and an increase in p27 following treatment with PD-0332991 (Fig.3). As an extension of these studies in cell lines, a panel of primary T-ALL and B-ALL xenografts have been established. Sources of T-ALL cells for these xenografts were identified from the Children's Oncology Group (COG) Cell Bank and all human cells have been sequenced. Disease regression has been observed following treatment for 5 days with PD-0332991 in both B- and T-lineage ALL xenografts (Fig. 4). Combinations of chemotherapy with palbociclib have also been delivered in T and B-ALL xenografts. To determine the impact of drug sequence, xenografts were treated on two different schedules: palbociclib days 1-5

followed by chemotherapy with vincristine, *Erwinia* asparaginase or dexamethasone starting on day 8, or concomitant administration of palbociclib and chemotherapy. No antagonism was observed with either dose schedule and a more significant reduction in disease burden was observed when palbociclib and chemotherapy were administered concomitantly (Fig. 5).

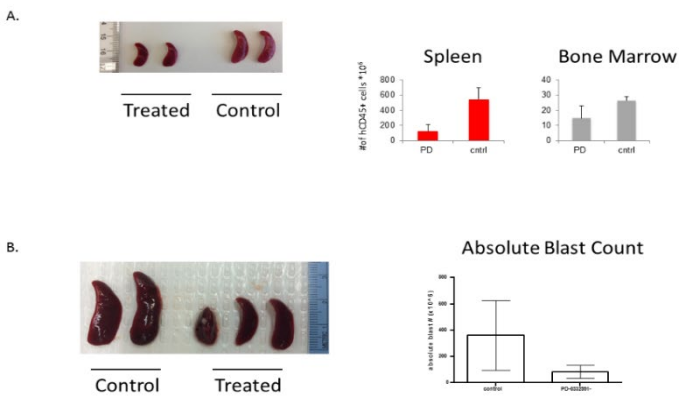


Figure 4. Reduction in disease burden following 5 days of treatment with PD-0332991 in T-ALL (A) and B-ALL (B) xenografts.

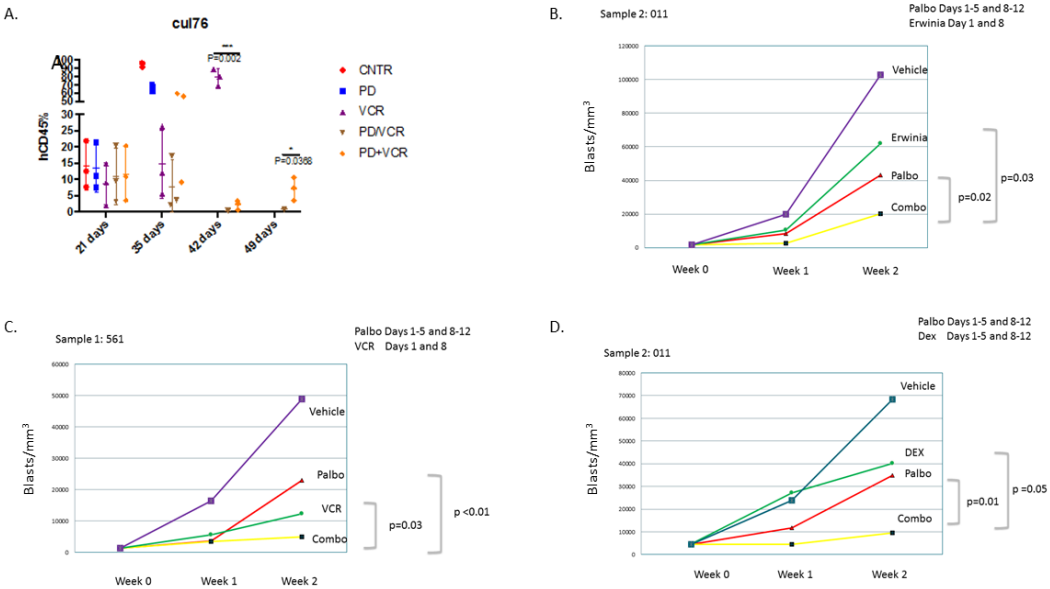


Figure 5. Significant added reduction in disease burden following concomitant treatment with palbociclib plus chemotherapy in T-ALL (A) and B-ALL (B, C and D) xenografts.

2.2.2 Animal Toxicology

Palbociclib has been evaluated in toxicology and safety pharmacology studies of up to 39 weeks in duration (see Investigator Brochure for detailed information). The primary palbociclib toxicities in preclinical studies were to the bone marrow, lymphoid tissues, and testes. These toxicities occurred in both rats and dogs and are consistent with cell cycle inhibition produced by the drug. Bone marrow pancytopenia resulted in decreases in various hematology parameters; however, the changes were reversible following cessation of dosing. Reversible myelosuppression is anticipated in clinical studies and may be dose-limiting. Palbociclib demonstrated a potential for aneugenicity in the in vitro and in vivo micronucleus assays. In addition, palbociclib was determined non-phototoxic.

2.2.3 Preclinical Pharmacokinetic Studies

In nonclinical species (rat, dog, and monkey), palbociclib exhibits low to moderate plasma clearance, large volume of distribution, and moderate oral bioavailability ranging from 23% to 56%. Plasma protein binding of palbociclib is moderate in mouse, rat, rabbit, dog, and human plasma. Radioequivalents were widely distributed to most rat tissues and fluids following an oral dose of [14C]palbociclib, with radioactivity levels consistently greater than those observed in blood. In vitro, palbociclib is primarily metabolized by cytochrome P450 (CYP)3A and sulfotransferase (SULT) 2A1 enzymes. The major primary metabolic pathways for [14C]palbociclib in rats and humans involved sulfonation and oxidation. In rats and dogs, [14C]palbociclib was mainly eliminated via the feces; the high fecal elimination occurred via biliary excretion in rats. Palbociclib and its oxidative metabolite, PF-05089326, demonstrated little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 enzyme activities and thus, showed low potential for CYP-mediated pharmacokinetic drug interactions. However, palbociclib and PF-05089326 caused time dependent inhibition of CYP3A midazolam 1-hydroxylase and testosterone 6β-hydroxylase activities and may have the potential for pharmacokinetic drug interactions with compounds for which CYP3A-mediated metabolism constitutes the primary mechanism of clearance. Palbociclib did not cause induction of CYP1A2, CYP2B6, CYP2C8, or CYP3A4 mRNA expression and/or enzyme activity in vitro in human hepatocytes; thus, the potential for palbociclib to induce these enzymes is considered to be low at clinically relevant concentrations. The potential for palbociclib to inhibit uridine diphosphate glucuronosyltransferase (UGT) enzymes (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) was assessed and the likelihood of drug-drug interaction (DDI) at clinically relevant concentrations is considered low. Overall, based on the in vitro results, palbociclib showed a low potential to inhibit P-glycoprotein (P-gp) (systemically), breast cancer resistance protein (BCRP) (systemically), organic anion transporting polypeptide (OATP)1B1, OATP1B3, bile salt export pump (BSEP), organic anion transporter (OAT)1, OAT3, and organic cation transporter (OCT)2 at clinically relevant concentrations. However, palbociclib has the potential to inhibit OCT1 at clinically relevant concentrations, as well as the potential to inhibit P-gp or BCRP in the GI tract at the proposed clinical dose. Additional details are included in the Investigator Brochure.

2.3 Adult Studies

Palbociclib has been studied as monotherapy or in combination with other agents in several clinical trials for adults with advanced Rb-expressing hematopoietic and solid tumors and it has been well tolerated with dose limiting toxicities of neutropenia and thrombocytopenia. The recommended dose in adults is 125 mg orally once daily for 21 consecutive days in 28-day cycles. Palbociclib has been most extensively studied in post-menopausal women with estrogen-receptor (ER)-positive, human epidermal growth factor receptor (HER) 2-negative advanced breast cancer. Palbociclib received accelerated approval in the US in February 2015 for first-line systemic treatment of post-menopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer and investigation in other malignancies is presently underway.[7] The approval of palbociclib was based on the phase 2 PALOMA-1/TRIO-18 study, where 165 patients were randomized to palbociclib plus letrozole vs. letrozole alone.[8] Median progression-free survival (PFS) was 10.2 months for the letrozole group and 20.2 months for the palbociclib plus letrozole group ($p=0.0004$). These results were confirmed in a double-blind randomized phase 3 trial in 666 post-menopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer. [9] The median PFS was 24.8 months in the palbociclib-letrozole group vs. 14.5 months in the placebo-letrozole group ($p<0.001$). Therapy was well tolerated and the most common treatment-related adverse events in the palbociclib arm were neutropenia, leukopenia, anemia and fatigue. In February 2016, the FDA granted an expanded indication for palbociclib for women with ER-positive, HER2-negative metastatic breast cancer that progressed after prior endocrine therapy after the PALOMA-3 randomized phase 3 trial demonstrated that palbociclib and fulvestrant were associated with a significant improvement in PFS compared with fulvestrant plus placebo (median PFS 9.5 months vs. 4.6 months; $p<0.0001$). [10] While palbociclib has been studied most extensively in combination with hormone therapy, it has also been studied in combination with paclitaxel in metastatic breast cancer. This regimen was well tolerated and prolonged tumor responses were observed. [11]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

There has been one pediatric study of palbociclib (PBTC 042; NCT02255461) to date. The phase 1 single agent trial of palbociclib in children with Rb-positive relapsed, progressive or refractory central nervous system (CNS) tumors conducted by the Pediatric Brain Tumor Consortium opened in October 2014. [12] Patients aged 4-21 years are eligible and the starting dose level for this trial was 50 mg/m^2/day of palbociclib for 21 days consecutively in 28 day cycles for up to 2 years. Among 14 evaluable patients, grade 4 neutropenia in 2 of 4 patients treated at 95 mg/m^2/day (dose level 3) was the only observed dose limiting toxicity (DLT). The maximum tolerated dose (MTD) was defined as 75 mg/m^2/day and the trial is currently enrolling an expansion cohort at this dose. Enrollment will also be expanded to include a cohort of more heavily pre-treated patients, who have received more than 4 prior regimens at a starting dose of 50 mg/m^2/day.

2.5 Overview of Proposed Pediatric Study

AINV18P1 is a pilot study where palbociclib will be administrated in combination with a standard re-induction platform in pediatric relapsed ALL and lymphoblastic lymphoma

(LL). LL patients are included because the patient population is rare and these patients are most commonly treated with ALL regimens. Based on the current pediatric phase 1 trial investigating palbociclib in children with CNS tumors (NCT02255461), the proposed starting dose for this study will be 50 mg/m^2/day for 21 days. Although the MTD was defined as 75 mg/m^2/day, this was in non-heavily pretreated patients and a cohort of more heavily pre-treated patients is currently enrolling at a dose of 50 mg/m^2/day, which is approximately 70% of the recommended dose in adults. Since the most common DLT for palbociclib to date has been myelosuppression and palbociclib will be given in combination with cytotoxic chemotherapy, this trial will start at the lower 50 mg/m^2/day dose level. A pediatric formulation is available.

Block 1 therapy from COG AALL01P2 [13] was selected as the re-induction platform for this study because this regimen has a well-established response, safety and feasibility track record in studies we have conducted previously, both alone and in combination with novel agents.[14,15] The only modification that has been made to this regimen is reducing the number of doses of pegaspargase from 4 to 2 in an effort to minimize the risk for toxicity, particularly among the adolescent and young adult patients. Prior preclinical studies have shown that pretreatment with palbociclib led to synchronous S phase entry and a potentiation of the response to the administration of subsequent cytarabine. [16] However, our preclinical studies in B- and T-ALL xenografts have shown more significant reduction in leukemic burden when palbociclib was given with chemotherapy concomitantly vs. sequentially (Fig. 5) and this is in agreement with preclinical studies in solid tumors in adults (personal communication, Pfizer).

The rolling six trial design will be used for dose determination in this study.[17] Per this design, if 2 or more of a cohort of up to 6 patients experience dose-limiting toxicity (DLT) at the initial dose level, then the MTD has been exceeded and a single dose de-escalation will be conducted. The DLT observation period for the purposes of dose confirmation will be the first cycle of therapy. We plan to study no more than 2 dose levels. After completion of the feasibility portion of the study an expanded cohort will be enrolled at the MTD and/or recommended phase 2 dose (RP2D) of palbociclib to further assess the safety and feasibility of this regimen and to preliminarily explore the biological and clinical activity within the confines of a pilot study. Patients with relapsed B and T-ALL/LL will be eligible and study treatment will consist of a single cycle of palbociclib in combination with chemotherapy.

3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

3.1 Current Study Status

Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the Studies Requiring Reservations page to ensure that a reservation for the study is available. To access the Studies Requiring Reservations page:

1. Log in to https://www.cogmembers.org.
2. From the menu bar, click **eRDES**. *The eRDES sub-menu appears.*
3. Click **Reservation**. *The Studies requiring Reservations page appears.*

3.2 IRB Approval

Local IRB/REB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit IRB/REB approvals to the COG Operations Regulatory email and allow 3 business days for processing. The submission must include a fax coversheet and the IRB approval document(s) emailed (COG email address TBD). When a site has a pending patient enrollment within the next 24 hours, this is considered a "Time of Need" registration. For Time of Need registrations, in addition to marking your submissions as 'URGENT'.

3.3 Patient Registration

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry in the OPEN system (https://open.ctsu.org/open/logonForm.open) once authorization for the release of protected health information (PHI) has been obtained. To register a patient or update an existing registry record in the COG Patient Registry, please go to the OPEN Portal at https://open.ctsu.org and click the COG Patient Registry link on OPEN's Welcome screen.

3.4 Reservation and Contact Requirements

Prior to enrolling a patient on study, a reservation must be made through the OPEN website and the Study Chair or Vice Chair should be notified. (The patient will need a COG patient ID number in order to obtain a reservation). Patients must be enrolled within 7 calendar days of making a reservation.

Reservations may be obtained 24-hours a day through the COG website. Please refer to the Reservation System eRDES User Guide that can be downloaded at: https://cogmembers.org/site/help/defaultUserguides.aspx

3.5 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

3.6 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine

eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.7 **Eligibility Checklist**
Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

3.8 **Institutional Pathology Report**
Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission.

3.9 **Study Enrollment**
Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment is accomplished by going to the Enrollment application in the eRDES system. (https://cogmembers.org/apps/erdes) If you have problems with enrollment, refer to online help in the Applications area of the COG website. Patients must be enrolled before treatment begins with the exception of Day 1 intrathecal chemotherapy, which can be administered at the time of the diagnostic LP. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. Patients must not receive any protocol therapy prior to enrollment.

3.10 **Dose Assignment**
The dose level will be assigned via eRDES at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow biopsy and/or aspirate must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be *enrolled* until September 8th.

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived. All clinical and laboratory data required for determining eligibility of a patient

enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.

4.1 Inclusion Criteria

4.1.1 Age: Patients must be ⩾ 12 months and < 31 years of age at the time of study enrollment.

4.1.2 Diagnosis: Patients with recurrent or refractory B- or T-lineage lymphoblastic leukemia and lymphoma. Patients with leukemia must have ≥ 5% (M2 or M3) bone marrow blasts with or without an extramedullary site of relapse. Morphologic relapse for M2 should be confirmed using flow cytometry, FISH and/or cytogenetics or molecular techniques. Patients with LL must have either measurable or evaluable disease.

4.1.3 **Disease Status:** Patients with first or greater relapsed T-lineage ALL or LL and second or greater relapsed B-lineage ALL or LL are eligible. Patients with primary refractory disease with at least 2 prior induction attempts or first relapse refractory to at least one prior re-induction attempt are eligible. Patients with refractory disease, however, must not have received a standard 4-drug re-induction inclusive of a steroid, anthracycline, asparaginase and vincristine in combination (e.g., UKALLR3 or AALL01P2) as their most recent prior therapy but they may have received a re-induction regimen that contain some of these agents.

4.1.4 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I). Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

4.1.5 Prior Therapy:

4.1.5.1 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the numerical eligibility criteria are met, e.g., blood count criteria, the patient is considered to have recovered adequately.

a. Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive. See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.

- A waiting period prior to enrollment is not required for patients receiving standard cytotoxic maintenance chemotherapy (i.e., corticosteroid, vincristine, 6MP, and/or methotrexate).

- Intrathecal cytotoxic therapy: No waiting period is required for patients having received intrathecal cytarabine, methotrexate, and/or hydrocortisone. Intrathecal chemotherapy given at the time of diagnostic LP to evaluate for relapse prior to study enrollment is allowed.
- ≥ 14 days must have elapsed after the completion of other cytotoxic therapy, with the exception of hydroxyurea, for patients not receiving standard maintenance therapy. Additionally, patients must have fully recovered from all acute toxic effects of prior therapy.

NOTE: Cytoreduction with hydroxyurea in patients can be initiated and continued for up to 24 hours prior to the start of protocol therapy.

Note: **Intrathecal chemotherapy that is given up to 72 hours prior to initiation of systemic chemotherapy per AINV18P1 counts as protocol therapy and not prior anti-cancer therapy. Intrathecal chemotherapy given > 72 hours prior does not count as protocol therapy.**

b. Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent. See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.

NOTE: Cytoreduction with prednisone or methylprednisolone for ≤ 120 hours (5 days) in patients can be initiated and continued for up to 24 hours prior to the start of protocol therapy.

c. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody with the exception of blinatumomab, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1. Patients must have been off blinatumomab infusion for at least 14 days and all drug related toxicity must have resolved to Grade ≤ 1.

d. Corticosteroids: See Section 4.2.2.1. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid and toxicity related to prior immune therapy must be recovered to Grade ≤ 1 off corticosteroids.

e. Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g. pegfilgrastim) or 7 days

for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator.

f. Interleukins, Interferons and Cytokines (other than Hematopoetic Growth Factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than Hematopoietic Growth Factors)

g. Stem cell Infusions (with or without TBI):
- Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion: ≥ 84 days after infusion and no evidence of GVHD.
- Autologous stem cell infusion including boost infusion: ≥ 42 days.

h. Cellular Therapy: ≥ 30 days after the completion of any type of cellular therapy (e.g. modified T cells, NK cells, dendritic cells, etc.)

i. XRT/External Beam Irradiation including Protons: ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation.

j. Patients must not have received prior exposure to palbociclib or another CDK4/6 inhibitor.

4.1.6 Organ Function Requirements

4.1.6.1 Adequate Renal Function Defined as:

- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

4.1.6.2 Adequate Liver Function Defined as:

- bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 225 U/L unless disease-related. For the purpose of this study, the ULN for SGPT is 45 U/L.
- Serum albumin ≥ 2 g/dL.

4.1.6.3 Adequate Cardiac Function Defined As:

- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by gated radionuclide study.

4.1.7 Informed Consent: All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies. Based on the mechanism of action, palbociclib may be expected to cause fetal harm if used during pregnancy. Pregnancy tests must be obtained in girls who are post-menarche. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method for the duration of study therapy. Women of reproductive potential should use effective contraception during treatment and for at least 3 weeks after the last dose of palbociclib. Males with female partners of reproductive potential should use effective contraception during treatment and for 3 months after the last dose of palbociclib. Animal data suggests that palbociclib may affect male fertility.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids: Prednisone or methylprednisolone for ≤ 120 hours (5 days) may be administered for cytoreduction up to 24 hours prior to the start of protocol therapy and as treatment for allergic reactions or for physiologic replacement/stress dosing of hydrocortisone for documented adrenal insufficiency. Corticosteroids are not allowed for other indications. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid (See Section 4.1.6.1.d).

4.2.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug.

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible [except patients receiving hydroxyurea, which may be continued until 24 hours prior to start of protocol therapy].

4.2.2.4 CYP3A4 Agents: Patients who are currently receiving drugs that are strong inhibitors and/or inducers of CYP3A4 or sensitive CYP3A4 substrates and CYP3A4 substrates with a narrow therapeutic range are not eligible. Strong inducers or inhibitors of CYP3A4 are prohibited from 14 days prior to enrollment to the end of the study. See Appendix III for a list of agents.

4.2.2.5 Anti-GVHD agents post-transplant:
Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant.

4.2.3 Patients must be able to swallow intact capsules or liquid. Patients that are unable to swallow oral medications may receive palbociclib oral solution through an NG tube. G tube administration is not allowed.

4.2.4 Infection: Patients who have an uncontrolled infection defined as below:

- Positive bacterial blood culture within 48 hours of study enrollment;
- Fever above 38.2°C within 48 hours of study enrollment with clinical signs of infection. Fever that is determined to be due to tumor burden is allowed if patients have documented negative blood cultures for at least 48 hours prior to enrollment and no concurrent signs or symptoms of active infection or hemodynamic instability.
- A positive fungal culture within 30 days of study enrollment or active therapy for presumed invasive fungal infection.
- Patients may be receiving IV or oral antibiotics to complete a course of therapy for a prior documented infection as long as cultures have been negative for at least 48 hours and signs or symptoms of active infection have resolved. For patients with *c. difficile* diarrhea, at least 72 hours of antibacterial therapy must have elapsed and stools must have normalized to baseline.
- Active viral or protozoal infection requiring IV treatment.

4.2.5 Patients known to have one of the following concomitant genetic syndromes: Down syndrome, Bloom syndrome, ataxia-telangiectasia, Fanconi anemia, Kostmann syndrome, Shwachmann syndrome or any other known bone marrow failure syndrome.

4.2.6 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study.

4.2.7 Cumulative prior anthracycline exposure must not exceed 400 mg/m2 of DOXOrubicin equivalents.

For the purposes of determining eligibility for this protocol, the following cardiotoxicity multipliers will be used to determine DOXOrubicin equivalents:

DOXOrubicin: Multiply total dose x 1
DAUNOrubicin: Multiply total dose x 0.5
EpiRUBicin: Multiply total dose x 0.67
IDArubicin: Multiply total dose x 5

MitoXANTRONE: Multiply total dose x 4

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

DRUG	ROUTE	DOSAGE	DAYS
Palbociclib IND# 141416	PO (or via NG- tube)	DL1: 50 mg/m^2 (max 100 mg/day) DL-1: 35 mg/m^2 (max 75 mg/day)	Once daily on Days 1-21
Intrathecal Cytarabine (IT ARAC): All patients on Day 1 (before CNS status is known)@	IT	**Age (yrs) Dose** 1-1.99 30 mg 2-2.99 50 mg ≥3 70 mg	1@
Intrathecal Methotrexate (IT MTX): CNS1 and 2	IT	**Age (yrs) Dose** 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥9 15 mg	18,32
Intrathecal Triple Therapy (ITT)@: Methotrexate (MTX)/ Hydrocortisone (HC)/Cytarabine (ARAC) if CNS3	IT	**Age (yrs) Dose** 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 MTX: 15 mg HC: 15 mg ARAC: 30 mg	1@, 4, 11, 18, 25
Doxorubicin (DOXO)	slow IV push or infusion over 1-15 min	60 mg/m²/dose	4
PrediSO(LO)NE (PRED)*	PO	40 mg/m²/day divided BID or TID	4-31
VinCRIStine (VCR)	IV push or mini-bag per institutional policy	1.5 mg/m²/dose (MAX dose 2 mg)	4, 11, 18, 25
Pegaspargase (PEG-ASP)#	IV over 1-2 hours	2500 International units/m²/dose	5, 18

* IV methylprednisolone may be given at 80 % of the oral predniSONE or predniSOLONE dose
# If allergic to PEGaspargase then see Section 6.2.1 for Asparaginase *Erwinia Chrysanthemi* dosing.
@ Patients with known CNS3 disease at the time of study enrollment may receive triple intrathecal chemotherapy on Day 1 **as a substitute for** intrathecal cytarabine, at the discretion of the treating investigator. Patients are NOT to receive both intrathecal triples and intrathecal cytarabine on Day 1, regardless of CNS status.

A cycle of therapy is considered to be 32 days. Please see Therapy Delivery Maps (TDMs) in Appendix VI (patients with ALL) and Appendix VII (Patients with LL).

It is recommended that drugs be administered in the order listed below.

Drug doses should be adjusted based on the BSA calculated from height and weight obtained within one week prior to the beginning of protocol therapy. For patients able to swallow capsule, please refer to the dosing nomogram in Appendix V-A. Patients unable to swallow capsules should use the oral solution, please refer to Appendix V-B.

Palbociclib: PO (or via NG- tube)
Days: Once daily on Days 1-21
Administer with food. Take at approximately the same time each day. Swallow capsules whole, do not crush, chew, or open capsules prior to swallowing (do not ingest if capsules are broken, cracked, or not fully intact). The oral solution can be administered without regard to food intake. If a patient vomits, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. Avoid grapefruit or grapefruit juice for the duration of the protocol therapy. It a dose is inadvertently missed, do not make it up. If a dose is missed and the next dose is more than 12 hours away, the missed dose should be administered. If the next dose is less than 12 hours away, the missed dose should not be administered. Missed doses should not be made up. See Appendices V-A and V-B for palbociclib capsule and liquid formulation dosing.

Only use palbociclib provided for investigational use specifically for AINV18P1.

Cytarabine: IT- All patients (before CNS status is known)
Day 1

Age (yrs)	Dose
1-1.99	30 mg
2-2.99	50 mg
≥3	70 mg

Methotrexate: IT - for CNS-negative (CNS1/CNS2) patients only.
Day 18 and 32.

Aged – based dosing:

Age (yrs):	Dose:
1 – 1.99	8 mg
2 – 2.99	10 mg
3 – 8.99	12 mg
≥ 9	15 mg

Intrathecal Triple Therapy (ITT): Methotrexate (MTX)/Hydrocortisone (HC)/Cytarabine (ARAC)- for CNS3 patients only
Days 1*, 4, 11, 18, 25

Age (yrs)	Dose
1-1.99	MTX:8mg HC: 8mg ARAC: 16mg
2-2.99	MTX: 10mg HC: 10 mg ARAC: 20 mg
3-8.99	MTX: 12 mg HC: 12 mg

≥ 9	ARAC: 24 mg MTX: 15 mg HC: 15 mg ARAC: 30 mg

*Intrathecal triple therapy can be administered on Day 1 instead of intrathecal cytarabine for patients already known to be CNS3 at study entry.

Doxorubicin: slow IV push or IV infusion over 1-15 minutes
Day: 4
Dose: 60 mg/m^2/dose

Administer at a concentration not to exceed 2 mg/mL by slow IV push or infusion over 1-15 minutes. Short infusion times may be lengthened slightly (and up to 60 minutes) if institutional policies mandate. It is suggested that DOXOrubicin be administered through the tubing of rapidly infusing solution of D5W or 0.9% NaCl and that it is infused into a large vein or central venous access device.

PrednisO(LO)NE: PO
Days: 4-31
Dose 40 mg/m^2/day divided BID or TID
Note: If a patient in unable to take predniSONE or predniSOLONE by mouth, IV methylprednisolone may be given at 80 % of the oral dose

VinCRIStine: IV push over 1-5 minutes or infusion via minibag as per institutional policy
Days 4, 11, 18, and 25
Dose: 1.5 mg/m^2/dose (maximum dose 2 mg).

Special precautions: vinCRIStine: FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

Medication errors have occurred due to confusion between vinCRIStine and vinBLAStine. VinCRIStine is available in a liposomal formulation (vinCRIStine sulfate liposomal injection, VSLI, Marqibo®). Use conventional vincristine only; the conventional and liposomal formulations are NOT interchangeable.

PEGaspargase: IV over 1-2 hours
Days 5 and 18.
Dose: 2,500 International units/m^2/dose.
Administer IV infusion through the tubing of a rapidly infusing solution of D5W or 0.9% NaCl. Use anaphylaxis precautions per institutional policy. Observe patient for at least ONE hour after administration for signs of hypersensitivity reactions.

#If allergic to PEGaspargase then see Section 6.2.1 for Asparaginase *Erwinia Chrysanthemi* dosing.

Special precautions:

1. Pegaspargase is contraindicated with a history of severe pancreatitis with any prior asparaginase therapy. Caution should be used if serious thrombosis or hemorrhagic events have occurred with any prior asparaginase therapy.
2. Pegaspargase may affect coagulation factors and predispose to bleeding and/or thrombosis. Caution should be used when administering any concurrent anticoagulant therapy.
3. Suggested monitoring during and after administration: Because pegaspargase is long acting, hypersensitivity reactions may not appear for hours after drug administration. Monitor vital signs, for signs of fever, chills, or acute allergic reactions including anaphylaxis. Have medications to treat hypersensitivity reactions readily available at each administration (e.g., epinephrine, IV corticosteroids, antihistamines). Consider prescribing an EpiPen® for home use.

DUE TO A SIGNIFICANTLY INCREASED RISK OF MORBIDITY AND MORTALITY IN CHILDREN WITH MULTIPLY RELAPSED ALL UNDERGOING INTENSIVE THERAPY, HOSPITALIZATION FROM INITIATION OF THERAPY IS STRONGLY RECOMMENDED.

5.2 Dosing Schema

5.2.1 Inter-Patient Dosing Schema

Dose Level	Palbociclib (mg/m^2)	Palbociclib max dose (mg/day)
-1	35	75
1*	**50**	**100**

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose of 35 mg/m^2 (Dose Level -1). If Dose Level -1 is not well tolerated, further de-escalation will not occur. The study will be closed to accrual.

See Appendix V-A and Appendix V-B for palbociclib capsule and liquid formulation dosing.

5.2.2 Intra-Patient Escalation

Intra-patient dose escalation is not allowed.

5.3 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. 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). Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.4 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events that are possibly, probably or definitely attributable to palbociclib. The DLT observation period for the purposes of dose-confirmation will be the first cycle of therapy.

Dose limiting hematological and non-hematological toxicities are defined differently.

5.4.1 Non-hematological dose-limiting toxicity attributable to palbociclib

5.4.1.1 Any Grade 3 or greater non-hematological toxicity possibly, probably or definitely attributable to palbociclib with the specific **exclusion** of:

- Grade 3 nausea, anorexia, fatigue, malaise, weight loss, vomiting or diarrhea that returns to ≤ Grade 2 or baseline within 3 days with supportive care
- Grade 3 or 4 liver enzyme elevation, including ALT/AST/GGT, that returns to Grade ≤ 2 within 42 days of the start of therapy. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L. Adverse event grades will be based on increases above the upper limit of normal, regardless of the subject's baseline. See Appendix XI for toxicity grading table
- Grade 3 direct bilirubin elevation that is asymptomatic and returns to ≤ Grade 1 within 42 days of the start of therapy
- Grade 3 total bilirubin elevation that resolves to ≤ Grade 1 within 42 days of the start of therapy
- Grade 3 or 4 fever, febrile neutropenia or infections with or without hospitalization
- Grade 3 or 4 hypotension explained by sepsis
- Grade 3 or 4 isolated electrolyte abnormalities that resolve, with or without intervention, to ≤ Grade 2 within 3 days. Electrolyte supplementation is encouraged.
- Grade 3 tumor lysis syndrome that resolves to ≤ Grade 2 within 3 days
- Grade 3 mucositis that resolves to ≤ Grade 2 within 3 days
- Grade 3 epistaxis
- Grade 3 bone and/or pain in extremity
- If a patient requires more than 4 doses of palbociclib to be held due to toxicity this is a DLT.

5.4.1.2 Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.

5.4.1.3 Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.4.2 Hematological dose limiting toxicity

DLT will be defined as failure to recover a peripheral ANC > 500/mm^3 and platelets > 20,000/mm^3 by 42 days after the first treatment day, not due to malignant infiltration.

5.4.2.1 Note: Grade 3 or 4 febrile neutropenia will not be considered a dose-limiting toxicity.

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modification or use of myeloid growth factor.

6.1 Dose Modifications for Non-Hematological Toxicity Attributable to Palbociclib

6.1.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.4.1, palbociclib will be held until the toxicity is ⩽ Grade 1 or as otherwise indicated below (see Section 6.2 for dose modifications for other backbone chemotherapy agents). When the toxicity resolves to meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level. For patients enrolled at Dose Level -1, palbociclib should be discontinued but the backbone chemotherapy can be continued if this is not contributing to the toxicity. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose. Missed doses will not be made up.

6.1.2 If toxicity does not resolve to meet eligibility or baseline parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

6.1.3 If a dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose level, the patient must be removed from protocol therapy.

6.2 Dose Modifications for Specific Toxicities Defined Per Drug

Notify the Study Chair at the time of removing a patient from protocol therapy for toxicity. The drugs are listed in alphabetical order.

6.2.1 Asparaginase [Pegaspargase (PEG-Asparaginase) or Erwinia]

6.2.1.1 Allergy

Systemic Allergic Reactions/Anaphylaxis:
For severe allergic reaction, discontinue pegaspargase and substitute Asparaginase *Erwinia* (Erwinia). Erwinia therapy should begin within 72 hours of the pegaspargase reaction or as soon as possible. Erwinia dosing: 25,000 international units (IU)/m^2 IM/IV M-W-F for six doses substituted for each dose of pegaspargase. If Erwinia is given IV it should be given as a 1-2 hour infusion.

For mild-moderate reversible reaction:

1. If the infusion was completed, consider sending an asparaginase activity level. Note that an asparaginase level of at least 0.1 IU/ml 14 days after administration is considered therapeutic. There are several reports that suggest different thresholds for switching to Asparaginase *Erwinia*; after evaluating these, the following guidelines are recommended for

consideration to switch to Asparaginase *Erwinia*, but decisions are ultimately up to the treating clinician.

Time point after completion of pegaspargase infusion	Asparaginase activity level	Action
1 hour – 1 day	< 0.5 IU/mL	Substitute asparaginase *Erwinia*
7 days	< 0.3 IU/mL	Substitute asparaginase *Erwinia*
14 days	< 0.1 IU/mL	Substitute asparaginase *Erwinia*

2. If the infusion was discontinued early, consider re-challenging with pegaspargase after premedication and send asparaginase levels as above.

Premedication with antihistamines in the absence of prior hypersensitivity has been discouraged in the past since antihistamine use may mask the appearance of systemic allergy and fail to alert the provider of the presence of asparaginase neutralizing antibodies. The use of asparaginase activity assays, as described above, are now commercially available and may help determine if neutralizing antibodies are present, thus the use of premedications is left to the discretion of the provider.

If there is a question of silent inactivation, check levels as described above between 1 hour and 7 days after the dose. Subsequent doses of asparaginase should be changed to asparaginase *Erwinia* based on the activity levels described above. Whether the dose after which levels were checked should be substituted with asparaginase *Erwinia* will depend on when the results are received, the patient's clinical status, and what other therapy is being administered, and is ultimately left to the discretion of the treating physician. Of note, asparaginase *Erwinia* is recommended only for pegaspargase hypersensitivity reactions and/or in the presence of silent antibody. It is not recommended as a substitute for pancreatitis, transaminitis, hyperbilirubinemia, coagulation abnormalities, or other non-hypersensitivity toxicities associated with pegaspargase.

6.2.1.2 Coagulopathy/bleeding:
If symptomatic, hold asparaginase until symptoms resolve, then resume with the next scheduled dose. Consider factor replacement (FFP, cryoprecipitate, factor VIIa). Do not withhold dose for abnormal laboratory findings without clinical symptoms.

6.2.1.3 Hyperbilirubinemia:
Asparaginase may need to be withheld in patients with an elevated direct bilirubin, since asparaginase has been associated with hepatic toxicity. No specific dose adjustment guidelines are provided in the manufacturer's labeling. Below are proposed dose adjustment guidelines from published literature[18]:

Direct Bilirubin*	Dose Modification for Asparaginase [Pegaspargase (PEG-Asparaginase) or Erwinia
≤ 3.0 mg/dl	Full dose
3.1 – 5.0 mg/dl	Hold pegaspargase and resume when direct bilirubin is < 2 mg/dl
≥ 5.1 mg/dl	Hold the dose of pegasparagase; do not substitute other asparaginase products; do not make up the missed dose

*Refer to Appendix XI for guidelines

6.2.1.4 Hyperglycemia:
Do not modify dose. Treat hyperglycemia as medically indicated.

6.2.1.5 Hyperlipidemia:
Do not modify dose. Treat hyperlipidemia as medically indicated.

6.2.1.6 Ketoacidosis:
Hold asparaginase until blood glucose can be regulated with insulin.

6.2.1.7 Pancreatitis:
Discontinue asparaginase in the presence of Grade 3 or 4 pancreatitis. In the case of asymptomatic Grade 2 pancreatitis (enzyme elevation or radiologic findings only), asparaginase should be held until amylase/lipase levels return to normal, and/or other signs subside, and then resumed.

6.2.1.8 Thrombosis (including CNS and non-CNS events): Withhold asparaginase until acute symptoms resolve and treat with appropriate antithrombotic therapy and consider repletion of AT-III, as indicated. Upon resolution of symptoms, consider resuming asparaginase while continuing low molecular weight heparin (LMWH) or antithrombotic therapy. Consider measurement and repletion of AT-III during subsequent courses of asparaginase if unable to achieve therapeutic Anti-Xa levels. For significant thrombosis (not catheter-related) consider evaluation for inherited predisposition to thrombosis.

6.2.2 Doxorubicin (Anthracyclines)
Consider Dexrazoxane prior to each dose for patients with:

• Anticipated cumulative anthracycline dose ≥ 250 mg/m^2 of DOXOrubicin equivalent.

Anthracycline Dose Conversion:

DOXOrubicin: Multiply total dose x 1
DAUNOrubicin: Multiply total dose x 0.5

EpiRUBicin: Multiply total dose x 0.67
IDArubicin: Multiply total dose x 5
MitoXANTRONE: Multiply total dose x 4

• Past or anticipated radiation with potential impact to the heart (radiation to chest, abdomen, spine, or TBI).
• Recommended dose of dexrazoxane is 10 x the DOXOrubicin dose given over 5-15 minutes immediately before the chemotherapeutic agent.

6.2.2.1 Monitoring Cardiac Echocardiogram:
At baseline and then recommended after cumulative dose of 175, 300, 375, and 450 mg/m^2. Please see COG Long Term Follow Up Guidelines for additional monitoring recommendations at http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf

6.2.2.2 Dose modification for cardiac toxicity:
If left ventricular ejection fraction (EF) < 50% (as determined by the Biplane Simpson method), or if EF inevaluable shortening fraction (SF) < 24%, hold the anthracycline or anthracenedione and repeat the echocardiogram in one week. If EF remains < 50% (or if EF inevaluable, SF < 24%), discontinue the anthracycline or anthracenedione and deliver alternate therapy as per the protocol or provider decision. Resuming cardiotoxic therapy depends on the cause of the cardiac dysfunction and the results of further cardiac evaluation.

6.2.2.3 Myelosuppression:
If patient has severe infection or severe mucositis, consider modifying or omitting anthracycline.

6.2.2.4 Hyperbilirubinemia:

Direct Bilirubin	Dose Adjustment
≤ 3.0 mg/dl	Full dose
3.1 – 5.0 mg/dl	Administer 50% of calculated dose
5.1 – 6.0 mg/dl	Administer 25% of calculated dose
> 6.0 mg/dl	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

*Refer to Appendix XI for guidelines

6.2.2.5 Extravasation:
In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Also, see https://cogmembers.org/_files/disc/pharmacy/ExtravasationReference.pdf for COG reference.

6.2.3 Intrathecal Methotrexate/Triple Intrathecal Therapy

6.2.3.1 Systemic toxicity:
The dosage for IT methotrexate will not be reduced for systemic toxicity (myelosuppression, mucositis, etc.). Instead, leucovorin may be used at a dose of 5 mg/m^2/dose IV/PO every 6 hours x 2 doses, beginning 24 hours after the IT therapy has been delivered. This may reduce the risk of worsening already existent myelosuppression (ANC < 500/µL) or mucositis. Do not administer leucovorin solely to prevent myelosuppression.

6.2.3.2 Dose modifications following an episode of acute neurotoxicity:
Neurotoxicity has extremely protean manifestations, ranging from transient events, seizures or episodes of acute hemiparesis, to severe necrotizing encephalopathies.[19-21]

The following guidelines are offered for consideration following an acute event, but it must be recognized that there are little data to support these approaches or any others.

Many acute events, seizures or episodes of transient hemiparesis, are temporally related to the administration of intrathecal therapy, commonly 9 to 11 days after the IT administration.[22]

Complete clinical evaluation including imaging of the brain is strongly recommended.

For patients who return to their baseline pre-event neurological status, clinicians may

1. Hold the next planned dose of IT therapy, or
2. Substitute IT cytarabine or IT cytarabine/hydrocortisone for 1 dose of IT methotrexate, or
3. Proceed with IT methotrexate and include leucovorin rescue at a dose of 5 mg/m^2 IV/PO q 6 hrs x 2 doses beginning 24 hours after the LP. If the event does not recur, resumption of standard therapy should be considered for subsequent intrathecal therapy.

For patients who do not return to baseline pre-event neurological status or for those with recurrent events, or evidence of progressive encephalopathy, additional evaluations may be warranted and the treating physician may consider a more prolonged or definitive change in therapy upon discussion with the Study Chair.

6.2.3.3 Hydrocephalus, microcephaly or known abnormality of CSF flow precluding intrathecal chemotherapy via lumbar puncture:
Intraventricular chemotherapy via Ommaya catheter may be used in place of intrathecal therapy delivered by LP. Intraventricular chemotherapy should be given according to the same schedule, but at **50% of the corresponding age-based**

doses that would be given by LP. NOTE: Obstruction to CSF flow may be a contraindication to intrathecal and/or intraventricular therapy.

6.2.3.4 Viral, bacterial, or fungal meningitis:
Omit until resolved.

6.2.4 Steroids (Prednisone, Prednisolone or Methylprednisolone)

6.2.4.1 Hypertension:
Dose should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension.

6.2.4.2 Hyperglycemia:
Dose should not be reduced for hyperglycemia.

6.2.4.3 Pancreatitis:
Every effort should be made not to hold any re-induction steroids. Do not modify dose for asymptomatic elevations of amylase and/or lipase. In extreme circumstances, consider discontinuation of steroids, except for stress doses, in the presence of Grade 3 or 4 pancreatitis.

6.2.4.4 Osteonecrosis (ON):
Do not modify corticosteroid therapy for osteonecrosis (also referred to as avascular necrosis) during re-induction.

6.2.4.5 Varicella:
Steroids should be held during active infection except during re-induction. Do not hold during incubation period following exposure in patients with laboratory evidence of immunity or patients who received appropriate post-exposure prophylaxis.

6.2.4.6 Inability to use oral doses:
For dexamethasone, substitute the IV preparation mg for mg. For prednisone, substitute IV methylprednisolone at 80% of the oral prednisone dose. Note that if substituting oral prednisolone for prednisone, the doses are the same; prednisone is converted in the liver to prednisolone.

6.2.4.7 Severe infection:
Do not hold or discontinue steroids during re-induction without serious consideration, as this is a critical period in the treatment of ALL. Later in therapy, one may consider holding steroid until patient achieves cardiovascular stability, except for “stress doses.”

6.2.5 Vincristine

PLEASE USE "BALIS" SCALE FOR GRADING NEUROPATHY (See text box below)

6.2.5.1 Severe Neuropathic Pain (Grade 3 or greater):
Hold dose(s). When symptoms subside, resume at 50% previous **calculated** dose (**maximum dose: 1 mg**), and then escalate to full dose as tolerated. NOTE: neuropathic pain can be severe and difficult to treat. However, because vinCRIStine is an important component of curative therapy and the majority of neuropathies are ultimately reversible, vinCRIStine therapy may be given at full dose at investigator discretion. Severe peripheral neuropathies, with or without a positive family history might suggest the need for a molecular diagnostic evaluation to rule out Charcot Marie Tooth Disease (CMT), Type 1A or Hereditary neuropathy with liability to pressure palsies. Drugs such as gabapentin may be of value.

6.2.5.2 Vocal Cord Paralysis:
Hold dose(s). When symptoms subside, resume at 50% previous calculated dose (maximum dose: 1 mg), and then escalate to full dose as tolerated. See above for comment on CMT.

6.2.5.3 Foot Drop, Paresis:
(Grade 3 or greater): Consider holding or decreasing dose. These toxicities are largely reversible but over months to years. Accordingly, holding doses of vinCRIStine and/or lowering the dose may not result in rapid resolution of symptoms and may compromise cure. See above for comment on CMT. Physical therapy may be beneficial to maintain range of motion as well as to provide ankle-foot orthotics (AFOs) and other forms of support. Drugs such as gabapentin may be of value.

6.2.5.4 Jaw Pain:
Treat with analgesics; do not modify vinCRIStine dose.

6.2.5.5 Hyperbilirubinemia[23,24]:

Direct Bilirubin*	VinCRIStine Dose Adjustment
≤ 3.0 mg/dL	None (**maximum dose: 2 mg**)
3.1- 5.0 mg/dL	50% of **calculated** dose (**maximum dose: 1 mg**)
5.1-6.0 mg/dL	25% of **calculated** dose (**maximum dose: 0.5 mg**)
> 6.0 mg/dL	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses

*Refer to Appendix XI for guidelines

6.2.5.6 Constipation or ileus (≥ Grade 3) or typhlitis:
Hold dose(s); institute aggressive regimen to treat constipation if present. When symptoms abate resume at 50% of calculated dose (maximum dose: 1 mg) and escalate to full dose as tolerated.

6.2.5.7 Extravasation:
In the event of an extravasation, discontinue the IV administration of the drug and institute appropriate measures to prevent further extravasation and damage according to institutional guidelines. Also see https://members.childrensoncologygroup.org/_files/disc/Nursing/extravasationguidelines.pdf for COG reference.

Modified ("Balis") Pediatric Scale of Peripheral Neuropathies

Peripheral Motor Neuropathy:

- Grade 1: Subjective weakness, but no deficits detected on neurological exam, other than abnormal deep tendon reflexes.
- Grade 2: Weakness that alters fine motor skills (buttoning shirt, coloring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks.
- Grade 3: Unable to perform fine motor tasks (buttoning shirt, coloring, writing or drawing, using eating utensils) or unable to ambulate without assistance.
- Grade 4: Paralysis.

Peripheral Sensory Neuropathy:

- Grade 1: Paresthesias, pain, or numbness that do not require treatment or interfere with extremity function.
- Grade 2: Paresthesias, pain, or numbness that are controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks.
- Grade 3: Paresthesias or pain that are controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired).
- Grade 4: Complete loss of sensation, or pain that is not controlled by narcotics.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 Concurrent Anticancer Therapy

Additional cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or may NOT be administered to patients receiving protocol therapy. If these treatments are administered the patient will be removed from protocol therapy.

7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. See COG Supportive Care Guideline at

https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines. See below for recommendations on management of specific toxicities associated with palbociclib.

All patients should receive trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of TMP 2.5 mg/kg/dose (maximum dose 160 mg/dose) by mouth twice daily on 2 or 3 sequential days per week. Patients allergic to or experiencing excessive myelosuppression with TMP/SMX can receive prophylaxis per institutional guidelines with alternative agents.

7.3.1 Infection Control

Patients with relapsed ALL have a significant risk of morbidity and mortality with intensive salvage therapy. Patients in first relapse have a 4-5% induction mortality rate, the majority associated with infection. They have also been found to have a 45% rate of Grade 3 and 4 infection during re-induction on recent COG ALL trials[13] (and personal communication T. Horton, E. Raetz, and M. O'Brien), and other relapsed ALL re-induction trials.[25-27] Therefore patients with multiply relapsed ALL require a very conservative approach to infection prevention and treatment as outlined below.

7.3.1.1 Due to the substantial risk of infection in patients with relapsed ALL receiving intensive induction therapy, it is strongly recommended that they remain hospitalized from the initiation of therapy until: 1) there is evidence of ANC recovery defined as $\geqslant$ 200/microliter and increasing, and 2) they are afebrile and clinically stable.

7.3.1.2 It is strongly recommended that patients receive broad spectrum gram positive and negative antibiotic prophylaxis at initiation of re-induction therapy and until they have met the criteria for discharge outlined in Section 7.3.1.1. The specific choice of prophylactic antibiotics should be guided by the individual institution, although levofloxacin is recommended.[28,29]

7.3.1.3 Prophylactic anti-fungal therapy with IV caspofungin, micafungin or amphotericin is also highly recommended.[30] The patient should remain on prophylactic anti-fungal therapy until their ANC has fallen and recovered to 200/microliter and rising and the patient is afebrile and clinically stable.

7.3.1.4 Empiric broad spectrum antibacterial and anti-fungal therapy should be initiated immediately for patients with an ANC < 500/microliters (or < 1000 /microliters and falling) and an oral temperature > 38° C twice in 12 hours or $\geqslant$ 38.5° C once or as clinically indicated. Broad-spectrum antibiotics and anti-fungals, once started, should be continued until there is evidence of ANC recovery defined as $\geqslant$ 200/microliter. Also, please see the COG Fever and Neutropenia Guidelines at: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines

7.3.1.5 If clinical symptoms or radiographic evidence of enterocolitis or typhilitis develop, broad spectrum antibiotics which provide

coverage for gram negatives, and anaerobes and fungal infections is highly recommended.

7.3.1.6 When possible during hospitalization it is recommended patients be assigned to rooms with special air filtration systems such as high efficiency particulate air filters (HEPA) or clean-air rooms with constant positive pressure.[31]

7.3.2 Acute Tumor Lysis Syndrome

Patients with ALL and lymphoblastic lymphoma are at high risk of tumor lysis should be assessed rapidly for evidence of symptomatic hyperleukocytosis, tumor lysis syndrome, and coagulopathy. Suggested initial studies, obtained prior to initiating antileukemia therapy, may include a complete blood count (CBC), prothrombin and activated partial thromboplastin times, fibrinogen, D-dimer, and serum electrolytes, including creatinine, BUN, uric acid, phosphorus, and calcium. Continued monitoring of these studies should be carried out at suitable intervals until abnormalities have resolved or the risk has abated.

The risk for serious acute tumor lysis syndrome (TLS) is usually restricted to the first 72 hours after initiation of therapy; however, it may spontaneously occur prior to treatment. To manage the metabolic derangements caused by hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia, the following steps should be initiated:

- Begin allopurinol at a dose of 300 mg/m²/day or 10 mg/kg/day (maximum 800 mg/day) in 2 - 3 divided doses and continue until peripheral blasts and extramedullary disease are reduced. In some patients, such as those with oliguria or severe renal dysfunction, or in those with marked hyperuricemia, it may be also be appropriate to use rasburicase. Note that rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.
- Hydrate at 2,400-3,000 mL/m²/day to maintain urine output > 100 mL/m²/hour until peripheral blasts and extramedullary disease are reduced. Potassium should not be added to the hydration fluids.

Urine alkalinization is NOT necessary for TLS prophylaxis. There is paucity of evidence demonstrating benefit of urine alkalinization and it can potentially lead to calcium phosphate precipitation and/or metabolic acidosis.

7.4 Growth Factors

Growth factors that support white cell number or function can only be administered culture proven bacteremia or invasive fungal infection. The Study Chair should be notified before growth factors are initiated.

7.5 Concomitant Medications

7.5.1 Cytochrome P450 and antileukemic drugs

Since concurrent use of enzyme inducing anticonvulsants (e.g., phenytoin, phenobarbital, and carbamazepine) with anti-leukemic therapy has recently been associated with inferior EFS, every effort should be made to avoid these agents, as well as rifampin, which also induces many drug metabolizing enzymes.[24] Neither gabapentin nor levetiracetam induce hepatic drug metabolizing enzymes

and may be suitable alternative anticonvulsants. Azole antifungals (listed in the table below) and the macrolide group of antibiotics (listed in the table below) may have potent inhibitory effects on drug-metabolizing enzymes. Patients receiving some anti-leukemic drugs (e.g., vincristine, anthracyclines, etoposide) may experience excess toxicity when these agents are given concomitantly; alternate antifungal and antibacterial therapy should be used where possible (see table below).

DRUGS	POTENTIAL INTERACTION	ACTION TO BE TAKEN
Anticonvulsants	Induction of drug metabolizing enzymes Lowered EFS	AVOID phenytoin, phenobarbital, carbamazepine Consider gabapentin or levetiracetam as alternative
Rifampin	Induction of drug metabolizing enzymes	DO NOT USE
Azole Antifungals (itraconazole*, posaconazole, voriconazole, ketoconazole, isavuconazole)	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vincristine*, anthracyclines, etoposide, steroids
Macrolide Antibiotics (erythromycin, clarithromycin, azithromycin, roxithromycin, telithromycin)	Inhibition of drug metabolizing enzymes	CONSIDER ALTERNATIVE MEDICATIONS May need dose reductions of vincristine, anthracyclines, etoposide, steroids

* Itraconazole should NOT be used in patients who are receiving vincristine due to a serious drug-drug interaction leading to severe neurotoxicity.[32,33]

This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

7.5.2 CYP3A4 Interactions and palbociclib

In vitro data indicate that CYP3A and sulfotransferase (SULT) enzyme SULT2A1 are mainly involved in the metabolism of palbociclib. Palbociclib is a strong substrate of CYP3A4 isozyme.

The concomitant use of strong CYP3A4 inhibitors including, but not limited to atazanavir, boceprevir, clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, ritonavir, telaprevir, telithromycin, voriconazole, and grapefruit or grapefruit juice, may increase palbociclib plasma concentrations and should be avoided (see Appendix III for list of agents).

The concomitant use of strong CYP3A4 inducers including, but not limited to carbamazepine, enzalutamide, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort, may decrease palbociclib plasma concentrations and should be avoided (see Appendix III for list of agents).

Strong inducers and/or strong inhibitors of CYP3A4 are prohibited from 14 days prior to enrollment to the end of the study. See Appendix III for a list of agents.

The use of moderate inhibitors and/or inducers of CYP3A4 should be avoided as well for the duration of the study, if reasonable alternatives exist.

Palbociclib is a weak time-dependent inhibitor of CYP3A4 in humans. The use of sensitive CYP3A4 substrates and CYP3A4 substrates with a narrow therapeutic range should be avoided for the duration of the study if reasonable alternatives exist (Appendix III).

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies, bone marrow aspirate and/or biopsy, must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	End of Protocol Therapy- Day 32^
History	X	Weekly	
Physical exam with vital signs	X	Weekly	X
Height, weight, BSA	X		X
Performance status	X		X
Pregnancy test[1]	X		
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)[3]	X
CSF cell count & cytospin	X*	With each IT	
Pharmacokinetics[2]	X	X	
Urinalysis	X		
Electrolytes including Ca^{++}	X	Weekly	X
Creatinine, ALT, bilirubin	X	Weekly	X
Direct Bilirubin	X[12]		
Albumin	X		
ECHO or gated radionuclide study	X		X
12-lead EKG	X		X
Chest x-ray	X		
Patient Diary[11]		Weekly	X
ADDITIONAL STUDIES: ALL ONLY			
Bone marrow aspirate for morphology and MRD	X		X[4]
Absolute Blast Count (ABC)		Day 4[5]	
Correlative biology studies[6]	X	Day 4	X
ADDITIONAL STUDIES: LL ONLY			
Chest[7] and neck CT	X		X[7,8]
Abdomen/Pelvis CT or MRI	X		X[8]
Chest x-ray	X		
PET scan (recommended)	X		X
Bone scan[9]	X[9]		X[9]
Bilateral bone marrow aspirates and biopsies for morphology	X		Only if positive at diagnosis[10]

^ Abnormal laboratory tests must be re-checked by Day 42 since some toxicities require resolutions to ≤ Grade 2 or baseline by Day 42 (see DLT criteria).

* May be done with the Day 1 lumbar puncture with IT therapy.

1 Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.

2 See Section 8.2 for timing of PK studies.

3 If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3.

4 Bone marrow aspirate must be obtained on Day 32 ± 2 days. MRD should be obtained with this end of cycle bone marrow if patient < 5% blasts by morphology. If peripheral blood count recovery is delayed at the end of the cycle, repeat a bone marrow aspirate just prior to or on Day 42 regardless of counts. If still delayed repeat a bone marrow every 7-14 days after Day 42 until count recovery or relapse.

5 Absolute blast count should be performed on Day 4 prior to administration of chemotherapy.

6 See Section 8.3 for timing of Correlative Biology studies (optional). Peripheral blood samples should be collected PRIOR to administration of Day 4 chemotherapy, if absolute blast count is >1000/mm^3.

7 Obtain chest CT for all LL patients at baseline and on Day 32. The baseline chest CT may be delayed until the patient is stable. A PET-CT can be used instead of a CT (See Section 12.4).

8 If imaging studies are negative at baseline, no further imaging is needed on Day 32. A PET-CT can be used instead of a CT (See Section 12.4).

9 Bone scan as clinically indicated; perform at Day 32 only if patient has disease at baseline. May substitute a PET scan for a bone scan, however, a bone scan is preferred for bone symptoms.

10 LL should have bone marrow aspirates and biopsies on Day 32 ± 2 days if ≥ 5% marrow involvement was present at diagnosis

11 Patient diary (see Appendix XII) should be reviewed after completion of each treatment cycle and uploaded into RAVE. The patient diary should be collected and reviewed weekly during Cycle 1.

12 Collect direct bilirubin before start of protocol therapy and as clinically indicated.

8.2 Pharmacology (required)

8.2.1 Description of Studies and Assay

Palbociclib PK studies will be determined by a validated LC-MS/MS method.

8.2.2 Sampling Schedule (See Appendix VIII)

Plasma samples will be obtained at the following time points:

- **Day 1 of Cycle 1:** pre-dose, and at 1, 2, 4, 8 and 24 hours post-dose of palbociclib.
- **Day 11 of Cycle 1**: pre-dose, and at 1, 2 and 4, 8 and 24 hours post-dose of palbociclib.

8.2.3 Sample Collection and Handling Instructions

Blood samples (3-4 mL) to provide a minimum of 1.0 mL of plasma for PK analysis of palbociclib will be collected in tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA). Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.2.4 Sample Processing

Upon collection of the blood PK samples, keep the samples on wet ice at all times prior to processing to plasma.

- The blood samples have to be processed to plasma and placed in a freezer at -20ºC within 1 hour of collection.

- To process the blood samples to plasma, centrifuge the blood samples in a refrigerated centrifuge at approximately 4 ºC at about 1700 x g for approximately 10 minutes.
- Using a clean separate pipette for each time point, transfer the plasma samples into pre-labeled 4 or 5 mL polypropylene cryovials and store in the freezer at approximately -20ºC until shipment. If a -20ºC freezer is not available at the site the samples may be stored at -80ºC. Palbociclib is stable at -20ºC and -80ºC for 439 days in frozen K2EDTA plasma.
- Ship the frozen samples on dry ice to the contract bioanalytical laboratory.

8.2.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form (Appendix VIII), which must accompany the sample(s).

8.2.6 Sample Shipping Instructions

A phone call or fax communication should precede all sample shipments. A phone or fax communication must precede all HIV positive or other known infectious sample shipments.

Detailed sample inventory information (Appendix VIII) must accompany the samples. Lack of paperwork or illegible information will delay sample login and analysis. Samples that are unclearly or incompletely labeled may also lead to delayed analysis.

Samples should be batched and shipped via overnight courier at the end of each cycle on Mondays, Tuesdays, or Wednesdays. Samples should be shipped to the following address:

[redacted]

8.3 Correlative Biology Studies (Optional)

8.3.1 Description of Studies

Correlative biology studies in bone marrow and peripheral blood will be performed in consenting patients to determine the biological activity of CDK4/6 inhibition. RNA sequencing and Western blotting will be used to determine gene and protein expression. Cell cycle analyses will be performed to determine the percentage of S phase cells prior to and after palbociclib exposure.

8.3.2 Sampling Schedule (See Appendix II)

One bone marrow or blood sample (10-15mL) for each time point will be collected to assess for the studies outlined below. Peripheral blood also can be

substituted or used to augment bone marrow samples if the absolute blast count is >1000/μL: 10 mL per samples (<10 kg) or 15 mL (≥10 kg).

	Pre-study Marrow	**Day 4 Blood**	**Day 32* Marrow**
Targeted DNA sequencing to identify somatic mutations in both T-ALL and B-ALL samples	X		
***CDKN2A* deletions (using FISH)**	**X**		
RB1 expression and RB1 phosphorylation status (Immunoblotting)	X	X**	X
$p27^{Kip1}$ expression (Immunoblotting)	X	X**	X
Cyclin D3 and CDK4/6 protein expression (Immunoblotting)	X	X**	X
Cell cycle analysis (response to Palbociclib)	X	X**	X
Peripheral blood absolute blast count	X	X**	

* End of therapy analyses in patients with persistent disease. End of therapy analyses must be obtained on Day 32 ± 2 days.
** Peripheral blood samples should be collected PRIOR to administration of Day 4 chemotherapy, if absolute blast count is >1000/mm3

8.3.3 Sample Collection and Handling Instructions
Bone marrow 5mL per sample or peripheral blood**: 10 mL per samples (<10 kg) or 15 mL (≥ 10 kg) if absolute blast count is >1000/mm^3.

8.3.4 Sample Processing (See Appendix II for details)
Lymphoblasts will be isolated from bone marrow or blood within 4 hours of collection using Ficoll-Paque Plus (Amersham Biosciences, Brown Deer, WI) at participating centers to avoid potential artifacts associated with prolonged sample storage or shipping. Blasts will then be frozen and batch shipped on dry ice to the Carroll/Aifantis labs for DNA and protein purification (per Section 8.3.6). Email or call Nikki Evensen, PhD (Nikki.Evensen@nyulangone.org; (212) 263-2327 or (516) 765-6832) for any questions regarding sample processing.

8.3.5 Sample Labeling
Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Correlative Study Form (Appendix IX), which must accompany the sample(s).

8.3.6 Sample Shipping Instructions
Samples should be batched per patient and shipped frozen on dry ice to arrive Monday-Friday. Do not ship samples for delivery on a weekend or holiday.

Ship samples to:

Carroll/Aifantis Labs
Laura and Isaac Perlmutter Cancer Center at NYU Langone
522 First Avenue, Smilow Building 12 Floor, Room 1211
Tel: 212.263.2327 • Fax: 212.263.9190
New York, NY 10016

[redacted]

Ship samples by FedEx using Carroll/Aifantis Labs **FedEx account number: 320569834**.

9.0 AGENT INFORMATION

9.1 Palbociclib

[redacted]

9.1.1 [redacted]

[redacted]

9.1.2 [redacted]

9.1.3 [redacted]

9.1.3.1 [redacted]

[redacted]

9.1.3.2 [redacted]

[redacted]

9.1.4 [redacted]

9.1.5 [redacted]

- [redacted]

9.1.6 [redacted]

9.1.7 [redacted]

9.1.8 [redacted]

9.1.9 [redacted]

[redacted]

9.1.10 Toxicities

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Palbociclib (PD-0332991, NSC 772256)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. 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 1751 patients. Below is the CAEPR for Palbociclib (PD-0332991).*

Version 2.4, September 13, 2019[1]

Adverse Events with Possible Relationship to Palbociclib (PD-0332991) (CTCAE 5.0 Term) [n= 1751]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
		Febrile neutropenia
EYE DISORDERS		
	Blurred vision	
	Dry eye	
	Watering eyes	
GASTROINTESTINAL DISORDERS		
	Constipation	
	Diarrhea	
	Mucositis oral	
Nausea		
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue		
	Fever	
INFECTIONS AND INFESTATIONS		
Infection[2]		
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Aspartate aminotransferase increased	
	Lymphocyte count decreased	
Neutrophil count decreased		
	Platelet count decreased	

Adverse Events with Possible Relationship to Palbociclib (PD-0332991) (CTCAE 5.0 Term) [n= 1751]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
NERVOUS SYSTEM DISORDERS		
	Dysgeusia	
	Headache[3]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Epistaxis	
		Pneumonitis
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Dry skin	
	Skin and subcutaneous tissue disorders - Other (rash)[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.

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

[3]Headache has been observed in trials using Palbociclib (PD-0332991) in combination with fulvestrant.

[4] Rash includes rash, rash maculo-papular, erythema, erythematous rash, erysipelas, rash pruritic, rash papular, generalized rash, exanthema, allergic dermatitis, dermatitis acneiform, dermatitis.

[5] Peripheral neuropathy includes both peripheral motor neuropathy and peripheral sensory neuropathy under the NERVOUS SYSTEM DISORDERS SOC.

Adverse events reported on Palbociclib (PD-0332991) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Palbociclib (PD-0332991) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Blood and lymphatic system disorders - Other (pancytopenia)
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Cardiac disorders - Other (paroxysmal atrial fibrillation with rapid ventricular response); Palpitations; Pericarditis; Sinus bradycardia; Supraventricular tachycardia
EYE DISORDERS - Cataract; Eye disorders - Other (retinal hemorrhage)
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Colitis; Colonic perforation; Dry mouth; Dyspepsia; Dysphagia; Esophageal stenosis; Flatulence; Gastric hemorrhage; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Intra-abdominal hemorrhage; Lower gastrointestinal hemorrhage; Small intestinal obstruction; Small intestinal perforation; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Edema limbs; Localized edema; Malaise; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice)
IMMUNE SYSTEM DISORDERS - Allergic reaction
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Fracture

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Creatinine increased; Ejection fraction decreased; GGT increased; INR increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Flank pain; Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (osteomyelitis); Myalgia; Neck pain; Osteonecrosis; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL. CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dizziness; Dysesthesia; Dysphasia; Intracranial hemorrhage; Nervous system disorders - Other (peripheral neuropathy)[5]; Syncope
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Psychiatric disorders - Other (altered mental status)
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Oropharyngeal pain; Pleural effusion; Postnasal drip; Pulmonary edema; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Pruritus
VASCULAR DISORDERS - Hypertension; Hypotension

Note: Palbociclib (PD-0332991) 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.

9.1.11 Agent Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. The investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. 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 using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) for oral agents 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. Before destroying any unused inventory, site should contact the COG Operations Center to confirm that it should not instead be returned to Pfizer. These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all palbociclib received from Pfizer. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers.

All opened (i.e. aluminum overseal broken) bottles (full, partially used, and empty) may be destroyed at the site by the appropriate site personnel (e.g. Pharmacist; Study Nurse/Coordinator) following local environmental requirements and institutional policies. Discarded volumes of palbociclib solutions must be disposed of as hazardous waste according to local site procedures. Other items used in the dose preparation and administration must be disposed of according to local site procedures.

All unused or expired palbociclib will be returned to Pfizer or if authorized, disposed of at the study site and documented. All material containing palbociclib will be treated and disposed of as hazardous waste in accordance with governing regulations.

9.1.12 Obtaining the Agent

Palbociclib will be supplied by Pfizer. **Only use palbociclib provided for investigational use specifically for AINV18P1**.

Palbociclib can be obtained by following the instructions on the agent request form provided on the AINV18P1 protocol page of the COG website (https://members.childrensoncologygroup.org/).

The drug supply must be stored in a locked limited access area. Palbociclib is for investigational use only, and is to be used only within the context of this study. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, subjects, or clinics, or allow supplies to be used other than directed by this protocol.

9.2 Cytarabine (07/13/15)

(Cytosine arabinoside, Ara-C, Cytosar®) NSC #63878

9.2.1 Source and Pharmacology:

Cytarabine appears to act through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate (Ara-CTP), an effective inhibitor of DNA polymerase. Ara-CTP is inactivated by a pyrimidine nucleoside deaminase, which converts it to the nontoxic uracil derivative (Ara-U). It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine. It has an initial distributive phase $t_{½}$ of about 10 minutes, with a secondary elimination phase $t_{½}$ of about 1 to 3 hours. Peak levels after intramuscular or subcutaneous administration of cytarabine occur about 20 to 60 minutes after injection and are lower than IV administration. Intrathecally administered doses are metabolized and eliminated more slowly with a $t_{½}$ of about 2 hours.

Intrathecal Therapy (Cytarabine Single Agent) Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, headache	Arachnoiditis	Rash, somnolence, meningismus, convulsions, paresis
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia
Delayed: Any time later during therapy, excluding the above condition			Necrotizing leukoencephalopathy, paraplegia, blindness (in combination with XRT & systemic therapy)

9.2.2 Formulation:
Cytarabine for Injection is available in vials of 100 mg, 500 mg, 1 g, and 2 g containing a sterile powder for reconstitution. It is also available at a 20 mg/mL concentration with benzyl alcohol (25 mL per vial) or as a preservative free solution (5 mL, 50 mL per vial), and at a 100 mg/mL concentration with benzyl alcohol (20 mL vial) or as preservative free solution (20 mL vial). Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Cytarabine solutions should be protected from light.

9.2.3 Guidelines for Administration:
See Treatment and Dose Modification sections of the protocol.

Intrathecal:
For intrathecal administration, dilute with 5-10 mL (or volume per institutional practice) preservative free 0.9% sodium chloride injection, lactated Ringer's injection, Elliot's B solution. The volume of CSF removed should be equal to at least ½ the volume delivered.

Patient Age (years)	Recommended volume	10% CSF volume	CSF Volume *
1 – 1.99	5 – 10 mL	5 mL	50 ± 10 mL (babies)
2 – 2.99	5 – 10 mL	8 mL	80 ± 20 mL (younger children)
3 – 8.99	5 – 10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	5 – 10 mL	13 mL	130 ± 30 mL (adults)

**Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; N Engl J Med. 1962 Dec 20; 267:1273-8*

Of Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Intrathecal cytarabine mixed in NS, lactated Ringer's injection, or Elliot's B solution is stable for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

9.2.4 Supplier:
Commercially available from various manufacturers. See package insert for further information.

9.3 Methotrexate (05/07/19)

(MTX, amethopterin, Trexall®, Xatmep®) NSC #000740

9.3.1 Source and Pharmacology:
A folate analogue which reversibly inhibits dihydrofolate reductase, the enzyme that reduces folic acid to tetrahydrofolic acid. Inhibition of tetrahydrofolate formation limits the availability of one carbon fragments necessary for the synthesis of purines and the conversion of deoxyuridylate to thymidylate in the synthesis of DNA and cell reproduction. The polyglutamated metabolites of MTX

also contribute to the cytotoxic effect of MTX on DNA repair and/or strand breaks. MTX cytotoxicity is highly dependent on the absolute drug concentration and the duration of drug exposure. MTX is actively transported across cell membranes. At serum methotrexate concentrations exceeding 0.1 µmol/mL, passive diffusion becomes a major means of intracellular transport of MTX. The drug is widely distributed throughout the body with the highest concentration in the kidney, liver, spleen, gallbladder and skin. Plasma concentrations following high dose IV MTX decline in a biphasic manner with an initial half-life of 1.5-3.5 hours, and a terminal half life of 8-15 hours. About 50% is bound to protein. After oral administration, approximately 60% of a 30 mg/m^2 dose is rapidly absorbed from the GI tract, with peak blood levels at 1 hour. At doses > 30 mg/m² absorption decreases significantly. Even at low doses absorption may be very erratic, varying between 23% and 95%. The elimination of MTX from the CSF after an intrathecal dose is characterized by a biphasic curve with half-lives of 4.5 and 14 hours. After intrathecal administration of 12 mg/m², the lumbar concentration of MTX is ~100 times higher than in plasma. (Ventricular concentration is ~ 10% of lumbar concentration). MTX is excreted primarily by the kidneys via glomerular filtration and active secretion into the proximal tubules. Renal clearance usually equals or exceeds creatinine clearance. Small amounts are excreted in the feces. There is significant entero-hepatic circulation of MTX. The distribution of MTX into third-space fluid collections, such as pleural effusions and ascitic fluid, can substantially alter MTX pharmacokinetics. The slow release of accumulated MTX from these third spaces over time prolongs the terminal half-life of the drug, leading to potentially increased clinical toxicity.

Intrathecal Therapy (Methotrexate Single Agent) Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, headache	Arachnoditis: (headache, fever, vomiting, meningismus, nuchal rigidity, and pleocytosis)	Anaphylaxis, vomiting, seizures(L), malaise, confusion, back pain, rash, bleeding into subarachnoid or subdural space (risk > with platelet counts < 20,000),
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia, somnolence, cranial nerve palsy, subacute myelopathy (paraparesis/paraplegia), speech disorders, pain in the legs, bladder dysfunction
Delayed: Any time later during therapy, excluding the above condition		Cognitive disturbances (L)[1], learning disability (L)[1]	Leukoencephalopathy[1] (L)
Late: Any time after the completion of treatment			Progressive CNS deterioration[1]

[1] *May be enhanced by HDMTX and/or cranial irradiation.*
(L) Toxicity may also occur later.

9.3.2 Formulation & Stability:

Methotrexate for Injection is available as a lyophilized powder for injection in 1000 mg vials. The powder for injection contains approximately 7 mEq sodium

in the 1000 mg vial. Methotrexate for Injection is also available as a 25 mg/mL solution in 2, 4, 8, 10, and 40 mL preservative free vials and 2 and 10 mL vials with preservative. The 2, 4, 8, 10, and 40 mL solutions contain approximately 0.43, 0.86, 1.72, 2.15, and 8.6 mEq sodium per vial, respectively. The preserved vials contain 0.9% benzyl alcohol as a preservative.

Sterile methotrexate powder or solution is stable at 20º-25ºC (68º-77ºF); excursions permitted to 15º-30ºC (59º- 86 Fº). Protect from light

9.3.3 Guidelines for Administration:
See Treatment and Dose Modifications sections of protocol.

For Intrathecal use: Use **preservative free** 25 mg/mL solution.

For intrathecal administration, dilute with 5-10 mL preservative free NS, lactated Ringer's, or Elliot's B solution as per institutional standard of practice. The volume of CSF removed should be equal to at least half the volume delivered.

Patient Age (years)	Methotrexate dose	Recommended volume	10% CSF volume	CSF Volume *
1–1.99	8 mg	5–10 mL	5 mL	50 ± 10 mL (babies)
2–2.99	10 mg	5-10 mL	8 mL	80 ± 20 mL (younger children)
3–8.99	12 mg	5-10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	15 mg	5-10 mL	13 mL	130 ± 30 mL (adults)

**Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; N Engl J Med. 1962 Dec 20; 267:1273-8*

Of Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Diluted methotrexate for intrathecal administration is stable for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

9.3.4 Supplier:
Commercially available from various manufacturers. See package insert for further information.

9.4 Intrathecal Triples (05/08/12)

(Methotrexate/Hydrocortisone/Cytarabine, IT-3)

9.4.1 Source and Pharmacology:
The intrathecal route of administration of a drug produces more consistent CSF drug concentrations at relatively smaller doses because of the volume difference between the CSF and blood compartments (140 mL vs. 3500 mL in an adult). (The

CSF volume of children after the first 3 years is equivalent to that of an adult). Drug half-lives are longer as well because clearance is related to flow rather than metabolism or protein binding. Intrathecal methotrexate has a biphasic elimination curve from the CSF with a $t_{½}$ of 4.5 and 14 hours respectively. Following IT injection of cytarabine the elimination of the drug from the CSF is biphasic with a $t_{½}$ of 1 and 3.4 hours respectively which is 8-fold longer than the clearance from plasma. The elimination of hydrocortisone is similarly prolonged.

Intrathecal Triple Therapy (Methotrexate/Hydrocortisone/Cytarabine) Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, headache	Arachnoditis: (headache, fever, vomiting, meningismus and pleocytosis)	Rash, anaphylaxis (L), paresis, bleeding into subarachnoid or subdural space (risk > with platelet counts <20,000), confusion, fatigue, disorientation, seizures
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, somnolence, ataxia, cranial nerve palsy, transient and rarely permanent paraplegia (L), speech disorders
Delayed: Any time later during therapy, excluding the above condition		Cognitive disturbances (L), learning disabilities (L)	Demyelinating leukoencephalopathy[1] (L), blindness[1]
Late: Any time after the completion of treatment			Progressive CNS deterioration[1]

[1] *May be enhanced by systemic therapy such as high dose methotrexate or cytarabine and/or cranial irradiation.*
(L) Toxicity may also occur later.

9.4.2 Formulation and Stability:

Methotrexate 25 mg/mL **preservative free** 2 mL vial or methotrexate 20 mg preservative free sterile powder for injection vial. Cytarabine 100 mg preservative free sterile powder for injection. Hydrocortisone sodium succinate 100 mg vial sterile powder for injection.

9.4.3 Guidelines for Administration:

See Treatment and Dose Modification sections of the protocol.

For intrathecal administration, dilute each agent with 5-10 mL preservative free NS, lactated ringers or Elliot's B solution or as per institutional standard of practice. The volume of CSF removed should be equal to at least half the volume delivered.

Patient Age (years)	**Doses (MTX/Hydrocortisone/Ara-C)**	**Recommended volume**	**10% CSF volume**	**CSF Volume ***
0 – 0.99	7.5 mg / 7.5 mg / 15 mg	5-10 mL	5 mL	50 ± 10 mL (babies)
1 – 1.99	8 mg / 8 mg / 16 mg	5-10 mL	5 mL	50 ± 10 mL (babies)
2 – 2.99	10 mg / 10 mg / 20 mg	5-10 mL	8 mL	80 ± 20 mL

				(younger children)
3 – 8.99	12 mg / 12 mg / 24 mg	5-10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	15 mg / 15 mg / 30 mg	5-10 mL	13 mL	130 ± 30 mL (adults)

**Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection. N Engl J Med 1962 Dec 20; 267:1273-8*

Of note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Intrathecal triples are stable in NS for 24 hours at 25ºC but contain no preservative and should be administered as soon as possible after preparation.

9.4.4 Supplier:
Commercially available from various manufacturers. See package insert for further information.

9.5 Doxorubicin (05/09/11)

(Adriamycin®) NSC #123127

9.5.1 Source and Pharmacology:
An anthracycline antibiotic isolated from cultures of *Streptomyces peucetius*. The cytotoxic effect of doxorubicin on malignant cells and its toxic effects on various organs are thought to be related to nucleotide base intercalation and cell membrane lipid binding activities of doxorubicin. Intercalation inhibits nucleotide replication and action of DNA and RNA polymerases. The interaction of doxorubicin with topoisomerase II to form DNA-cleavable complexes appears to be an important mechanism of doxorubicin cytocidal activity. Doxorubicin cellular membrane binding may affect a variety of cellular functions. Enzymatic electron reduction of doxorubicin by a variety of oxidases, reductases, and dehydrogenases generate highly reactive species including the hydroxyl free radical (OH•). Free radical formation has been implicated in doxorubicin cardiotoxicity by means of Cu (II) and Fe (III) reduction at the cellular level. Cells treated with doxorubicin have been shown to manifest the characteristic morphologic changes associated with apoptosis or programmed cell death. Doxorubicin-induced apoptosis may be an integral component of the cellular mechanism of action relating to therapeutic effects, toxicities, or both.

Doxorubicin serum decay pattern is multiphasic. The initial distributive $t_{½}$ is approximately 5 minutes suggesting rapid tissue uptake of doxorubicin. The terminal $t_{½}$ of 20 to 48 hours reflects a slow elimination from tissues. Steady-state distribution volumes exceed 20 to 30 L/kg and are indicative of extensive drug uptake into tissues. Plasma clearance is in the range of 8 to 20 mL/min/kg and is predominately by metabolism and biliary excretion. The P450 cytochromes which appear to be involved with doxorubicin metabolism are CYP2D6 and CYP3A4. Approximately 40% of the dose appears in the bile in 5 days, while only 5 to 12% of the drug and its metabolites appear in the urine during the same time period. Binding of doxorubicin and its major metabolite,

doxorubicinol, to plasma proteins is about 74 to 76% and is independent of plasma concentration of doxorubicin.

9.5.2 Doxorubicin Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, pink or red color to urine, sweat, tears, and saliva	Hyperuricemia, facial flushing, sclerosis of the vein	Diarrhea, anorexia, erythematous streaking of the vein (flare reaction), extravasation (rare) but if occurs = local ulceration, anaphylaxis, fever, chills, urticaria, acute arrhythmias
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (leukopenia, thrombocytopenia, anemia), alopecia	Mucositis (stomatitis and esophagitis), hepatotoxicity	Radiation recall reactions, conjunctivitis and lacrimation
Delayed: Any time later during therapy		Cardiomyopathy[1] (CHF occurs in 5-20% at cumulative doses ≥ 450 mg/m²) (L)	Cardiomyopathy[1] (CHF occurs in < 5% at cumulative doses ≤ 400 mg/m²) (L), ulceration and necrosis of colon, hyper-pigmentation of nail bed and dermal crease, onycholysis
Late: Any time after completion of treatment	Subclinical cardiac dysfunction	CHF (on long term follow up in pediatric patients)	Secondary malignancy (in combination regimens)
Unknown Frequency and Timing:	Fetal and teratogenic toxicities. Carcinogenic and mutagenic effects of doxorubicin have been noted in animal models. Doxorubicin is excreted into breast milk in humans		

[1] *Risk increases with cardiac irradiation, exposure at a young or advanced age.*
(L) Toxicity may also occur later.

9.5.3 Formulation and Stability:

Doxorubicin is available as red-orange lyophilized powder for injection in 10 mg[1], 20 mg[1], 50 mg[1] vials and a preservative-free 2 mg/mL solution in 10 mg[1], 20 mg[1], 50 mg[1], 200 mg[2] vials.

[1]*:Contains lactose monohydrate, 0.9 NS, HCl to adjust pH to 3. The Adriamycin RDF® (rapid dissolution formula) also contains methylparaben, 1 mg per each 10 mg of doxorubicin, to enhance dissolution.*

[2] *Multiple dose vial contains lactose, 0.9% NS, HCl to adjust pH to 3.*

Aqueous Solution: Store refrigerated 2°-8°C, (36°-46°F). Protect from light. Retain in carton until contents are used.

Powder for Injection: Store unreconstituted vial at room temperature, 15°-30°C (59°-86°F). Retain in carton until contents are used. Reconstitute with preservative-free NS to a final concentration of 2 mg/mL. After adding the diluent, the vial should be shaken and the contents allowed to dissolve. The reconstituted solution is stable for 7 days at room temperature and 15 days under refrigeration,

2°-8°C (36°-46°F) when protected from light. Doxorubicin further diluted in 50 – 1000 mL of NS or D5W is stable for up to 48 hours at room temperature (25°C) when protected from light.

9.5.4 Guidelines for Administration:
See Treatment and Dose Modification sections of the protocol.

Administer IV through the tubing of rapidly infusing solution of D_5W or 0.9% NaCl preferably into a large vein. Protect the diluted solution from sunlight. To avoid extravasation, the use of a central line is suggested.

9.5.5 Supplier:
Commercially available from various manufacturers. See package insert for further information.

9.6 **PREDNISO(LO)NE (11/16/17)**
(Deltasone®, PrediSONE Intensol®, Rayos®, Meticorten®, Liquid Pred®, Pediapred®, Millipred®, OraPred ODT®) NSC #10023 (prednisone), NSC# 9151 (prednisolone)

9.6.1 Source and Pharmacology:
Prednisone and prednisolone are a synthetic compounds closely related to hydrocortisone. Glucocorticoids produce widespread and diverse physiologic effects on carbohydrate, protein, and lipid metabolism, electrolyte and water balance, functions of the cardiovascular system, kidney, skeletal muscle, and the nervous systems. Glucocorticoids reduce the concentration of thymus-dependent lymphocytes (T-lymphocytes), monocytes, and eosinophils. Glucocorticoids selectively bind to the cortisol receptors on human lymphoid cells which are found in larger numbers on leukemic lymphoblasts. They also decrease binding of immunoglobulin to cell surface receptors and inhibit the synthesis and/or release of interleukins, thereby decreasing T-lymphocyte blastogenesis and reducing expansion of the primary immune response. The specific cellular mechanisms that act to halt DNA synthesis are thought to be related to inhibition of glucose transport or phosphorylation, retardation of mitosis, and inhibition of protein synthesis. Peak blood levels occur within 2 hours of oral intake. Prednisone is approximately 75% protein bound with a plasma $t_{½}$ of 3.2 to 4 hours. (Biologic half-life is 12- 36 hours.)

PREDNISO(LO)NE Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Insomnia, hyperphagia	Gastritis	Hyperuricemia
Prompt: Within 2-3 weeks, prior to the next course	Immunosuppression, personality changes (mood swings, euphoria, anxiety, depression), pituitary-adrenal axis suppression, acne (L)	Hyperglycemia, facial erythema, poor wound healing, infections (bacterial, fungal, parasitic, viral), edema	Pancreatitis (L), electrolyte imbalance (Na retention, hypokalemia, hypocalcemia) (L), increased intraocular pressure (L), hypertension, psychosis, vertigo, headache
Delayed:	Cushing's syndrome (moon facies, truncal obesity)	Striae and thinning of the skin, easy bruising,	Spontaneous fractures (L), growth suppression, peptic ulcer and GI

Any time later during therapy		muscle weakness, osteopenia	bleeding, pseudotumor cerebri (increased intracranial pressure with papilledema, headache), aseptic necrosis of the femoral and humeral heads (L), urolithiasis[1] (L)
Late: Any time after completion of treatment		Cataracts (which may be reversible on discontinuation of prednisone in children)	
Unknown Frequency and Timing:	Fetal and teratogenic toxicities: Corticosteroids cross the placenta (prednisone has the poorest transport). In animal studies, large doses of cortisol administered early in pregnancy produced cleft palate, stillborn fetuses, and decreased fetal size. Chronic maternal ingestion during the first trimester has shown a 1% incidence of cleft palate in humans. Prednisone is excreted into breast milk in humans; however, several studies suggest that amounts excreted in breast milk are negligible with prednisone doses ≤ 20 mg/day.		

[1] *Mainly reported in pediatric patients with ALL. Howard SC et al. Urolithiasis in pediatric patients with acute lymphoblastic leukemia. Leukemia 2003; 17: 541-6.*
(L) Toxicity may also occur later.

9.6.2 Formulation and Stability:
Prednisone is available in 1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg, and 50 mg tablets. Also available as a solution in 1 mg/1 mL or 5 mg/mL concentrations. Inactive ingredients vary depending on manufacturer but tablet formulations may include calcium or magnesium stearate, corn starch, lactose, erythrosine sodium, mineral oil, sorbic acid, sucrose, talc and various dyes. The solution may include 5-30% alcohol, fructose, sucrose, saccharin, and sorbitol.

Prednisolone is available as 5 mg scored tablets (base) and 10 mg, 15 mg, and 30 mg orally disintegrating tablets (ODT; sodium phosphate [strength expressed as base]). Liquid formulations of prednisolone are available as 15 mg/5 mL oral solution (base); 5 mg/5 mL, 10 mg/5 mL, 15 mg/5 mL, 20 mg/5 mL oral solution (sodium phosphate [strength expressed as base]; and 15 mg/5 mL oral syrup (base). Inactive ingredients vary depending on manufacturer. Tablet formulations may contain dyes and liquid formulations may contain edetate disodium, methylparaben, saccharin sodium.

9.6.3 Guidelines for Administration:
See Treatment and Dose Modifications sections of the protocol.

PredniSONE and prednisoLONE are equipotent corticosteroids.

9.6.4 Supplier:
Commercially available from various sources. See package insert for further information.

9.7 Vincristine (08/16/12)

(Oncovin®, VCR, LCR) NSC #67574

9.7.1 Source and Pharmacology:
Vincristine is an alkaloid isolated from *Vinca rosea* Linn (periwinkle). It binds to tubulin, disrupting microtubules and inducing metaphase arrest. Its serum decay pattern is triphasic. The initial, middle, and terminal half-lives are 5 minutes,

2.3 hours, and 85 hours respectively; however, the range of the terminal half-life in humans is from 19 to 155 hours. The liver is the major excretory organ in humans and animals; about 80% of an injected dose of vincristine sulfate appears in the feces and 10% to 20% can be found in the urine. The p450 cytochrome involved with vincristine metabolism is CYP3A4. Within 15 to 30 minutes after injection, over 90% of the drug is distributed from the blood into tissue, where it remains tightly, but not irreversibly bound. It is excreted in the bile and feces. There is poor CSF penetration.

9.7.2 Vincristine Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Jaw pain, headache	Extravasation (rare) but if occurs = local ulceration, shortness of breath, and bronchospasm
Prompt: Within 2-3 weeks, prior to the next course	Alopecia, constipation	Weakness, abdominal pain, mild brief myelosuppression (leukopenia, thrombocytopenia, anemia)	Paralytic ileus, ptosis, diplopia, night blindness, hoarseness, vocal cord paralysis, SIADH, seizure, defective sweating
Delayed: Any time later during therapy	Loss of deep tendon reflexes	Peripheral paresthesias including numbness, tingling and pain; clumsiness; wrist drop, foot drop, abnormal gait	Difficulty walking or inability to walk; sinusoidal obstruction syndrome (SOS, formerly VOD) (in combination); blindness, optic atrophy; urinary tract disorders (including bladder atony, dysuria, polyuria, nocturia, and urinary retention); autonomic neuropathy with postural hypotension; 8th cranial nerve damage with dizziness, nystagmus, vertigo and hearing loss
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of vincristine (either alone or in combination with other antineoplastic agents) have been noted in humans. The toxicities include: chromosome abnormalities, malformation, pancytopenia, and low birth weight. It is unknown whether the drug is excreted in breast milk.		

9.7.3 Formulation and Stability:

Vincristine is supplied in 1 mL and 2 mL vials in which each mL contains vincristine sulfate 1 mg (1.08 µmol), mannitol 100 mg, SWFI; acetic acid and sodium acetate are added for pH control. The pH of vincristine sulfate injection, *USP* ranges from 3.5 to 5.5. This product is a sterile, preservative free solution. Store refrigerated at 2˚-8˚C or 36˚-46˚F. Protect from light and retain in carton until time of use.

Do not mix with any IV solutions other than those containing dextrose or saline.

9.7.4 Guidelines for Administration:

See Treatment and Dose Modifications sections of protocol.

The World Health Organization, the Institute of Safe Medicine Practices (United States) and the Safety and Quality Council (Australia) all support the use of

minibag rather than syringe for the infusion of vincristine. The delivery of vincristine via either IV slow push or minibag is acceptable for COG protocols. Vincristine should **NOT** be delivered to the patient at the same time with any medications intended for central nervous system administration. Vincristine is fatal if given intrathecally.

Injection of vincristine sulfate should be accomplished as per institutional policy. Vincristine sulfate must be administered via an intact, free-flowing intravenous needle or catheter. Care should be taken to ensure that the needle or catheter is securely within the vein to avoid extravasation during administration. The solution may be injected either directly into a vein or into the tubing of a running intravenous infusion.

Special precautions:
FOR INTRAVENOUS USE ONLY.
The container or the syringe containing vinCRIStine must be enclosed in an overwrap bearing the statement: "Do not remove covering until moment of injection. For intravenous use only - Fatal if given by other routes."

9.7.5 Supplier:
Commercially available from various manufacturers. See package insert for more detailed information.

9.8 Pegaspargase (06/05/17)

(PEG-asparaginase, PEGLA, PEG-L-asparaginase, polyethylene glycol-L-asparaginase, Oncaspar®) NSC #624239

9.8.1 Source and Pharmacology:
Pegaspargase is a modified version of the enzyme L-asparaginase. L-asparaginase is modified by covalently conjugating units of monomethoxypolyethylene glycol (PEG), molecular weight of 5000, to the enzyme, forming the active ingredient PEG-L-asparaginase. The L-asparaginase (L-asparagine amidohydrolase, type EC-2, EC 3.5.1.1) used in the manufacture of Pegaspargase is derived from *Escherichia coli* which is purchased in bulk from Merck, Sharp and Dohme. L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. The ability to synthesize asparagine is notably lacking in malignancies of lymphoid origin. Asparaginase depletes L-asparagine from leukemic cells (especially lymphoblasts) by catalyzing the conversion of L-asparagine to aspartic acid and ammonia. In predominately L-asparaginase naive adult patients with leukemia and lymphoma, initial plasma levels of L-asparaginase following intravenous administration of pegaspargase were determined. Apparent volume of distribution was equal to estimated plasma volume. L-asparaginase was measurable for at least 15 days following the initial treatment with Pegaspargase. The approximate $t_{½}$ in adult patients is 5.73 days. The enzyme could not be detected in the urine. The half-life is independent of the dose administered, disease status, renal or hepatic function, age, or gender. In a study of newly diagnosed pediatric patients with ALL who received either a single intramuscular injection of pegaspargase (2500 IU/m^2), *E. coli* L-asparaginase (25000 IU/m^2), or *Erwinia* (25000 IU/m^2), the plasma half-lives for the three forms of L-asparaginase were: 5.73 ± 3.24 days,

1.24 ± 0.17 days, and 0.65 ± 0.13 days respectively. The plasma half-life of pegaspargase is shortened in patients who are previously hypersensitive to native L-asparaginase as compared to non-hypersensitive patients. L-asparaginase is cleared by the reticuloendothelial system and very little is excreted in the urine or bile. Cerebrospinal fluid levels are < 1% of plasma levels.

9.8.2 Pegaspargase Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Allergic reactions (total likelihood of local, and or systemic reaction especially if previous hypersensitivity reaction to native asparaginase), pain at injection site, weakness, fatigue, diarrhea	Allergic reactions (total likelihood of local, and or systemic reaction if **no** previous hypersensitivity reaction to native asparaginase), rash	Anaphylaxis, hyper/hypotension, tachycardia, periorbital edema, chills, fever, dizziness, dyspnea, bronchospasm, lip edema, arthralgia, myalgia, urticaria, mild nausea/vomiting, abdominal pain, flatulence, somnolence, lethargy, headache, seizures (L), hyperuricemia
Prompt: Within 2-3 weeks, prior to the next course	Hyperammonemia (L), coagulation abnormalities with prolonged PTT, PT and bleeding times (secondary to decreased synthesis of fibrinogen, AT-III & other clotting factors) (L)	Hyperglycemia, abnormal liver function tests, pancreatitis (L), increased serum lipase/amylase	Hemorrhage (L), DIC, thrombosis, anorexia, weight loss, CNS ischemic attacks, edema, azotemia and decreased renal function, mild leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, hemolytic anemia, infections (sepsis with/without septic shock, subacute bacterial endocarditis [SBE], URI), CNS changes including irritability, depression, confusion, EEG changes, hallucinations, coma and stupor, paresthesias, hypertriglyceridemia, hyperlipidemia, Parkinson-like syndrome with tremor and increase in muscular tone, hyperbilirubinemia, chest pain
Delayed: Any time later during therapy			Renal failure, urinary frequency, hemorrhagic cystitis, elevated creatinine and BUN, fatty liver deposits, hepatomegaly, liver failure
Unknown Frequency and Timing:	Animal reproduction studies have not been conducted with pegaspargase. It is not known whether pegaspargase can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. However, fetal toxicities and teratogenic effects of asparaginase have been noted in animals. It is unknown whether the drug is excreted in breast milk.		

(L)Toxicity may also occur later.

9.8.3 Formulation and Stability:

Each milliliter of pegaspargase contains: PEG-L-asparaginase 750 IU ± 20%, monobasic sodium phosphate, *USP* 1.20 mg ± 5% dibasic sodium phosphate, *USP* 5.58 mg ± 5%, sodium chloride, *USP* 8.50 mg ± 5% , Water for Injection, *USP* qs to 1 mL. The specific activity of pegaspargase is at least 85 IU per milligram protein. Available in 5 mL vials as Sterile Solution for Injection in ready to use single-use vials, preservative free. Keep refrigerated at 2°-8°C (36°-46°F). Do not

use if stored at room temperature for more than 48 hours. **DO NOT FREEZE.** Do not use product if it is known to have been frozen. Freezing destroys activity, which cannot be detected visually.

9.8.4 Guidelines for Administration:
See Treatment and Dose Modifications sections of the protocol.

For IM administration: the volume at a single injection site should be limited to 2 mL. If the volume to be administered is greater than 2 mL, multiple injection sites should be used.

For IV administration: dilute pegaspargase in 100 mL of NS or D5W and infuse over 1 to 2 hours through a NS or D5W running infusion line. Pegaspargase admixed in 100 mL of NS or D5W is stable for 48 hours at room temperature. Pegaspargase diluted in 100 mL of NS is stable for up to 72 hours refrigerated (4ºC [39°F]) (refrigerated stability data on file with Sigma-Tau). Avoid excessive agitation. DO NOT SHAKE. Do not use if cloudy of if precipitate is present.

Have available during and after the infusion: antihistamine, epinephrine, oxygen, and IV corticosteroids. Observe patient for ONE hour after administration for signs of hypersensitivity reactions.

9.8.5 Supplier:
Commercially available. See package insert for further information.

9.9 Asparaginase Erwinia Chrysanthemi

(05/07/19)

(Erwinia Chrysanthemi, Erwinase®, Erwinazetm, Crisantaspase) NSC #106977

9.9.1 Source and Pharmacology:
L-asparagine is a nonessential amino acid synthesized by the transamination of L-aspartic acid by a reaction catalyzed by the enzyme L-asparagine synthetase. Neoplastic cells associated with acute lymphoblastic leukemia, acute myeloid leukemia and lymphoblastic lymphosarcoma are asparagine-dependent but lack asparagine synthetase activity. The administration of L-asparaginase produces an anti-neoplastic effect by catalyzing asparagine into aspartic acid and ammonia. As a result, these cells lack the ability to produce the asparagine necessary for protein metabolism and survival. Deamination of glutamine may also play a role in the antineoplastic activity of asparaginase.

Asparaginase Erwinia chrysanthemi (Erwinaze®) is asparaginase derived from cultures of Erwinia chrysanthemi. L-asparaginase is a tetrameric enzyme; each of the four identical subunits has a molecular weight of approximately 35 kDa. Asparaginase Erwinia chrysanthemi is immunologically distinct from E.coli L-asparaginase and may allow continued asparaginase therapy when a hypersensitivity reaction occurs to Escherichia coli-derived asparaginase. The package labeling states that there is insufficient information to characterize the incidence of antibodies to asparaginase Erwinia chrysanthemi. Several factors are involved in immunogenicity assay results and the assessment of antibodies, including assay methodology, assay sensitivity and specificity, sample handling, timing of sample collection, concomitant medications, and the underlying disease

state. The following data have been reported on each of the three preparations of asparaginase:

Clinical Pharmacology of Asparaginase Formulation	Elimination half-life (IM)	% Anti-Asparaginase Antibody positive patients
Native *Escherichia Coli*	26-30 hours	45-75
Pegylated-asparaginase	5.5-7 days	5-18
Erwinia Asparaginase	16 hours (7-13 hrs package insert)	30-50

From: Avramis, V; Panosyan, E; Pharmacokinetic/Pharmacodynamic Relationships of Asparaginase Formulations: The Past, the Present and Recommendations for the Future. Clin Pharmacokinet 2005; 44 (4): 367-393.

Effective asparaginase levels have been defined as activity of ⩾ 0.1 International Units per mL. Clinical trials with asparaginase Erwinia chrysanthemi demonstrated that 100% of patients achieved effective asparaginase levels at 48 and 72 hours (n=35 and n=13, respectively) following the third total dose when given on a Monday, Wednesday, Friday schedule using the IM route of administration. In a multicenter study characterizing the pharmacokinetic profile of 25,000 International Units/m2 Erwinaze® given intravenously over one hour on the same dosing schedule of Monday, Wednesday, Friday for 2 consecutive weeks, 83% (20/24) and 43% (9/21) of evaluable patients achieved an asparaginase activity level of ≥ 0.1 International Units/mL at 48 post-dose 5 and 72 hours post-dose 6, respectively. No formal drug interaction studies have been performed with asparaginase Erwinia chrysanthemi.

9.9.2 Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug		Allergic reactions, anaphylaxis, urticaria	Local injection site reactions, fever
Prompt: Within 2-3 weeks, prior to the next course			Pancreatitis, glucose intolerance, thrombosis, hemorrhage, transient ischemic attack, disseminated intravascular coagulation, hyperbilirubinemia, alanine aminotransferase increased, aspartate aminotransferase increased, hyperglycemia, hyperammonemia, vomiting, nausea, abdominal pain, headache, diarrhea, seizure
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of L-asparaginase have been noted in animals. Adequate, well-controlled studies of asparaginase *Erwinia chrysanthemi* have NOT been conducted. It is not known whether asparaginase *Erwinia chrysanthemi* will cause fetal harm or affect the ability to reproduce. It is not known if asparaginase *Erwinia chrysanthemi* is excreted into breast milk. The use of asparaginase *Erwinia chrysanthemi* should be avoided in pregnant or lactating patients.		

(L) Toxicity may also occur later.

9.9.3 Formulation and Stability:
Asparaginase Erwinia chrysanthemi is supplied as a sterile, white lyophilized powder for reconstitution in a clear glass vial with a 3 mL capacity. Each vial contains 10,000 International Units of asparaginase Erwinia chrysanthemi and the following inactive ingredients: glucose monohydrate (5.0 mg), sodium chloride (0.5 mg). Store intact vials between 2°C and 8°C (36° to 46ºF). Protect from light.

9.9.4 Guidelines for Administration:
See Treatment and Dose Modification sections of the protocol.

Erwinia asparaginase can be administered by intramuscular injection or by intravenous infusion. Use appropriate precautions for preparation of a hazardous agent. Visually inspect the powder in vial for foreign particles or discoloration prior to reconstitution.

For intramuscular administration, the contents of each vial should be reconstituted by slowly adding 1 mL or 2 mL of sterile, preservative-free NS to the inner vial wall. The final concentration is 10,000 International Units per mL when using 1 mL for reconstitution or 5,000 International Units per mL when using 2 mL for reconstitution. Gently mix or swirl the contents to dissolve the contents of the vial. Do not shake or invert the vial. The resulting solution should be clear and colorless. Discard if any particulate matter or protein aggregates are visible. Withdraw the appropriate dosing volume into a polypropylene syringe within 15 minutes of reconstitution. Polycarbonate luer-lok syringes from B-D (1 mL) are also acceptable (personal communication, EUSA Pharma). Discard any unused drug; do not save or use any unused drug remaining the in the vial. No more than 2 mL should be given at any one injection site. Doses larger than 2 mL should be divided and given in separate administration sites.

For intravenous use, slowly inject the appropriate volume of reconstituted solution into a Normal Saline 100 mL infusion bag; do not shake or squeeze the bag. Infuse Erwinia asparaginase over 1-2 hours. Do not infuse other intravenous drugs through the same intravenous line while infusing Erwinia asparaginase. Please see http://www.erwinazesupply.com to check which batches may require the use a 0.2-micron, low protein binding, in-line filter for IV administration.

Administer the dose within a 4 hour time period from reconstitution. If the dose is not used within this time period, discard the dose. Do not freeze or refrigerate the reconstituted solution.

The product used in Australia has an 8 hour expiry (from Porton Biopharma, Salisbury, UK).

Have available during and after the infusion: antihistamine, epinephrine, oxygen, and IV corticosteroids. Observe patient for ONE hour after administration for signs of hypersensitivity reactions.

9.9.5 Drug Ordering:
In the United States, asparaginase Erwinia chrysanthemi (Erwinaze®) is distributed by McKesson Plasma and Biologics. Verify your institution has a

contract with McKesson Plasma and Biologics before ordering. If not, contact McKesson at 877-625-2566 for assistance setting up an account.

Orders may be placed online or via phone, fax, or email.
Orders may be placed online via http://Connect.McKesson.com
Orders may be submitted via fax to 888-752-7626
Orders may be submitted via email or MPBOrders@McKesson.com
Email all other information requests to MPB@McKesson.com
Regular order hours: M-F 9:00 am – 7:30 pm EST;
Emergency order after hours services (24/7/365): 877-625-2566
Orders placed by 7:30 pm EST will ship the next day.

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12).
b) Adverse Events requiring removal from protocol therapy (See Section 6).
c) Refusal of protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of planned therapy.
f) Physician determines it is not in the patient's best interest.
g) Repeated eligibility laboratory studies (bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of systemic chemotherapy (See Section 8.1).
h) Study is terminated by Sponsor.
i) Pregnancy

Patients who are removed from protocol therapy during Cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and SAE Report submitted via RAVE (if applicable). Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent.
b) Death
c) Lost to follow-up

d) Withdrawal of consent for any required observations or data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study
f) Patient did not receive protocol treatment after study enrollment

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

The minimum number of evaluable patients required for is 4. The projected maximum number of evaluable patients required for the dose confirmation is 15. This allows for 6 patients at each of 2 dose levels and 20% inevaluability. Therefore, this part is expected to be completed within 8-15 months assuming that 1-2 patients per month are enrolled into the study. An absolute maximum of 30 patients is possible in the unlikely event that each of 2 dose levels is expanded to 12 patients because of DLTs of different classes and 20% inevaluability. If this scenario occurred, the study would be expected to be completed within 15-30 months.

Up to six evaluable patients with relapsed B- or T-ALL/LL will be enrolled at the RP2D/MTD for further pharmacokinetic and efficacy assessment. This part of the study would be expected to be accrue over 6-12 months.

The entire study is expected to accrue a maximum of 21 patients and is expected to be completed within 14-27 months. An absolute maximum accrual of 36 patients for the entire protocol is expected to take up to 18-36 months.

11.2 Definitions

11.2.1 Evaluable for Adverse Events

Any patient who receives at least one dose of the study drug(s) or who experiences a dose-limiting toxicity is considered evaluable for Adverse Events. In addition, for the dose-confirmation portion during Cycle 1, patients must receive at least 85% of the prescribed dose per protocol guidelines and must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. Patients who do not have DLT and are not considered evaluable for toxicity will be replaced.

11.2.2 Maximum Tolerated Dose

- The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See Section 5.5) during Cycle 1 of therapy.

- In the unlikely event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), AND all of the following conditions are met, expansion of the cohort to 12 patients will be considered:

  - One of the DLTs does not appear to be dose- and/or drug-related
  - The Adverse Effects are readily reversible
  - The study chair, DVL statistician, DVL committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose confirmation can proceed.

- The DLTs observed in the expansion pharmacokinetic (PK)/efficacy phase (Part B) will be counted towards the total number of DLTs observed at the MTD during the dose confirmation portion of the study. If ≥ 1/3 of the cohort of patients at the MTD (during the dose confirmation plus the PK expansion) experience DLT then the MTD will be exceeded.

11.3 Dose Confirmation and Determination of MTD

The rolling six phase 1 trial design will be used for the conduct of this study. [17] Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	*Decision*
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*

5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.
**If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see Section 11.2.2 for exception to rule).

In addition to determination of the RP2D/MTD, a descriptive summary of all toxicities will be reported.

11.4 Inclusion of Children, Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past COG studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Efforts will be made to extend the accrual to a representative population, but in a Phase 1 trial which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

11.5 Pharmacokinetic and Correlative Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of palbociclib will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

While the primary aim of this study is to evaluate the toxicity of palbociclib, patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to leukemia/lymphoma specific criteria (Section 12.0) and will be reported descriptively.

All these analyses will be descriptive and exploratory and hypotheses generating in nature.

11.6 Study Design

This study is designed using a rolling six model to confirm the recommended phase 2 dose or maximally tolerated dose of Palbociclib in patients with relapsed B- or T-ALL/LL. Once the RP2D/MTD is established a non-statistical feasibility expansion cohort of up to 6 evaluable patients will be enrolled. If the proportion of patients who experience a DLT in cycle 1 is >33% at any time, then the study will suspend enrollment pending DVL leadership discussion.

11.7 Method of Analysis

Response will be determined as defined in Section 12.0. A report on the efficacy assessment will be posted on the completed disease stratum as part of a semi-annual study committee meeting book report.

Toxicities for patients will be described separately for the expansion cohort.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

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).

12.2 Response Criteria for Patients with Relapsed Acute Lymphoblastic Leukemia

12.2.1 Bone marrow status

M1 < 5% blasts in a bone marrow aspirate with at least 200 cells counted.
M2 5 - 25% lymphoblasts in a bone marrow aspirate with at least 200 cells counted.
M3 > 25% lymphoblasts in a bone marrow aspirate with at least 200 cells counted.

12.2.2 Leukemia Relapse

- **Isolated Bone Marrow Relapse**: Patients with an M2 or M3 marrow at any point after achieving initial remission without involvement of any extramedullary site. Morphologic relapse should be confirmed using flow cytometry, FISH and/or cytogenetics or molecular techniques.
- **CNS Relapse**: Positive cytomorphology and WBC ≥ 5/μL OR clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome that are, in the opinion of the investigator, more likely due to recurrent CNS leukemia than to alternative causes (e.g., viral infection or chemotherapy toxicity). If any CSF evaluation shows positive cytomorphology and WBC < 5/μL, a second CSF evaluation is recommended within 2 - 4 weeks. While identification of a leukemic clone in CSF by flow cytometry (TdT, CD19, CD10, etc.) or FISH for diagnostic karyotypic abnormality may be useful, definitive evidence of CNS

involvement (i.e. WBC ≥ 5/μL OR clinical signs of CNS leukemia) is required for the diagnosis of a CNS relapse.

- **Testicular Relapse**: Confirmation by testicular biopsy preferred but not required if associated with marrow relapse.
- **Combined Relapse**: M2 or M3 marrow at any point after achieving remission with concomitant CNS and/or testicular relapse.

12.2.3 Complete Response (CR)
Complete response (CR) is defined as an M1 marrow (< 5% blasts) with no evidence of circulating blasts or extramedullary disease and with peripheral count recovery, defined as absolute neutrophil count (ANC) ≥ 500/μL and platelet count ≥ to 50,000/μL without transfusion for 7 days.
Resolution of extramedullary disease (non-CNS, non-testicular) is defined as improvement of any nodal or organ disease with lesion resolution to < 1cm or FDG-PET SUV improved to Deauville 3 or less (< hepatic or mediastinal uptake) if initially FDG-avid. Skin lesions must be clinically resolved.

12.2.4 Complete Response with Incomplete Count Recovery (CRi)
Complete response with incomplete recovery of peripheral blood counts (CRi) is defined as an M1 marrow (< 5% blasts) with no evidence of circulating blasts or extramedullary disease and with an ANC < 500/μL and/or platelet count < 50,000/μL.

12.2.5 Partial Response (PR)
Complete disappearance of circulating blasts and achievement of M2 marrow status if M3 originally, without new sites of extramedullary disease, and with recovery of absolute neutrophil count (ANC ≥ 500/μL). Complete response in the marrow without resolution of extramedullary sites is a PR.

12.2.6 Stable Disease (SD)
Patient does not satisfy the criteria for PD, or has recovery of ANC ≥ 500/μL and fails to qualify for CR, CRi, or PR.

12.2.7 Progressive Disease (PD)
An increase of at least 25% in the absolute number of bone marrow leukemic cells, development of new sites of extramedullary disease, or other laboratory or clinical evidence of PD, with or without recovery of ANC or platelets.

12.2.8 MRD Negative
Patients will be considered MRD negative if their bone marrow has less than 0.01% blasts by flow cytometric evaluation. MRD should be performed by a COG approved laboratory.

12.2.9 Treatment Failure: Failure to achieve the following:

	Marrow	**CNS**	**Testicular/Other Extramedullary Disease**
End of Cycle 1	M1	CNS1	Clinical and imaging resolution (if

			applicable) of all sites of extramedullary disease

12.3 Central Nervous System (CNS) involvement of leukemia or lymphoma at relapse

CNS 1: In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of WBCs.

CNS 2: In CSF, presence < 5/μL WBCs and cytospin positive for blasts, or ≥ 5/μL WBCs but negative by Steinherz/Bleyer algorithm:
- CNS 2a: < 10/μL red blood cells (RBCs); < 5/μL WBCs and cytospin positive for blasts;
- CNS 2b: ≥ 10/μL RBCs; < 5/μL WBCs and cytospin positive for blasts; and
- CNS 2c: ≥ 10/μL RBCs; ≥ 5/μL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm (see below);

CNS 3: In CSF, presence of ≥ 5/μL WBCs and cytospin positive for blasts **and/or** clinical signs of CNS leukemia or lymphoma:
- CNS 3a: < 10/μL RBCs; ≥ 5/μL WBCs and cytospin positive for blasts;
- CNS 3b: ≥ 10/μL RBCs, ≥ 5/μL WBCs and positive by Steinherz/Bleyer algorithm (see below);
- CNS 3c: Clinical signs of CNS leukemia or lymphoma (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

Method of evaluating initial traumatic lumbar punctures (LPs)

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥5 WBC/μL and blasts, the following Steinherz/Bleyer algorithm should be used to distinguish between CNS2 and CNS3 disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF WBC ≥5/μL blasts, whose CSF WBC/RBC ratio is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis.

Example: CSF WBC = 60/μL; CSF RBC = 1,500/μL; blood WBC = 46000/μL; blood RBC = 3.0×10^6/μL:

$$\frac{60}{1{,}500} = 0.04 > 2X \frac{46{,}000}{3.0 \times 10^6} = 0.015$$

12.4 Response Criteria for Patients with Relapsed Lymphoblastic Lymphoma

12.4.1 Response Criteria

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Pediatric Non-Hodgkin Lymphoma Criteria[34], with modification from the Lugano classification. [34-36] Patients will LL must have either measurable or evaluable disease.

12.4.2 Evaluable for objective response:
Only those patients who have measurable disease present at baseline and have received at least one dose of protocol therapy will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of Course 1 will also be considered evaluable.)

12.4.3 Disease Parameters

12.4.3.1 Measurable disease:
A measurable node must have an LDi (longest diameter) greater than 1.5 cm. A measurable extranodal lesion should have an LDi greater than 1.0 cm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

12.4.3.2 Non-measured disease:
All other lesions (including nodal, extranodal, and assessable disease) should be followed as nonmeasured disease (e.g., cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

12.4.3.3 Target lesions:
For patients staged with CT, up to six of the largest target nodes, nodal masses, or other lymphomatous lesions that are measurable in two diameters (longest diameter [LDi] and shortest diameter) should be identified from different body regions representative of the patient's overall disease burden and include mediastinal and retroperitoneal disease, if involved.

12.4.4 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 2 weeks prior to the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

12.4.4.1 Clinical lesions:
Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

12.4.4.2 Conventional CT and MRI:

The major response designations will be established by CT or MRI of involved sites in conjunction with morphologic evaluation of bone marrow (BM) if involved at diagnosis. With growing concerns about the risks of cumulative ionizing radiation exposure to children from CT, MRI could be considered as an alternative to CT for evaluating non-pulmonary disease sites. e.g., assessment of abdominal/pelvic disease. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the response guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Pulse sequences should include at a minimum, axial and coronal fat-saturated FRFSE-T2, coronal T1 and axial and coronal post-gadolinium fat-saturated T1 weighted imaging. Body scans should be performed with breath-hold scanning techniques, if possible.

12.4.4.3 PET-CT:

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for International Pediatric Non-Hodgkin Lymphoma Response Criteria measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data, which may bias an investigator if it is not routinely or serially performed.

12.4.4.4 Ultrasound:

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

12.4.4.5 Endoscopy, Laparoscopy:

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

12.4.4.6 FDG-PET:

For patients with a positive PET scan at diagnosis, PET can be used to follow response in addition to a CT scan using the International Pediatric Non-Hodgkin Lymphoma Response Criteria.[34]

12.4.5 Response Criteria

12.4.5.1 Evaluation of Measurable Disease

Complete Response (CR): Disappearance of all disease. CT or MRI should be free of residual mass or evidence of new disease. FDG-PET should be negative.

CR unconfirmed (Cru): Residual mass is negative by FDG-PET; no new lesions by imaging examination; no new and/or progressive disease elsewhere

Partial Response (PR): 50% decrease in SPD (the sum of the products of the largest diameter and the perpendicular diameter for a tumor mass) on CT or MRI; FDG-PET may be positive (Deauville score or 4 or 5 with reduced lesional uptake compared with baseline); no new and/or PD; morphologic evidence of disease may be present in BM if present at diagnosis; however, there should be 50% reduction in percentage of lymphoma cells

Progressive Disease (PD): For those with > 25% increase in SPD on CT or MRI, Deauville score 4 or 5 on FDG-PET with increase in lesional uptake from baseline, or development of new morphologic evidence of disease in BM

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.4.6 Evaluation of Non-measured Lesions (CT-based response, PET/CT based response not applicable)[36]

Complete Response (CR): Absent non-measured lesions.

Partial response (PR): Absent/normal, regressed, lesions, but no increase.

Stable Disease (SD): No increase consistent with progression

Progressive Disease (PD): New or clear progression of preexisting non-measured lesions.

12.4.7 Evaluation of organ enlargement[36]

Complete Response (CR): Regress to normal

Partial response (PR): Spleen must have regressed by > 50% in length beyond normal

Stable Disease (SD): No increase consistent with progression

Progressive Disease (PD): In the setting of splenomegaly, the splenic length must increase by 50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline.

New or recurrent splenomegaly

12.4.8 Duration of Response

12.4.8.1 Duration of overall response:
The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).
The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

12.4.8.2 Duration of stable disease:
Stable disease is measured from the start of the treatment until the criteria for progression are met.

12.4.8.3 Progression-Free Survival
PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.4.8.4 Response Review
Response will be as per institutional evaluations.

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the Case Report Forms for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) whether the adverse event is considered serious; 3) the grade (severity); and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

13.1 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the NCI CTCAE version 5.0. The descriptions and grading scales found in the revised CTCAE version 5.0 will be used 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).

Step 2: Grade the adverse event using the NCI CTCAE.

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions in the table below. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Complete the MedWatch Form FDA 3500A SAE Report found on the protocol homepage and load into RAVE per the CRF guidelines. **CTEP AERS will NOT be used for reporting of Serious Adverse Events**

Table A: 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 **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.

6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported via MedWatch Form FDA 3500A within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via MedWatch within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 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 7 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

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

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via MedWatch Form FDA 3500A in RAVE if the event occurs following treatment with an agent under a COG IND.

13.2 Reporting of Adverse Events for commercial agents – AINV18P1 abbreviated pathway

The following are expedited reporting requirements for adverse events experienced by patients on study who have not received any doses of an investigational agent on this study.

Commercial reporting requirements are provided in Table B.

COG requires the MedWatch Form FDA 3500A report to be submitted in RAVE **within 7 calendar days** of learning of the event.

Table B
Reporting requirements for adverse events experienced by patients on study who have NOT received any doses of an investigational agent on this study.

Reporting Requirements for Adverse Events That Occur During Therapy with a Commercial Agent or Within 30 Days[1]

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			MedWatch Form FDA 3500A
Possible, Probable, Definite	MedWatch Form FDA 3500A		MedWatch Form FDA 3500A

[1]This includes all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent that can be attributed (possibly, probably, or definitely) to the agent and is not due to cancer recurrence must be reported via MedWatch reporting.

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

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via MedWatch Form FDA 3500A if the event occurs following treatment with an agent under a COG IND.

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

Additional Instructions or Exceptions to SAE Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via MedWatch Form FDA 3500A in RAVE for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents that may be teratogenic. For this reason, pregnancy needs to be reported in an expedited manner via MedWatch Form FDA 3500A in RAVE. Pregnancy needs to be followed **until the outcome of the pregnancy is known** at intervals deemed appropriate by her physicians. If the baby is born with a birth defect or anomaly, then a second expedited report is required. Any pregnancy loss must also be reported expeditiously.

- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased
BLOOD/LYMPHATICS DISORDERS	Anemia

- Grade 1 and 2 adverse events listed in the table below do not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
EYE DISORDERS	Dry Eye
EYE DISORDERS	Watering Eyes
EYE DISORDERS	Blurred vision
GASTROINTESTINAL DISORDERS	Decreased Appetite
GASTROINTESTINAL DISORDERS	Diarrhea
GASTROINTESTINAL DISORDERS	Nausea
GASTROINTESTINAL DISORDERS	Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fever
INFECTIONS AND INFESTATIONS	Infections and Infestations-Other, specify.
INFECTIONS AND INFESTATIONS	Infections and Infestations-Other, specify (stomatitis)
NERVOUS SYSTEM DISORDERS	Nervous system disorders-Other, specify (asthenia)
NERVOUS SYSTEM DISORDERS	Dysgeusia
NERVOUS SYSTEM DISORDERS	Headache
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Alopecia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Dry Skin
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash Maculo-papular

13.3 When to Report an Event in an Expedited Manner

- Some adverse events require notification **within 24 hours** (refer to Table A) to the study sponsor.
- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).
- Expedited AE reporting for this study must only use the MedWatch Form FDA 3500A Reporting upload mechanism within Rave for AINV18P1

13.4 Expedited Reporting Methods

13.4.1 SAE Expedited Reporting

To report adverse events in an expedited fashion use the MedWatch Form FDA 3500A report template found on the protocol homepage, and submit the completed form via the SAE Reporting mechanism in Rave for AINV18P1.

A MedWatch Form FDA 3500A must be submitted electronically via the Med Watch Form FDA 3500A CRF in RAVE

Send supporting documentation by email to the AINV18P1 COG Study Assigned Research Coordinator. **ALWAYS include the COG patient ID on all emailed documents**.

13.5 Definition of Onset and Resolution of Adverse Events

Note: These guidelines below are for reporting adverse events on the COG case report forms and do not alter the guidelines for SAE Expedited reporting.

13.5.1 If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

13.5.2 If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

13.5.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.5.4 The resolution date of the AE is defined as the date at which the AE returns to baseline or less than or equal to Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

13.5.5 An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.6 Other Recipients of Adverse Event Reports

13.6.1 Events that do not meet the criteria for SAE reporting (**Section 13.2**) should be reported at the end the cycle using the forms provided in the CRF packet (See **Section 14.1**).

13.6.2 COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

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

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories

1. Non-computerized Information: Roadmaps, Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.

2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.

3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the eRDES and RAVE screens) provided in the case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including a Protocol Safety Committee.

14.2.1 Protocol Safety Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the Protocol Safety Committee (PSC) is to protect the interests of patients and the scientific integrity of the study. The PSC consists is constituted of members who will serve as advisors to the study sponsors and to assist in achieving the successful completion of this clinical trial and to participate in the evaluation of the safety and trial results. The PSC members will be investigators participating in Study AINV18P1 who will work with the study committee and study sponsors to ensure the protection of the welfare of subjects participating in this clinical trial and to enhance the integrity of the conduct of the clinical trial. The PSC members should have experience in the conduct of clinical trials and have knowledge of good clinical practice (GCP) guidelines and a general understanding of regulatory requirements for drug development. The PSC members should be capable of conducting discussion, integrating differing points of view, and moving toward consensus on recommendations to be provided to the study sponsors

The PSC will meet on an as needed basis, at least every 6 months, to review the safety data for the determination of dose-limiting toxicities (DLT), feasibility decisions, analyses of the interim results, evaluate risk benefit throughout the conduct of the study and other issues relevant to the overall study conduct Approximately 6 weeks before each meeting of the PSC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the PSC. The PSC will provide recommendations to the COG Developmental Therapeutics Chair and the Group Chair for the study, or to continue the study unchanged. Study Progress reports for institutional review boards will be prepared using the public data monitoring report as posted on the

COG Web site.

14.2.2 Monitoring by the Study Chair and Developmental Therapeutics Leadership

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the Developmental Therapeutics Chair, Vice Chair and Statistician on a weekly conference call.

REFERENCES

1. Dickson MA: Molecular Pathways: CDK4 Inhibitors for Cancer Therapy. Clin Cancer Res, 2014
2. Raetz EA, Bhatla T: Where do we stand in the treatment of relapsed acute lymphoblastic leukemia? Hematology Am Soc Hematol Educ Program 2012:129-36, 2012
3. Ko RH, Ji L, Barnette P, et al: Outcome of patients treated for relapsed or refractory acute lymphoblastic leukemia: a Therapeutic Advances in Childhood Leukemia Consortium study. J Clin Oncol 28:648-54, 2010
4. Sun W, Malvar J, Sposto R, et al: Re-Induction Outcome for Pediatric Patients with Relapsed or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia: A Retrospective Cohort Study of the Therapeutic Advances in Childhood Leukemia Consortium. Blood 126:3760-3760, 2015
5. Sicinska E, Aifantis I, Le Cam L, et al: Requirement for cyclin D3 in lymphocyte development and T cell leukemias. Cancer Cell 4:451-61, 2003
6. Sawai CM, Freund J, Oh P, et al: Therapeutic targeting of the cyclin D3:CDK4/6 complex in T cell leukemia. Cancer Cell 22:452-65, 2012
7. Dhillon S: Palbociclib: first global approval. Drugs 75:543-51, 2015
8. Finn RS, Crown JP, Lang I, et al: The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol 16:25-35, 2015
9. Finn RS, Martin M, Rugo HS, et al: Palbociclib and Letrozole in Advanced Breast Cancer. N Engl J Med 375:1925-1936, 2016
10. Cristofanilli M, Turner NC, Bondarenko I, et al: Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 17:425-39, 2016
11. Clark AS, O'Dwyer PJ, Heitjan D, et al: A phase I trial of palbociclib and paclitaxel in metastatic breast cancer. Journal of Clinical Oncology 32:527-527, 2014
12. Gururangan S, Becher O, Leary S, et al: EPT-19 Phase I trial of palbociclib, a CDK4/6 inhibitor in children with retinoblastoma protein(RB1) + recurrent central nervous system (CNS) tumors (PBTC 042). Neuro-Oncology 18:iii28-iii28, 2016
13. Raetz EA, Borowitz MJ, Devidas M, et al: Reinduction platform for children with first marrow relapse of acute lymphoblastic Leukemia: A Children's Oncology Group Study[corrected]. J Clin Oncol 26:3971-8, 2008
14. Messinger Y, Gaynon P, Raetz E, et al: Phase I study of bortezomib combined with chemotherapy in children with relapsed childhood acute lymphoblastic leukemia (ALL): a report from the therapeutic advances in childhood leukemia (TACL) consortium. Pediatr Blood Cancer 55:254-9, 2010
15. Raetz EA, Cairo MS, Borowitz MJ, et al: Chemoimmunotherapy reinduction with epratuzumab in children with acute lymphoblastic leukemia in marrow relapse: a Children's Oncology Group Pilot Study. J Clin Oncol 26:3756-62, 2008
16. Yang C, Boyson CA, Di Liberto M, et al: CDK4/6 Inhibitor PD 0332991 Sensitizes Acute Myeloid Leukemia to Cytarabine-Mediated Cytotoxicity. Cancer Res 75:1838-45, 2015
17. Skolnik JM, Barrett JS, Jayaraman B, et al: Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol 26:190-5, 2008
18. Stock W, Douer D, DeAngelo DJ, et al: Prevention and management of asparaginase/pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leukemia & Lymphoma 52:2237-2253, 2011
19. Langer T, Martus P, Ottensmeier H, et al: CNS late-effects after ALL therapy in childhood. Part III: neuropsychological performance in long-term survivors of childhood ALL: impairments of concentration, attention, and memory. Med Pediatr Oncol 38(5):320-8, 2002

20. Mulhern RK, Palmer SL: Neurocognitive late effects in pediatric cancer. Curr Probl Cancer 27(4):177-97, 2003
21. Harila-Saari AH, Paakko EL, Vainionpaa LK, et al: A longitudinal magnetic resonance imaging study of the brain in survivors in childhood acute lymphoblastic leukemia. Cancer 83(12):2608-17, 1998
22. Winick NJ, Bowman WP, Kamen BA, et al: Unexpected acute neurologic toxicity in the treatment of children with acute lymphoblastic leukemia. J Natl Cancer Inst. 84(4):252-6, 1992
23. Van den Berg HW, Desai ZR, Wilson R, et al: The pharmacokinetics of vincristine in man: reduced drug clearance associated with raised serum alkaline phosphatase and dose-limited elimination. Cancer Chemother Pharmacol 8(2):215-9, 1982
24. Relling MV, Pui CH, Sandlund JT, et al: Adverse effect of anticonvulsants on efficacy of chemotherapy for acute lymphoblastic leukaemia. Lancet 356:285-90, 2000
25. Hughes WT, Armstrong D, Bodey GP, et al: 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. Clin Infect Dis 34:730-51, 2002
26. Lawson SE, Harrison G, Richards S, et al: The UK experience in treating relapsed childhood acute lymphoblastic leukaemia: a report on the medical research council UKALLR1 study. Br J Haematol 108:531-43, 2000
27. Thomson B, Park JR, Felgenhauer J, et al: Toxicity and efficacy of intensive chemotherapy for children with acute lymphoblastic leukemia (ALL) after first bone marrow or extramedullary relapse. Pediatr Blood Cancer 43:571-9, 2004
28. Bucaneve G, Micozzi A, Menichetti F, et al: Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. N Engl J Med 353:977-87, 2005
29. Gafter-Gvili A, Fraser A, Paul M, et al: Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. Ann Intern Med 142:979-95, 2005
30. Dvorak CC, Fisher BT, Sung L, et al: Antifungal prophylaxis in pediatric hematology/oncology: new choices & new data. Pediatr Blood Cancer 59:21-6
31. Oren I, Haddad N, Finkelstein R, et al: Invasive pulmonary aspergillosis in neutropenic patients during hospital construction: before and after chemoprophylaxis and institution of HEPA filters. Am J Hematol 66:257-62, 2001
32. Ariffin H, Omar KZ, Ang EL, et al: Severe vincristine neurotoxicity with concomitant use of itraconazole. J Paediatr Child Health 39:638-9, 2003
33. Bermudez M, Fuster JL, Llinares E, et al: Itraconazole-related increased vincristine neurotoxicity: case report and review of literature. J Pediatr Hematol Oncol 27:389-92, 2005
34. Sandlund JT, Guillerman RP, Perkins SL, et al: International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol 33:2106-11, 2015
35. Sandlund JT, Guillerman RP, Perkins SL, et al: International Pediatric Non-Hodgkin Lymphoma Response Criteria. Journal of Clinical Oncology 33:2106-2111, 2015
36. Cheson BD, Fisher RI, Barrington SF, et al: Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 32:3059-68, 2014
37. Zhang J, Ding L, Holmfeldt L, et al: The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature 481:157-63, 2012
38. Mullighan CG: Molecular genetics of B-precursor acute lymphoblastic leukemia. J Clin Invest 122:3407-15, 2012
39. Chung CT, Santos Gda C, Hwang DM, et al: FISH assay development for the detection of p16/CDKN2A deletion in malignant pleural mesothelioma. J Clin Pathol 63:630-4, 2010

APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX II: ASSESSING THE BIOLOGICAL ACTIVITY OF PALBOCICLIB: CORRELATIVE BIOLOGY STUDY SUMMARY

Bone marrow and/or peripheral blood samples will be collected at three time points:

- Pre-study (marrow)
- Day 4 (peripheral blood)- **Peripheral blood samples should be collected PRIOR to administration of Day 4 chemotherapy, if absolute blast count is > 1000/mm3**
- Day 32 $\pm$ 2 days (marrow, if a patient has persistent disease)

The pre-study and Day 32 time points coincide with times when bone marrow aspirates are performed as a part of routine clinical care so that extra procedures will not be done exclusively for research tests. Peripheral blood also can be substituted or used to augment bone marrow samples if the absolute blast count is >1000/µL: 10 mL per samples (<10 kg) or 15 mL (≥10 kg).

To substitute peripheral blood, patients must have an initial absolute blast count of at least 1000 lymphoblasts/µL. To calculate the absolute blast percentage, multiply the total WBC by the % peripheral blasts:

(WBC)(% blast)(1000) = absolute blast count/µL

As an example, if the patient has a WBC of 10 and 50% blasts, the absolute blast count is:
(10)(.5)(1000) = 5000/µL

Lymphoblasts will be isolated from bone marrow or blood within 4 hours of collection using Ficoll-Paque Plus (Amersham Biosciences, Brown Deer, WI) at participating centers to avoid potential artifacts associated with prolonged sample storage or shipping. Blasts will then be frozen and batch shipped on dry ice to the Carroll/Aifantis labs for DNA and protein purification. Participating sites will be required to purify the blast population from bone marrow by density gradient centrifugation using Ficoll-Paque Plus and freeze samples prior to batch shipment of the samples to our laboratory for analysis (see protocol for Ficoll purification below in section 2.0).

PBMC Isolation by Ficoll

Marrow blasts will be purified within 4 hours of collection at local centers using the protocol described below.

Required materials:

- 5 – 15 mL fresh marrow or blood sample
- Ficoll-Hypaque solution
- PBS
- 50 mL falcon tubes
- 1.8 mL Cryotubes
- DMSO
- Fetal Bovine Serum (FBS)
- 1 mL individually wrapped sterile transfer pipettes

Instructions:

All steps are carried out using a sterile technique, at room temperature – unless noted otherwise.

1) Fresh marrow or blood samples should be stored at 4°C prior to isolation.
2) Prepare all required materials and label falcon tubes.
3) Fill a tube with a volume of Ficoll-Hypaque that is equal to the volume of the marrow or blood sample (Ficoll:Marrow or Blood ratio is 1:1).
4) In a second tube, mix marrow or blood sample with an equal volume of PBS (1:1)
5) Slowly overlay diluted marrow or blood sample from Step 4 onto Ficoll-Hypaque from Step 3, avoiding the mixing of marrow or blood with Ficoll:
    - Suggestion: tilt the falcon tube with Ficoll at a 45° angle and add the diluted sample to the side of the tube using 10 mL serological pipette. You should see a clear interface.
6) Centrifuge 30 minutes at 400x*g* with **BRAKE OFF.**
7) Gently aspirate and discard the top layer of plasma. The layer below is the PBMC layer (buffy coat). Remove it using a 1 mL individually wrapped sterile transfer pipette and transfer to a new 50 mL tube leaving behind the clear Ficoll layer and bottom red blood layer.
8) Bring volume to 45 mL with PBS and mix cells by gently inverting several times.
9) Centrifuge 20 minutes at 200x*g* with the **BRAKE ON.**
10) Without disturbing the pellet, remove and discard the supernatant.
11) Bring volume to 10 mL with PBS and mix cells to obtain a uniform suspension.
    - Note: Pelleted cells will start dying if not resuspended immediately.
12) Count the cells and determine their viability. Keep the samples on ice during the count.
13) Centrifuge for 10 minutes at 400x*g* with the **BRAKE ON**.
14) Without disturbing the pellet, remove and discard the supernatant.
15) Resuspend cell pellet at 10 million cells per mL in 95% FBS/5% DMSO. Aliquot 10 million cells (1 mL) per cryo-tube and slow freeze at -80°C.

Cryopreserved marrow samples will be shipped on dry ice:

Ship the sample by Federal Express Priority Overnight delivery to:

Carroll/Aifantis Labs
Laura and Isaac Perlmutter Cancer Center at NYU Langone
522 First Avenue, Smilow Building 12 Floor, Room 1211
Tel: 212.263.2327 • Fax: 212.263.9190
New York, NY 10016

FedEx account # 320569834

- Email or call Nikki Evensen, PhD (Nikki.Evensen@nyulangone.org; 212-263-2327 or 516-765-6832) when the sample is being shipped.
- Do not ship samples for delivery on a weekend or holiday.

APPENDIX III: CYP3A4 SUBSTRATES, INDUCERS AND INHIBITORS

This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
acalabrutinib[5] alfentanil[4,5] amiodarone[4] aprepitant/fosaprepitant atorvastatin axitinib bortezomib bosutinib[5] budesonide[5] buspirone[5] cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib[5] conivaptan[5] copanlisib crizotinib cyclosporine[4] dabrafenib dapsone darifenacin[5] darunavir[5] dasatinib[5] dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] eletriptan[5] eplerenone[5] ergotamine[4] erlotinib estrogens etoposide everolimus[5] fentanyl[4] gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole ivacaftor	atazanavir boceprevir clarithromycin cobicistat darunavir delavirdine grapefruit[3] grapefruit juice[3] idelalisib indinavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	aprepitant conivaptan crizotinib diltiazem dronedarone erythromycin fluconazole fosamprenavir grapefruit[3] grapefruit juice[3] imatinib isavuconazole mifepristone nilotinib verapamil	barbiturates carbamazepine enzalutamide fosphenytoin phenobarbital phenytoin primidone rifampin St. John's wort	bosentan dabrafenib efavirenz etravirine modafinil nafcillin rifapentin

ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil nefazodone nilotinib olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib quetiapine[5] quinidine[4] regorafenib romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] tamoxifen telaprevir temsirolimus teniposide tetracycline tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 7.5 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors)

APPENDIX IV: ADDITIONAL INFORMATION FOR CORRELATIVE BIOLOGY STUDIES: DETERMINING THE BIOLOGICAL ACTIVITY OF PALBOCICLIB

Overview: Assays will be performed prior to and following palbociclib administration as summarized in Table 1 to determine the efficiency of cell cycle inhibition.

Table 1. Correlative Biology Studies

	Pre-study	Day 4	Day 32*
Targeted DNA sequencing to identify somatic mutations in both T-ALL and B-ALL samples	X		
CDKN2A deletions (using FISH)	X		
RB1 expression and RB1 phosphorylation status (Immunoblotting)	X	X**	X
$p27^{Kip1}$ expression (Immunoblotting)	X	X**	X
Cyclin D3 and CDK4/6 protein expression (Immunoblotting)	X	X**	X
Cell cycle analysis (response to Palbociclib)	X	X**	X
Peripheral blood absolute blast count	X	X**	

* End of therapy analyses in patients with persistent disease. End of therapy analyses must be obtained on Day 32 $\pm$ 2 days.
** Submit peripheral blood samples if absolute blast count is >1000/mm^3

Experimental Design:
Bone marrow and peripheral blood samples (5 mL) will be collected at the time points summarized in Table 1. The pre-study and Day 32 time points coincide with times when bone marrow aspirates are performed as a part of routine clinical care so that extra procedures will not be done exclusively for research tests. Peripheral blood also can be substituted or used to augment bone marrow samples if the absolute blast count is >1000/mm^3: 10 mL per samples (<10 kg) or 15 mL ($\geq$10 kg).

Lymphoblasts will be isolated from bone marrow within 4 hours of collection using Ficoll-Paque Plus (Amersham Biosciences, Brown Deer, WI) at participating COG Phase 1 centers to avoid potential artifacts associated with prolonged sample storage or shipping. Blasts will then be frozen and batch shipped on dry ice to the Carroll/Aifantis labs for DNA and protein purification. One third of the cells will be used for DNA sequencing and two thirds of cells per sample will be used for protein expression. Freshly harvested blasts will be collected and fixed prior to shipment for the proposed cell cycle analyses (see Appendix II for details regarding samples processing).

1) **Western Blotting (immunoblotting).** Expression of RB1, phospho-RB1, Cyclin D3, CDK4, CDK6 and $p27^{Kip1}$ will be performed using Western Blotting (immunoblotting).T-ALL and B-ALL blast cells will be resuspended in lysis buffer (20mM Tris, pH8; 150mM NaCl; 0.1% SDS; 0.5% Na-Deoxycholate) containing protease inhibitors (Roche, Basel, Switzerland) and sonicated for 30 sec at 4 watts, incubated on ice for 10 minutes and centrifuged at 14,000rpm for 10 min at 4ºC. The resulting supernatant will be collected and protein concentration will be determined using the DC Protein assay (Bio-Rad). 25 µg of protein will be fractionated by 15% SDS-PAGE and transferred to Immobilon-P membrane (Millipore, Billerica, MA). Immunoblotting will be performed with the following primary antibodies and dilutions: anti-RB1 (BD Pharmingen, cat #554162), anti-Cyclin D3 (Santa Cruz Biotechnology, sc-6283), anti-p27KIP1/CDKN1B (Santa Cruz Biotechnology, sc-393305), anti-CDK4 (Santa Cruz Biotechnology, sc-23896) and anti-CDK6 (Santa Cruz Biotechnology, sc-7961) and anti-actin, 1:4000 (Abcam, #8227), as a loading control. HRP-conjugated anti-rabbit IgG, 1:10,000 and anti- mouse IgG, 1:10,000 (NA934V, NA931V, GE Healthcare,) will be used as the secondary antibody. Reactive proteins will be visualized using ECL Plus (Amersham Life Sciences).

2) **Targeted DNA sequencing to identify somatic mutations.** ALL samples will be sequenced using a custom mutational gene panel that includes the most frequently mutated genes in B-ALL and T-ALL.[37,38] These include *RB1*, *PAX5, IKZF1, CRLF2, CREBBP*, *NOTCH1*, *FBXW7*, *NRAS*, *KRAS*, *IL7Ra*, *JAK1*, *JAK2, JAK3*, *TET2*, *RUNX1*, *EP300*, *IKZF1-3*, *EZH2*, *EED*, *SUZ12*, *GATA3*, *RUNX1* and *PHF6*. Samples will pre- prepped as previously described, DNA libraries will be generated and sequenced using the Ion Torrent platform that enables us to sequence reliably small numbers of cells. This technology is available at NYU Langone Medical Center.

3) **Dual-Colour FISH for detection of *CDKN2A* deletions.** *CDKN2A* deletions will be detected using fluorescence in situ hybridization (FISH) analysis as it is currently done in solid tumors. Dual-color FISH will be performed using a commercially available Spectrum Orange-labelled locus specific p16 (9p21) probe and Spectrum Green-labelled chromosome 9 centromeric probe [Vysis LSI p16 (9p21) SpectrumOrange/CEP9 SpectrumGreen Probe; Abbott Laboratories, Des Plaines, Illinois, USA] as previously described.[39] ALL cells will be cytospun on slides for FISH analysis. After washing in 2X standard saline citrate for 5 min, sections will be digested with pepsin (37 500 U in 0.1 N HCl) (Sigma, St Louis, Missouri, USA) at 37°C for 10–25 min. Slides will be co-denatured with the probes, allowed to hybridize and washed according to the manufacturer's protocol. Slides will be analyzed, blinded from the clinical data, using a Zeiss microscope (Axioplan 2, Jena, Germany) equipped with the appropriate filters. A minimum of 100 non-overlapped intact (uniform DAPI staining with intact nuclear contours) interphase nuclei of consecutive cells in at least two different areas of the section will be scored.

4) **Cell Cycle Analysis**. We will use standard flow cytometry protocols to combine surface staining for T-ALL markers (CD1a, CD3, CD4, CD8) and intracellular staining for the cell cycle (and apoptosis) markers Ki67 and DAPI. For intracellular Ki67 and DAPI staining in T-ALL cells, following staining of surface antigens, bone marrow/peripheral T-ALL cells will be fixed with 4% paraformaldehyde and permeabilized with 0.1% saponin prior to addition of anti-Ki67 (BD Biosciences) and 2 µg/mL DAPI. A similar procedure will be followed for B-ALL.

As an early measure of response to single agent palbociclib, the absolute peripheral blast count will be measured at baseline and after 72 hours of drug exposure.

For pre- and post-treatment measurements of absolute peripheral blast count protein expression, pairwise comparisons will be made using Fisher's exact test and paired t-test or an equivalent nonparametric tests as appropriate. Baseline expression of cell cycle proteins and the presence of somatic mutations and *CDKN2A* deletions will be correlated with treatment response. These analyses will be descriptive and exploratory in nature.

APPENDIX V-A: Palbociclib Capsule Dosing Nomogram

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle.

Palbociclib is available as 75 mg and 100 mg capsules. Patients receiving doses ≥ 75 mg/day may take either the capsule or liquid formulation. Patients receiving < 75 mg/day of palbociclib must receive the liquid formulation (See Appendix V-B for dosing preparation of palbociclib liquid formulation.)

Palbociclib Dose Assignment: 50 mg/m^2
(Dose Level 1)

BSA (m^2)	Total Daily Dose (mg/day)	Dose Reduction for Toxicity (mg/day)
< 1.37	Use liquid formulation (see Appendix V-B)	Reduce dose by 30%. Use liquid formulation (see Appendix V-B)
1.37-1.74	75	Reduce dose by 30%. Use liquid formulation (see Appendix V-B)
≥ 1.75	100	75

Palbociclib Dose Assignment: 35 mg/m^2
(Dose Level -1)

BSA (m^2)	Total Daily Dose (mg/day)	Dose Reduction for Toxicity (mg/day)
<1.95	Use liquid formulation (see Appendix V-B)	off protocol therapy
≥ 1.95	75	off protocol therapy

APPENDIX V-B: PALBOCICLIB DOSING PREPARATION (LIQUID FORMULATION)

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of the cycle.

Patients receiving doses ≥ 75 mg/day may take either the capsule or liquid formulation. (See Appendix V-A for dosing nomogram for palbociclib capsule formulation).

Patients receiving < 75 mg/day of palbociclib must receive the liquid formulation.

Patients receiving the liquid formulation who experience dose-limiting toxicity should have their dose reduced by 30%, so that patients receive 70% of the original prescribed dose.

The concentration of palbociclib liquid formulation is 25 mg/mL.

Calculated doses < 18.75 mg should be prepared in oral syringes ≤ 1 mL with dosing volumes of palbociclib liquid formulation rounded to the nearest 0.1 mL (2.5 mg). Calculated doses > 18.75 mg should be prepared in 5 mL oral syringes with dosing volumes of palbociclib liquid formulation rounded to the nearest 0.2 mL (5 mg). It is recommended that oral dosing syringes should be only filled up to 75% of the maximum volume.

To calculate dosing volumes for each patient based on BSA, the following formula should be used:

$$\textit{Dosing Volume (mL)} = \frac{\textit{Prescribed Dose (mg/m}^2\textit{) x BSA (m}^2\textit{)}}{\textit{25 (mg/mL)}}$$

Round dosing volumes according to the above rules.
***Examples**:*

- *Patient BSA 0.33 m^2, Dose Level 1 (50 mg/m^2) → Calculated Dose = 16.5 mg PO daily*
  Calculated Volume (mL) = (50 mg/m^2 x 0.33 m^2) / (25 mg/mL) = 0.66 mL
  Final Dosing Volume (mL) = 0.7 mL (rounded to nearest 0.1 mL for doses ≤ 18.75 mg)
  Final Dose to be administered = 0.7 mL x 25 mg/mL = 17.5 mg

- *Patient BSA 1.66 m^2, Dose Level -1 (35 mg/m^2) → Calculated Dose = 58.1 mg PO daily*
  Calculated Volume (mL) = (35 mg/m^2 x 1.66 m^2) / (25 mg/mL) =2.324 mL
  Final Dosing Volume (mL) = 2.4 mL (rounded to the nearest 0.2 mL for dose > 18.75 mg)
  Final Dose to be administered = 2.4 mL x 25 mg/mL = 60 mg

APPENDIX VI: THERAPY DELIVERY MAP (TDM) (PATIENTS WITH ALL)

Therapy Delivery Map – Cycle 1

This Therapy Delivery Map (TDM) relates to Cycle 1. Cycle 1 lasts 32 days. This TDM can be used for all dose levels of palbociclib. Please record the dose level below. This TDM is intended to serve as a tool to assist in scheduling the required observations for the study; the schedule indicated in the chart below should be considered an example. The actual schedule must comply with the timing of required observations per Section 8 of the protocol. This form is to be completed and uploaded into RAVE at the end of Cycle 1.

_____
Accession #

_____
Patient COG ID number

_____
Institution

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Palbociclib IND #141416	PO (or NG-Tube)	Dose Level -1: 35 mg/m^2 Dose Level 1: 50 mg/m^2	**Once daily on Days 1-21**	Dose Level -1: MAX dose 75 mg Dose Level 1: MAX dose 100 mg
Intrathecal Cytarabine (IT ARAC): All patients on Day 1 (before CNS status is known)	IT	**Age (yrs)** **Dose** 1-1.99 30 mg 2-2.99 50 mg ≥3 70 mg	1@	**Note age-based dosing** @Patients with known CNS3 disease at the time of study enrollment may receive triple intrathecal chemotherapy on Day 1 **as a substitute for** intrathecal cytarabine, at the discretion of the treating investigator. Patients are NOT to receive both intrathecal triples and intrathecal cytarabine on Day 1, regardless of CNS status.
Intrathecal Methotrexate (IT MTX): CNS1 and 2	IT	**Age (yrs)** **Dose** 1-1.99 8 mg 2-2.99 10 mg 3-8.99 12 mg ≥9 15 mg	18,32	**Note age-based dosing**
Intrathecal Triple Therapy (ITT): Methotrexate (MTX)/ Hydrocortisone (HC)/Cytarabine (ARAC) if CNS3	IT	**Age (yrs)** **Dose** 1-1.99 MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 MTX: 15 mg HC: 15 mg ARAC: 30 mg	1@, 4, 11, 18, 25	**Note age-based dosing** @Patients with known CNS3 disease at the time of study enrollment may receive triple intrathecal chemotherapy on Day 1 **as a substitute for** intrathecal cytarabine, at the discretion of the treating investigator. Patients are NOT to receive both intrathecal triples and intrathecal cytarabine on Day 1, regardless of CNS status.
DOXOrubicin (DOXO)	slow IV push or infusion over 1-15 min	60 mg/m²/dose	4	Administer through the tubing of a rapidly infusing D5W or 0.9% NaCL solution
PrednISO(LO)NE (PRED)*	PO	40 mg/m²/day divided BID or TID	4-31	
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose (MAX dose 2 mg)	4, 11, 18, 25	+ + Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**

Cycle 1

Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	5, 18	Administer IV infusion through the tubing of a rapidly infusing D5W or 0.9% NaCL solution. See section 5.1 for special precautions with pegaspargase administration.

* IV methylprednisolone may be given at 80 % of the oral predniSONE or predniSOLONE dose.

NOTE: All patients should receive trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of TMP 2.5 mg/kg/dose (maximum dose 160 mg/dose) by mouth twice daily on 2 or 3 sequential days per week.

Assigned Dose Level _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**Palbociclib** _____ mg	**IT ARAC** _____ mg	**IT MTX (CNS 1 and 2)** _____ mg	**Intrathecal Triple Therapy (CNS3):** MTX/ HC/ ARAC mg/ mg/ mg	**DOXO** _____ mg	**PRED** ____ mg BID or TID	**VCR** _____ mg	**PEG-ASP** _____ IU	**Studies to be obtained**
		1	_____ mg	_____ mg		_____ mg					
		2	_____ mg								i
		3	_____ mg								
		4	_____ mg			MTX/ HC/ ARAC __mg/___ mg/___mg	_____ mg	__ mg __ mg __ mg	_____ mg		a, b, f, h, j, p, q,n
		5	mg							IU	
		6	_____ mg								
		7	_____ mg								
		8	mg								f
		9	mg								
		10	_____ mg								
		11	_____ mg			MTX/ HC/ ARAC __mg/___ mg/___mg			_____ mg		a, b, f, h, i, j,n
		12	_____ mg								i
		13	_____ mg								
		14	mg								
		15	_____ mg								f
		16	_____ mg								
		17	mg								
		18	_____ mg		_____ mg	MTX/ HC/ ARAC __mg/___ mg/___mg			_____ mg	_____ IU	a, b, f, h, j,n
		19	_____ mg								
		20	_____ mg								
		21	_____ mg								
		22									f
		23									
		24									
		25				MTX/ HC/ ARAC __mg/___ mg/___mg			_____ mg		a, b, f, h, j,n
		26									
		27									
		28									

Cycle 1

		29									f
		30									
		31									
		32^			_____ mg						a, b, c, d, f, h, j, l, m, o, n

^ Abnormal laboratory tests must be re-checked by Day 42 since some toxicities require resolutions to ≤ Grade 2 or baseline by Day 42 (see DLT criteria).

See Section 6.0 for Dose Modifications for Adverse Events and Section 7.0 and the COG Member website for Supportive Care Guidelines

Cycle 1

Required Observations in Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. For information related to prestudy observations please refer to Section 8.0

a. History
b. Physical exam with vital signs
c. Height, weight, BSA
d. Performance status
e. Pregnancy test: Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable methods of birth control. All women of childbearing potential must have a pregnancy test done every cycle prior to initiation of a new cycle.
f. CBC, differential, platelets: Twice weekly during Cycle 1. If patients have Grade 4 neutropenia or thrombocytopenia, CBCs should be checked at least every other day until recovery to Grade 3 or until the criteria for dose limiting toxicity are met.
g. Urinalysis
h. Electrolytes including Ca^{++}
i. Pharmacokinetics (required): See Section 8.2 for details.
j. Creatinine, ALT, bilirubin
k. Albumin
l. ECHO or gated radionuclide study
m. 12-lead EKG
n. Patient Diary
o. Bone Marrow Aspirate for morphology and MRD. Must be performed on Day 32 $\pm$ 2 days.
p. Absolute Blast Count; Absolute blast count should be performed on Day 4 prior to administration of chemotherapy.
q. Correlative Biology Studies See Section 8.3 for details.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

Cycle 1

APPENDIX VII: THERAPY DELIVERY MAP (TDM) (PATIENTS WITH LL)

Therapy Delivery Map – Cycle 1

This Therapy Delivery Map (TDM) relates to Cycle 1. Cycle 1 lasts 32 days. This TDM can be used for all dose levels of palbociclib. Please record the dose level below. This TDM is intended to serve as a tool to assist in scheduling the required observations for the study; the schedule indicated in the chart below should be considered an example. The actual schedule must comply with the timing of required observations per Section 8 of the protocol. This form is to be completed and uploaded into RAVE at the end of Cycle 1.

_____
Accession #

_____
Patient COG ID number

_____
Institution

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Palbociclib IND #141416	PO (or NG-tube)	Dose Level -1: 35 mg/m^2 Dose Level 1: 50 mg/m^2	**Once daily on Days 1-21**	Dose Level -1: MAX dose 75 mg Dose Level 1: MAX dose 100 mg
Intrathecal Cytarabine (IT ARAC): All patients on Day 1 (before CNS status is known)	IT	**Age (yrs)** — **Dose** 1-1.99 — 30 mg 2-2.99 — 50 mg ≥3 — 70 mg	1@	**Note age-based dosing** @Patients with known CNS3 disease at the time of study enrollment may receive triple intrathecal chemotherapy on Day 1 **as a substitute for** intrathecal cytarabine, at the discretion of the treating investigator. Patients are NOT to receive both intrathecal triples and intrathecal cytarabine on Day 1, regardless of CNS status.
Intrathecal Methotrexate (IT MTX): CNS1 and 2	IT	**Age (yrs)** — **Dose** 1-1.99 — 8 mg 2-2.99 — 10 mg 3-8.99 — 12 mg ≥9 — 15 mg	18,32	**Note age-based dosing**
Intrathecal Triple Therapy (ITT): Methotrexate (MTX)/ Hydrocortisone (HC)/Cytarabine (ARAC) if CNS3	IT	**Age (yrs)** — **Dose** 1-1.99 — MTX:8mg, HC: 8mg, ARAC: 16mg 2-2.99 — MTX: 10mg HC: 10 mg ARAC: 20 mg 3-8.99 — MTX: 12 mg HC: 12 mg ARAC: 24 mg ≥9 — MTX: 15 mg HC: 15 mg ARAC: 30 mg	1@, 4, 11, 18, 25	**Note age-based dosing** @Patients with known CNS3 disease at the time of study enrollment may receive triple intrathecal chemotherapy on Day 1 **as a substitute for** intrathecal cytarabine, at the discretion of the treating investigator. Patients are NOT to receive both intrathecal triples and intrathecal cytarabine on Day 1, regardless of CNS status.
DOXOrubicin (DOXO)	slow IV push or infusion over 1-15 min	60 mg/m²/dose	4	Administer through the tubing of a rapidly infusing D5W or 0.9% NaCL solution
PrednISO(LO)NE (PRED)*	PO	40 mg/m²/day divided BID or TID	4-31	
VinCRIStine (VCR)	IV push over 1 min+	1.5 mg/m²/dose (MAX dose 2 mg)	4, 11, 18, 25	+ + Or infusion via minibag as per institutional policy **Maximum dose: 2 mg**

Cycle 1

Pegaspargase (PEG-ASP)	IV over 1-2 hours	2500 International units/m²/dose	5, 18	Administer IV infusion through the tubing of a rapidly infusing D5W or 0.9% NaCL solution. See section 5.1 for special precautions with pegaspargase administration.

* IV methylprednisolone may be given at 80 % of the oral predniSONE or predniSOLONE dose.

NOTE: All patients should receive trimethoprim/sulfamethoxazole (TMP/SMX) at a dose of TMP 2.5 mg/kg/dose (maximum dose 160 mg/dose) by mouth twice daily on 2 or 3 sequential days week.**Assigned Dose Level _____ Ht _____cm Wt _____kg BSA _____m²**

Date Due	Date Given	Day	**Palbociclib** _____ mg	**IT ARAC** _____ mg	**IT MTX (CNS 1 and 2)** _____ mg	**Intrathecal Triple Therapy (CNS3):** MTX/ HC/ ARAC mg/___mg/___mg	**DOXO** _____ mg	**PRED** ____ mg BID or TID	**VCR** _____ mg	**PEG-ASP** _____ IU	**Studies to be obtained**
		1	mg	mg							
		2	_____ mg								i
		3	_____ mg								
		4	_____ mg			MTX/ HC/ ARAC mg/___mg/___mg	_____ mg	__ mg __ mg __ mg	_____ mg		a, b, f, h, j,n
		5	_____ mg							_____ IU	
		6	_____ mg								
		7	_____ mg								
		8	_____ mg								f
		9	_____ mg								
		10	mg								
		11	_____ mg			MTX/ HC/ ARAC mg/ mg/ mg			_____ mg		a, b, f, h, i, j,n
		12	_____ mg								i
		13	_____ mg								
		14	_____ mg								
		15	_____ mg								f
		16	_____ mg								
		17	_____ mg								
		18	_____ mg		_____ mg	MTX/ HC/ ARAC mg/___mg/___mg			_____ mg	_____ IU	a, b, f, h, j,n
		19	_____ mg								
		20	mg								
		21	_____ mg								
		22									f
		23									
		24									
		25				MTX/ HC/ ARAC mg/ mg/ mg			_____ mg		a, b, f, h, j,n
		26									
		27									
		28									
		29									f

Cycle 1

		30									
		31									
		32^			_____ mg						a, b, c, d, f, h, j, l, m, o, p, q, r, s,n

^ Abnormal laboratory tests must be re-checked by Day 42 since some toxicities require resolutions to ≤ Grade 2 or baseline by Day 42 (see DLT criteria).

See Section 6.0 for Dose Modifications for Adverse Events and Section 7.0 and the COG Member website for Supportive Care Guidelines.

Cycle 1

Required Observations in Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below. For information related to prestudy observations please refer to Section 8.0.

a. History
b. Physical exam with vital signs
c. Height, weight, BSA
d. Performance status
e. Pregnancy test: Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable methods of birth control.
f. CBC, differential, platelets: Twice weekly during Cycle 1. If patients have Grade 4 neutropenia or thrombocytopenia, CBCs should be checked at least every other day until recovery to Grade 3.
g. Urinalysis
h. Electrolytes including Ca^{++}
i. Pharmacokinetics (required): See Section 8.2 for details.
j. Creatinine, ALT, bilirubin
k. Albumin
l. ECHO or gated radionuclide study
m. 12-lead EKG
n. Patient Diary
o. Chest and neck CT. Obtain chest CT for all LL patients at baseline and on Day 32. The baseline chest CT may be delayed until the patient is stable. A PET-CT can be used instead of a CT.
p. Abdomen/Pelvis CT or MRI. If scans are negative at baseline, not further imaging is needed on Day 32. A PET-CT can be used instead of a CT.
q. PET scan (recommended)
r. Bone scan. Bone scan only if patient has symptoms; perform at Day 32 only if patient has disease at baseline. May substitute a PET scan for a bone scan, however, a bone scan is preferred for bone symptoms.
s. Bilateral bone marrow aspirates and biopsies for morphology. LL should have bone marrow aspirates and biopsies on Day 32 $\pm$ 2 days if $\geq$ 5% marrow involvement was present at diagnosis

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

Cycle 1

APPENDIX VIII: PHARMACOKINETIC STUDY FORM

COG Pt ID # _____ Cycle 1, Day 1 Date: _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg Body Surface Area: _____m^2

Palbociclib Dose Level: _____mg/m^2 Palbociclib Total Daily Dose: _____mg

Palbociclib Route of Administration (oral solution/tablet): _____

Blood samples (2-3 mL) will be collected in K2 EDTA (lavender-top) tubes

- **Day 1 of Cycle 1:** pre-dose, and at 1, 2, 4, 8 and 24 hours post-dose of palbociclib.
- **Day 11 of Cycle 1**: pre-dose, and at 1, 2 and 4, 8 and 24 hours post-dose of palbociclib.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Day 1**	Prior to palbociclib dose on Day 1	___/___/___	|__|__| : |__|__|
Palbociclib Dose on Day 1 ____mg Date:___/___/___ Time: |__|__| : |__|__|				
2	**Day 1**	1 hr after palbociclib dose	___/___/___	|__|__| : |__|__|
3	**Day 1**	2 hr after palbociclib dose	___/___/___	|__|__| : |__|__|
4	**Day 1**	4 hr after palbociclib dose	___/___/___	|__|__| : |__|__|
5	**Day 1**	8 hr after palbociclib dose	___/___/___	|__|__| : |__|__|
6	**Day 2**	24 (±2) hrs after Day 1 palbociclib dose (prior to day 2 dose)	___/___/___	|__|__| : |__|__|
Palbociclib Dose on Day 2 ____mg Date:___/___/___ Time: |__|__| : |__|__|				
Vincristine Dose on Day 11 _____mg Date:___/___/___ Time: |__|__| : |__|__|				
7	**Day 11**	Prior to palbociclib dose on Day 11	___/___/___	|__|__| : |__|__|
Palbociclib Dose on Day 11 ____mg Date:___/___/___ Time: |__|__| : |__|__|				
8	**Day 11**	1 hr after palbociclib dose	___/___/___	|__|__| : |__|__|
9	**Day 11**	2 hr after palbociclib dose	___/___/___	|__|__| : |__|__|
10	**Day 11**	4 hr after palbociclib dose	___/___/___	|__|__| : |__|__|
11	**Day 11**	8 hr after palbociclib dose	___/___/___	|__|__| : |__|__|
12	**Day 12**	24 (±2) hrs after Day 11 palbociclib dose (prior to day 12 dose)	___/___/___	|__|__| : |__|__|
Palbociclib Dose on Day 12 ____mg Date:___/___/___ Time: |__|__| : |__|__|				

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.2.6. See Section 8.2 for detailed guidelines for packaging and shipping PK samples.

Signature: _____ Date:_____
(site personnel responsible for collection of samples)

APPENDIX IX: CORRRELATIVE BONE MARROW AND PERIPHERAL BLOOD STUDIES FORM (ONLY FOR PATIENTS WITH ALL)

COG Pt ID # _____ **ACC #** _____ **Cycle 1, Day 1 Date:** _____
Please do not write patient names on this form or on samples.

Institution: _____

Body Surface Area: ____ m^2 **Dose Level:** _____mg/m^2 **Total Dose:** _____**mg/day**

- Bone marrow samples (5 mL) will be obtained prior to starting Cycle 1 and on Day 32 ± 2 days, if persistent disease (≥5% blasts).
- Peripheral blood will be collected on Day 4 (15 mL if weight > 10 kg, 10 mL if weight ≤ 10kg) if absolute blast count is >1000/mm^3.
- Peripheral blood also can be substituted or used to augment bone marrow samples if the absolute blast count is >1000/µL: 10 mL per samples (<10 kg) or 15 mL (≥10 kg).

Collection of Bone Marrow or Peripheral Blood
Bone marrow or peripheral blood should be collected in a heparinized (green top) tube.

Sample No.	Time Point Cycle 1	Sample Type/Scheduled Collection Time	Actual Palbociclib Dose Given	Actual Date Sample Collected or Dose Given	Actual Time Collected or Dose Given (24-hr clock)
1	Pre-study	☐ Bone marrow (preferred) or peripheral blood if absolute blast count > 1000/mm^3 Pre-Day 1 dose		___/____/___	|__|__| : |__|__|
		Day 1 Dose	_____mg	___/____/___	|__|__| : |__|__|
		Day 4 Absolute Blast Count	_____mm^3		
2	Day 4 (PRIOR to chemotherapy administration)	☐ Peripheral blood if absolute blast count > 1000/mm^3		___/____/___	|__|__| : |__|__|
		Day 4 Dose	_____mg	___/____/___	|__|__| : |__|__|
3	Day 32	☐ Bone marrow if persistent disease (≥5% blasts)		___/____/___	|__|__| : |__|__|

Sample Processing (See Appendix X for details)

Lymphoblasts will be isolated from bone marrow or blood within 4 hours of collection using Ficoll-Paque Plus (Amersham Biosciences, Brown Deer, WI) at participating COG centers to avoid potential artifacts associated with prolonged sample storage or shipping. Blasts will then be frozen and batch shipped on dry ice to the Carroll/Aifantis labs for DNA and protein purification. **Samples can be shipped to arrive Monday-Friday. Ship samples to:**

Carroll/Iannis Aifantis Labs
Laura and Isaac Perlmutter Cancer Center at NYU Langone
522 First Avenue, Smilow Building 12 Floor, Room 1211
Tel: 212.263.2327 • Fax: 212.263.9190
New York, NY 10016 FedEx account # 320569834

- Email or call Nikki Evensen (Nikki.Evensen@nyumc.org; 212-263-2327) when the sample is being shipped.
- Do not ship samples for delivery on a weekend or holiday.

If this form will be used as a source document, the site personnel responsible for collection the samples must sign and date this form below:

Signature: _____ Date:_____

APPENDIX X: CORRELATIVES STUDIES GUIDE

Correlative Study	Appendix	Sample Volume		Tube Type
		Volume per sample	Total	
Pharmacokinetic Study (PK)	Appx. VIII	2-3 ml	24-36 ml	K2 EDTA (lavender-top)
Bone Marrow And Peripheral Blood Studies (ALL Only)	Appx II and IX	Bone marrow samples (5 mL) Peripheral Blood Day 4 (15 mL if weight > 10 kg, 10 mL if weight ≤ 10 kg)	Bone marrow samples (10 mL) Peripheral Blood Day 4 (15 mL if weight > 10 kg, 10 mL if weight ≤ 10 kg)	heparinized (green top) tube
		Total Volume	44-61 mL	

APPENDIX XI: TOXICITY-SPECIFIC GRADING

Total Bilirubin

Grade 1:	> ULN- ≤ 1.5 x ULN
Grade 2:	> 1.5 x ULN - 3.0 x ULN
Grade 3:	> 3.0 x ULN -10.0 x ULN
Grade 4:	> 10.0 x ULN

Direct Bilirubin Increase*

Grade 1:	< 3.0 mg/dl
Grade 2:	3.1 mg/dl - 5.0 mg/dl
Grade 3:	5.1 mg/dl-6.0 mg/dl
Grade 4:	≥ 6.1 mg/dl

*To be reported under the SOC of 'Investigations –Other, specify' as 'Direct Bilirubin Increased'

ALT: For the purpose of this study, the ULN for SGPT is 45 U/L regardless of baseline.

Grade 1:	> 45 U/L - ≤ 135 U/L
Grade 2:	136 U/L - 225 U/L
Grade 3:	226 U/L - 900 U/L
Grade 4:	> 900 U/L

AST: For the purpose of this study, the ULN for SGOT is 50 U/L regardless of baseline.

Grade 1:	> 50 U/L - ≤ 150 U/L
Grade 2:	151 U/L -250 U/L
Grade 3:	251 U/L -1000 U/L
Grade 4:	> 1000 U/L

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN - 5.0 x ULN
Grade 3:	> 5.0 x ULN -20.0 x ULN
Grade 4:	> 20.0 x ULN

APPENDIX XII: PATIENT DIARY FOR PALBOCICLIB

Specific Instructions for use of capsule or liquid formulation:
Complete each day with the time and dose given for palbociclib. Palbociclib will be given by mouth once daily on days 1-21. Palbociclib capsules should be taken with food. Palbociclib oral solution can be taken with or without food. Take at approximately the same time each day. If a dose is accidentally skipped leave that day blank. ***Make note of other drugs and supplements taken under the Comments section below***. Palbociclib capsules should not be opened or crushed but should be swallowed whole. Store capsules or oral solution bottles upright at room temperature. If a patient vomits after taking palbociclib, the dose should not be repeated. Avoid grapefruit or grapefruit juice for the duration of the protocol therapy. It a dose is inadvertently missed, do not make it up. If a dose is missed and the next dose is more than 12 hours away, the missed dose should be administered. If the next dose is less than 12 hours away, the missed dose should not be administered. Missed doses should not be made up. Inform your study doctor or nurse if a dose is missed. Add the dates to the calendar below and return the completed diary and the empty liquid formulation bottle(s) or any leftover liquid formulation to your institution after each treatment cycle.

EXAMPLE: Capsule Formulation				**For each day please indicate if palbociclib was taken as a capsule OR as liquid formulation.**				***Comments*** ***(Describe any missed or extra doses, if NG tube was used, vomiting and/or bothersome effects.)***
WEEK 1	***Date***	***Time***		**# of palbociclib capsules taken**		***OR***	***Amount of palbociclib liquid formulation taken (mL)***	
				75 mg	**100 mg**			
Day 1	*1/15/19*	*8:30*	*AM*	*X*				*She felt nauseated an hour after taking the drug but did not vomit.*
Day 2	*1/16/19*	*11:00*	*AM*	*X*				

EXAMPLE: liquid formulation				**For each day please indicate if palbociclib was taken as a capsule OR as liquid formulation.**				***Comments*** **(Describe any missed or extra doses, if NG tube was used, vomiting and/or bothersome effects.)**
WEEK 1	***Date***	***Time***		**# of palbociclib capsules taken**		***OR***	***Amount of palbociclib liquid formulation taken (mL)***	
				75 mg	**100 mg**			
Day 1	*1/15/19*	*8:30*	*AM*				2 mL	*He took the medicine through and NG tube and felt nauseated an hour after taking the drug but did not vomit.*
Day 2	*1/16/19*	*11:00*	*AM*				2 mL	

COG Patient ID:_____ Acc#_____
Institution :_____
Please do not write patient names on this form.

Cycle #: _____ Start Date: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__|

Dose Level: _____mg/m^2/dose

WEEK 1	Date	Time		For each day please indicate if palbociclib was taken as a capsule OR as liquid formulation.				Comments (Describe any missed or extra doses, if NG tube was used, vomiting and/or bothersome effects.)
				# of palbociclib capsules taken		OR	Amount of palbociclib liquid formulation taken (mL)	
				75 mg	100 mg			
Day 1			AM/PM					
Day 2			AM/PM					
Day 3			AM/PM					
Day 4			AM/PM					
Day 5			AM/PM					
Day 6			AM/PM					
Day 7			AM/PM					

COG Patient ID:_____ ACC # : _____ Institution :_____
Please do not write patient names on this form.

Cycle #: _____ Start Date: |__/__|__/__|__/__| **End Date**: |__/__|__/__|__/__|

Dose Level: _____mg/m^2/dose

WEEK 2	Date	Time		For each day please indicate if palbociclib was taken as a capsule OR as liquid formulation.				Comments (Describe any missed or extra doses, if NG tube was used, vomiting and/or bothersome effects.)
				# of palbociclib capsules taken			Amount of palbociclib liquid formulation taken (mL)	
				75 mg	100 mg			
Day 8			AM/PM					
Day 9			AM/PM					
Day 10			AM/PM					
Day 11			AM/PM					
Day 12			AM/PM					
Day 13			AM/PM					

Day 14			**AM/PM**					

COG Patient ID:_____ **ACC # :** _____ **Institution :**_____
Please do not write patient names on this form.

Cycle #: _____ **Start Date**: | _ _ / _ _ | _ _ / _ _ | _ _ / _ _ | **End Date**: | _ _ / _ _ | _ _ / _ _ | _ _ / _ _ |

Dose Level: _____mg/m^2/dose

WEEK 3	**Date**	**Time**		**For each day please indicate if palbociclib was taken as a capsule OR as liquid formulation.**				**Comments (Describe any missed or extra doses, if NG tube was used, vomiting and/or bothersome effects.)**
				# of palbociclib capsules taken		**OR**	**Amount of palbociclib liquid formulation taken (mL)**	
				75 mg	**100 mg**			
Day 15			**AM/PM**					
Day 16			**AM/PM**					
Day 17			**AM/PM**					
Day 18			**AM/PM**					
Day 19			**AM/PM**					
Day 20			**AM/PM**					
Day 21			**AM/PM**					

If this form will be used as a source document, the site personnel who administered the drug must sign and date this form below:

Signature: _____ Date: _____
(site personnel who collected samples)

APPENDIX XIII: POSSIBLE DRUG INTERACTIONS

Doxorubicin

Some drugs, food, and supplements may interact with doxorubicin. Examples include:

Drugs that may interact with doxorubicin*

• Antibiotics
  ○ Clarithromycin, erythromycin, nafcillin, rifapentin, rifampin, telithromycin
• Antidepressants and antipsychotics
  ○ Clozapine, fluoxetine, fluvoxamine, nefazodone, paroxetine
• Antibiotics and Antifungals
  ○ Fluconazole, isavuconazole, itraconazole, ketoconazole, posaconazole, voriconazole
• Arthritis medications
  ○ Leflunomide, tofacitinib
• Antiretrovirals and antivirals
  ○ Atazanavir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, Stribild®, telaprevir, tipranavir, zidovudine
• Anti-seizure medications
  ○ Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone
• Heart medications
  ○ Amiodarone, diltiazem, dronedenarone, ranolazine, verapamil
• Some chemotherapy (be sure to talk to your doctor about this)
  ○ Ado-trastuzumab emtansine, bevacizumab, idelalisib, trastuzumab, taxane derivatives
• Many other drugs, including the following:
  ○ Aprepitant, cyclosporine, fosaprepitant, fosnetupitant, deferasirox, ivacaftor, mifepristone, natalizumab, netupitant

Food and supplements that may interact with doxorubicin**
• Echinacea • Glucosamine • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit • Drinks, food, supplements, or vitamins containing "flavonoids" or other "antioxidants"

**Sometimes these drugs are used with doxorubicin on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

The list above does not include everything that may interact with your chemotherapy. Talk to your doctor before starting any new medications, over-the-counter medicines, or herbal supplements and before making a significant change in your diet.

Prednisone / Prednisolone

Some drugs, food, and supplements may interact with prednisone or prednisolone. Examples include:

Drugs that may interact with prednisone or prednisolone*
• Arthritis medications o Leflunomide, tofacitinib • Antidiabetic medications • Antiretrovirals and antivirals o Ritonavir, telaprevir • Anti-seizure medications o Phenobarbital, phenytoin, primidone • Growth hormones • Heart medications o Diltiazem, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Some oral contraceptives or birth control medications • Many other drugs, including the following: o Aprepitant, aripiprazole, aspirin, cyclosporine, deferasirox, desirudin, ibuprofen, itraconazole, mifepristone, natalizumab, pimecrolimus, rifampin, warfarin

Food and supplements that may interact with prednisone or prednisolone**
• Echinacea

**Sometimes these drugs are used with prednisone on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

The list above does not include everything that may interact with your chemotherapy. Talk to your doctor before starting any new medications, over-the-counter medicines, or herbal supplements and before making a significant change in your diet.

Vincristine

Some drugs, food, and supplements may interact with vincristine. Examples include:

Drugs that may interact with vincristine*
• Antibiotics o Clarithromycin, erythromycin, nafcillin, rifapentin, rifampin, telithromycin • Antifungals o Fluconazole, itraconazole, isavuconazole, ketoconazole, posaconazole, voriconazole • Arthritis medications o Leflunomide, tocilizumab, tofacitinib • Anti-rejection medications o Cyclosporine • Antiretrovirals and antivirals

○ Atazanavir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lapatinib, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild®, telaprevir, tenofovir, tipranavir • Anti-seizure medications ○ Carbamazepine, fosphenytoin, phenobarbital, phenytoin, primidone • Heart medications ○ Amiodarone, carvedilol, diltiazem, dronedarone, propafenone, quinidine, ranolazine, verapamil • Some chemotherapy (be sure to talk to your doctor about this) • Many other drugs, including the following: ○ Aprepitant, bosentan, cobicistat, conivapatan, deferasirox, fosnetupitant, ivacaftor, mifepristone, modafinil, natalizumab, nefazodone, netupitant

Food and supplements that may interact with vincristine**
• Echinacea • St. John's Wort • Grapefruit, grapefruit juice, Seville oranges, star fruit

**Sometimes these drugs are used with vincristine on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

The list above does not include everything that may interact with your chemotherapy. Talk to your doctor before starting any new medications, over-the-counter medicines, or herbal supplements and before making a significant change in your diet.

Pegaspargase

Some drugs, food, and supplements may interact with pegaspargase. Examples include:

Drugs that may interact with pegaspargase*
○ Leflunomide, natalizumab, pegloticase, tofacitinib

Food and supplements that may interact with pegaspargase**
• Echinacea

**Sometimes these drugs are used with pegaspargase on purpose. Discuss all drugs with your doctor.*

***Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

The list above does not include everything that may interact with your chemotherapy. Talk to your doctor before starting any new medications, over-the-counter medicines, or herbal supplements and before making a significant change in your diet