THOMAS JEFFERSON UNIVERSITY
Sidney Kimmel Cancer Center

A Phase I Trial of Palbociclib in Combination with Dexamethasone in Relapsed or Refractory Adult B-Cell Acute Lymphoblastic Leukemia (ALL)

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Name: Margaret Kasner, MD. MSCE

Title: Principal Investigator

Statement of Compliance

This study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and Thomas Jefferson University research policies

List of Abbreviations

AE	Adverse Event/Adverse Experience
ALL	Acute Lymphoblastic Leukemia
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
FWA	Federalwide Assurance
GCP	Good Clinical Practice
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to participants)
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator
PRC	Protocol Review Committee
QA	Quality Assurance
QC	Quality Control

SAE	Serious Adverse Event/Serious Adverse Experience
SDS	Safety Data Sheet (formerly MSDS; Material Safety Data Sheet)
SKCC	Sidney Kimmel Cancer Center
SOP	Standard Operating Procedure
TJU	Thomas Jefferson University
UAP	Unanticipated Problem

Study Summary

Title: A Phase I Trial of Palbociclib in Combination with Dexamethasone in Relapsed or Refractory **Adult B-Cell Acute Lymphoblastic Leukemia (ALL)**

Précis: This Phase I study will be conducted using a standard 3+3 dose escalation design. The initial cohort of patients will receive a 7-day lead-in with **palbociclib** 100mg daily. Patients will then undergo induction with palbociclib 100mg daily in combination with **dexamethasone** for 4 weeks. At the completion of cycle 1 (day 28), patients will undergo a bone marrow biopsy. If the marrow is empty, additional treatment will be held for count recovery. If there is evidence of response (CR, CRi, PR, or SD), patients will proceed to maintenance therapy. Maintenance will consist of 1 week of a dexamethasone taper plus palbociclib, followed by 3 weeks of palbociclib alone. A bone marrow biopsy will be obtained at the end of the first cycle of maintenance. If the marrow is empty, additional treatment will be held for count recovery. If there is evidence of response (CR, CRi, PR, SD), patients will continue maintenance therapy. Maintenance therapy will continue until disease progression, dose limiting toxicity, or availability of an alternative therapy. Patients who are not eligible for maintenance therapy will stop palbociclib and undergo a one week dexamethasone taper.

Objectives:

Primary:
1. To determine the dose and schedule of the combination of palbociclib and dexamethasone in patients with relapsed or refractory adult B-Cell ALL

2. To determine the safety and tolerability of the combination of palbociclib and dexamethasone in patients with relapsed or refractory adult B-Cell ALL

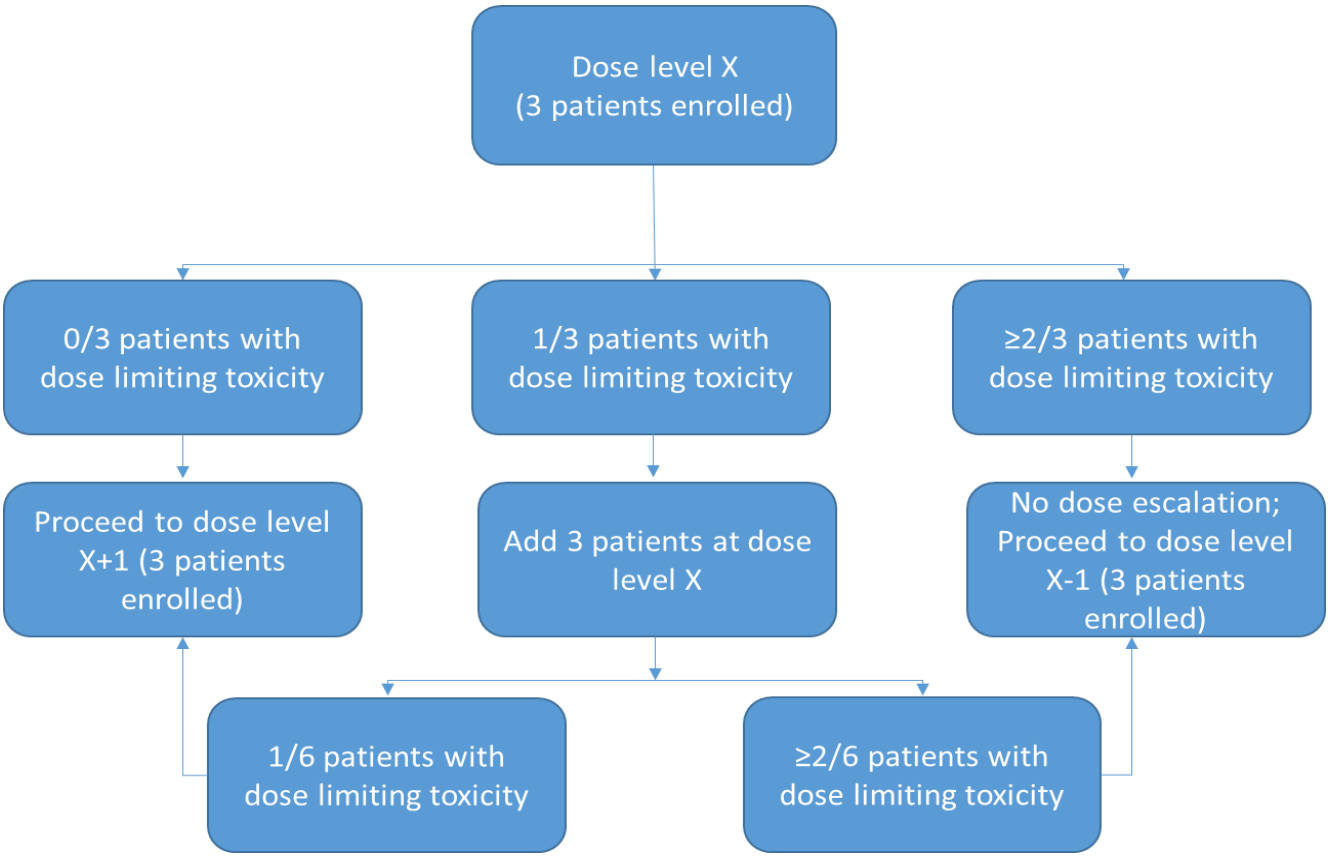
Secondary:
1. To evaluate the activity of palbociclib in combination with dexamethasone in patients with relapsed or refractory B-Cell ALL

Exploratory:
1. To determine the pharmacokinetic properties of palbociclib both alone and in combination with dexamethasone

2. To measure the on-target effects of palbociclib
3. To measure the on-target effects of dexamethasone
4. To measure cell cycle activity
5. To evaluate cellular proliferation and apoptosis

Population:	Adults age 18 or over with a confirmed diagnosis of relapsed or refractory B-Cell ALL; Adequate organ function; ECOG PS 0-2
Phase:	Phase I
Number of Sites:	1, Thomas Jefferson University Hospital
Description of Intervention:	Palbociclib at a starting dose of 100mg daily with dexamethasone
Study Duration:	66 months
Participant Participation Duration:	Until disease progression, dose limiting toxicity, or availability of an alternative therapy
Estimated Time to Complete Enrollment:	42 months

Schematic of Study Design:



1 Introduction

1.1 Background Information

Acute lymphoblastic leukemia (ALL) is a rare adult cancer, with approximately 6600 new cases diagnosed in 2016 [1]. In contrast to pediatric ALL, where improved understanding of disease biology and therapeutics have led to a 5-year event free survival rate of greater than 80%, adult ALL continues to have a poor prognosis with long-term disease free survival of only 40-45% [2, 3]. The prognosis for relapsed or refractory ALL in the adult population is even more grim, with a 5-year overall survival of about 10% [4, 5]. These statistics highlight the need for novel therapeutic options for these patients.

The Philadelphia chromosome, derived from the translocation t(9;22)(q34;q11.2) that results in the *BCR-ABL1* fusion gene, is present in approximately 25-30% of adult ALLs (Ph+ ALL) and is considered a high-risk feature [6]. Ph-like ALL is a newer high-risk entity that was first identified in children, but is now known to comprise 20-25% of adult ALLs; Ph-like ALL has a gene expression profile similar to that of Ph+ ALL, but does not express *BCR-ABL1* [7]. Several genetic alterations have been identified in Ph-like ALL, however, they all share the common feature of activating tyrosine kinase signaling. Patients with Ph-like ALL generally have a poor prognosis, particularly if they are of older age [7].

c-Myb, the cellular progenitor of the v-Myb oncogene, is a sequence specific DNA-binding transcription factor that is highly expressed in immature hematopoietic cells [8]. First identified in viruses that cause avian leukemia, c-Myb and its products have been shown to be essential in regulating normal hematopoiesis and in influencing leukemogenesis [8, 9]. The importance of c-Myb in hematopoiesis was first recognized when c-Myb homozygous null mice were found to die at embryonic day 15 due to a failure to convert from fetal to adult erythropoiesis [8, 10]. Additionally, mouse models have demonstrated that conditional knockdown of the c-Myb gene in adult hematopoietic stem cells leads to a cessation of cell growth and differentiation, which can be restored with restoration of c-Myb function [10].

The c-Myb gene is located on chromosome 6q and is frequently affected in both myeloid and lymphoid neoplasms, however, the exact role of c-Myb in ALL is under investigation [11]. A preclinical model has demonstrated that knockdown of c-Myb via a doxycycline controllable c-Myb specific shRNAmir causes cell cycle arrest in pre-B-ALL cells [12]. Furthermore, apoptosis, as measured both by PARP cleavage and by downregulation of Bcl-2 (an anti-apoptotic protein), was also induced in these cells [12]. A similar study conducted at our institution found that Ph+ acute lymphoblastic leukemia cells are dependent on Myb expression for proliferation and survival, ex vivo and in immunodeficient mice injected with primary Ph+ ALL cells (De Dominici et al, submitted for publication). Likewise, expression of MYB is required for disease maintenance in mouse models of p190-190BCR-ABL-induced ALL [11].

Analyses have shown that the effects of c-Myb depend on transcriptional regulation of CDK6 and Bcl-2, which may provide novel therapeutic targets in Ph+ ALL (De Dominici et al, submitted for publication). Both effectors appear to be functionally relevant because c-Myb-silenced Ph+ ALL cells exhibit Rb-dependent cell cycle arrest and apoptosis, both of which are

rescued by ectopic expression of cyclin D3, CDK6, and Bcl-2 expression. Preliminary experiments in immunodeficient NOD/SCID/IL-2Rnull (NSG) mice injected with primary Ph+ ALL cells and treated with the CDK4/CDK6 inhibitor palbociclib, the Bcl-2 pan-inhibitor sabutoclax, or the combination of palbociclib and sabutoclax show that treatment with palbociclib is more effective than sabutoclax in suppressing Ph+ ALL in NSG mice and that the palbociclib/sabutoclax combination is more effective than either drug alone. Palbociclib is a small molecule inhibitor of CDK4 and CDK6 that is currently FDA approved for use with the aromatase inhibitor letrozole as first-line treatment in postmenopausal women with metastatic breast cancer that is estrogen receptor positive and human epidermal growth factor receptor 2 negative.

Glucocorticoids play an integral role in the treatment of ALL. Dexamethasone has been shown to have superior activity compared to prednisone and is the steroid of choice in many treatment regimens [13]. Preclinical studies suggest that the enhanced cytotoxic activity of dexamethasone may be due to its ability to decrease c-Myb expression in ALL cells [14]. Furthermore, dexamethasone treatment reduces Bcl-2 levels in ALL cells through a Myb-dependent mechanism, thereby increasing apoptosis [15]. Dexamethasone resistance in ALL has been linked to Myb overexpression and can be overcome by Myb silencing [14, 15]. Prednisone, a steroid with similar activity to dexamethasone, has been tested in ALL cell lines in combination with palbociclib and has shown an additive effect (Calabretta, unpublished data).

1.2 Rationale for the Proposed Study

This study will evaluate the use of palbociclib in conjunction with dexamethasone for the treatment of relapsed or refractory ALL. We will begin giving palbociclib at a dose of 100mg PO daily with escalation in increments of 25mg to a maximum dose of 150mg. Initial Phase I testing of palbociclib in patients with advanced solid tumors revealed a maximum tolerated dose (MTD) of 125mg daily. The primary dose limiting toxicity was bone marrow suppression, an important consideration when treating sold tumors, but an expected, and possible surrogate marker for efficacy, in the treatment of leukemia. Dexamethasone may decrease serum drug levels of palbociclib, so we will begin with a palbociclib dose of 100mg and escalate from there. Dosing regimens in ALL vary; in this study, we propose giving dexamethasone at a starting dose of 20mg daily in conjunction with palbociclib, and then decreasing the dose by 4mg weekly over 4 weeks to minimize side effects.

If the combination of palbociclib and dexamethasone is found to be safe and well-tolerated, we would hope to move forward with a larger, Phase II study.

1.3 Correlative Studies

The following correlative studies will be performed in the Calabretta Laboratory:

1. RB phosphorylation (CDK4/6 phosphorylation sites) by Western blot as the primary read-out of palbociclib activity.
2. FOXM1 expression by Western blot as the secondary read-out of palbociclib activity (since FOXM1 is a CDK4/6 target)

3. RNA isolated from CD19+ cells will be used for gene expression profiles (microarray or RNA-Seq) to measure p21 expression as an indicator of cell cycle activity
4. RNA isolated from CD19+ cells will be used for gene expression profiles (microarray or RNA-Seq) to measure S-Phase, Annexin V/Caspase 3 activation as indicators of proliferation and apoptosis
5. RNA isolated from CD19+ cells will be used for gene expression profiles (microarray or RNA-Seq) to measure Expression of Myb and Bcl-2 as a read-out of dexamethasone sensitivity

These analyses will be performed on pre-treatment samples (peripheral blood and/or bone marrow) as well as on day +1 (after 1 week of palbociclib alone) and day +8 (after 1 week of combined therapy) of treatment (peripheral blood).

1.4 Potential Risks and Benefits

1.4.1 Potential Risks

Patients will be informed of all anticipated and possible unanticipated adverse effects of drug treatments. Anticipated treatment-related adverse events include myelosuppression, nausea, vomiting, fatigue, diarrhea, anorexia, neutropenic fever, infection, pulmonary embolism, hyperglycemia, insomnia, adrenal suppression, myopathy, and psychiatric disturbances. Treatment-related mortality can occur from intensive anti-leukemic therapy and is estimated at 5-10%. Alternative therapies, including standard chemotherapy, investigational agents, and supportive care-only, will be discussed with potential patients prior to informed consent.

1.4.2 Benefits

Should the combination of palbociclib and dexamethasone improve complete response rate--a surrogate for survival in ALL-- participation would provide substantial benefit for study participants. An additional and more certain benefit is the scientific knowledge gained from this clinical trial's correlative studies. This may improve understanding of the pathophysiology of ALL and provide insight into additional novel therapies. Although study participants cannot be guaranteed benefit, the information gained may benefit cancer patients in the future.

2 Study Objectives

2.1 Objectives

2.1.1 Primary

- To determine the dose and schedule of the combination of palbociclib and dexamethasone in patients with relapsed or refractory adult B-Cell ALL
- To determine the safety and tolerability of the combination of palbociclib and dexamethasone in patients with relapsed or refractory adult B-Cell ALL

2.1.2 Secondary

- To evaluate the activity of palbociclib in combination with dexamethasone in patients with relapsed or refractory B-Cell ALL

2.1.3 Exploratory

- To determine the pharmacokinetic properties of palbociclib both alone and in combination with dexamethasone
- To measure the on-target effects of palbociclib
- To measure the on-target effects of dexamethasone
- To measure cell cycle activity
- To evaluate cellular proliferation and apoptosis

2.2 Endpoints/Outcome Measures

2.2.1 Primary

- Dose limiting toxicity and maximum tolerated dose of the combination of palbociclib and dexamethasone

2.2.2 Secondary

- To observe clinically relevant responses to therapy (defined in section 11.2) as determined by bone marrow biopsy after cycle 1

2.2.3 Exploratory

- To evaluate a number of pharmacokinetic and pharmacodynamic biomarkers that measure the effect of the combination of palbociclib and dexamethasone including:
    - Plasma levels of palbociclib
    - Western blots of phospho-RB (using antibodies that recognize CDK4/6 phosphorylation sites on RB) and FOXM1 (CDK4/6 substrate which is stabilized by phosphorylation) on lysates from peripheral blood or bone marrow CD19+ cells (obtained by FACS sorting).
    - RNA isolated from CD19+ cells will be used for gene expression profiles (microarray or RNA-Seq) to measure Myb and Bcl-2 levels
    - RNA isolated from CD19+ cells will be used for gene expression profiles (microarray or RNA-Seq) to measure levels of p21, CDK2, and cyclin E as markers of cell cycle activity
    - RNA isolated from CD19+ cells will be used for gene expression profiles (microarray or RNA-Seq) to measure levels of S-Phase and Annexin V/Caspase 3 activation as indicators of proliferation and apoptosis

3 Study Design

This single arm, Phase I, single institution, dose escalation study will follow a traditional 3+3 design (See Section 11).Patients who are receiving treatment with steroids at the time of enrollment must undergo at least a 24 hour washout period prior to their first dose of palbociclib.

Patients will receive a 1-week lead-in (Day -7 to Day -1) of palbociclib alone at the appropriate dose level. This will be followed by induction with 4 weeks of palbociclib in combination with dexamethasone. Patients will receive dexamethasone 20mg daily from days 1-7, 16mg daily from days 8-14, 12mg daily from days 15-21, and 8mg daily from days 22-28. If a patient experiences a DLT as defined in section 6.2.1, the patient will stop the study drugs and come off of the trial. At the completion of induction therapy (Day +28), a bone marrow biopsy will be performed. If the marrow is hypoplastic (<10% cellularity), further treatment will be held (up to 4 weeks from the last day of the induction cycle) to await count recovery. Count recovery will be defined as ≥10% cellularity in the bone marrow, neutrophils ≥0.75 $x10^9$/L, and a platelet count ≥ 75 x 10^9/L. At the time of count recovery a repeat bone marrow biopsy will be performed. If a CR, CRi, PR, or SD is seen, the patient will move to maintenance therapy.

Maintenance will consist of 1 week of palbociclib plus dexamethasone (20mg daily), followed by 3 weeks of palbociclib alone. Patients will have a repeat bone marrow biopsy on day +28 of the first maintenance cycle with the same parameters for continuation that were used in induction. To proceed to subsequent maintenance cycles, the patient must have neutrophils ≥0.75 $x10^9$/L and a platelet count ≥ 75 x 10^9/L. If these criteria are not met, treatment will be held (up to 6 weeks) until count recovery occurs. Palbociclib will then be resumed with a level -1 dose reduction. Patients will be maintained on maintenance until disease progression, dose limiting toxicity, or availability of an alternative therapy.

Patients who do not meet the criteria for maintenance therapy will stop both palbociclib and dexamethasone.

3.1 Number of Participants

A minimum of 4 and a maximum of 18 patients will be enrolled.

3.2 Duration of Therapy

Initially, patients will receive single agent palbociclib during induction for pharmacokinetic/pharmacodynamics (PK/PD) evaluation followed by combination induction therapy with palbociclib and dexamethasone. Patients who do not achieve a CR, CRi, PR, or SD after induction therapy will be taken off the study. Patients who achieve a CR, CRi, PR, or SD will receive on palbociclib and dexamethasone maintenance until disease progression or dose limiting toxicity. Patients who are transplant ineligible at study entry but achieve a CR and thus become transplant eligible may come off study and proceed to transplant. Patients who achieve stable disease, but not a CR, will be re-consented after 6 cycles to continue on the study.

3.3 Duration of Follow Up

Patients will be followed for late toxicities for 1 year following the discontinuation of therapy.

3.4 Study Timeline

3.4.1 Primary Completion

We anticipate that accrual will be complete within 42 months.

3.4.2 Study Completion

The study will be complete 2 years after the enrollment of the last patient (66 months total study duration).

4 Study Enrollment and Withdrawal

4.1 Eligibility Criteria

4.1.1 Inclusion Criteria

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

1. Patients must have histologic evidence of relapsed or refractory B-cell ALL

2. Patients must be ≥18 years of age

3. Patients must have an ECOG performance status of 2 or less (see Appendix B)

4. Ph+ patients must be refractory to or intolerant of standard tyrosine kinase inhibitor therapy.

5. Patients must be able to consume oral medication.

6. Patients must have recovered to ≤ Grade 1 or stabilized from the toxic effects of any prior chemotherapy (except alopecia).

7. Required initial laboratory values: CrCL ≥60mL/min/1.73m^2 calculated by Cockroft-Gault; total bilirubin <1.5xULN; negative serum or urine pregnancy test for women with child-bearing potential.

8. Patients must be able to sign consent and be willing and able to comply with scheduled visits, treatment plan, procedures, and laboratory testing. When it is determined by the study investigator that a potential research participant is cognitively impaired, a surrogate consent from a caregiver or legally-authorized representative will be obtained. Caregiver or legally-authorized representative will ensure that they comply with the protocol in order for the subject to be considered eligible.

4.1.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Patients must not have evidence of active CNS disease

2. Patients must not be receiving any chemotherapy agents (except hydroxyurea). Intrathecal methotrexate and intrathecal cytarabine are permissible.

3. Patients must not be receiving growth factors (G-CSF, GM-CSF), except for erythropoietin.

4. Patient must not have a concurrent active malignancy for which they are receiving treatment..

5. Patients with other severe concurrent disease which in the judgment of the investigator would make the patient inappropriate for entry into this study are ineligible.

6. Patients must not have received any investigational agents within 30 days of study entry unless they have exceeded 5 terminal half-lives of the previous study drug used for treatment.7. Patients must not be pregnant or breastfeeding. Pregnancy tests must be obtained for all females of child-bearing potential within 10 days prior to enrollment. Pregnant or lactating patients are ineligible for this study due to the potential human fetal or teratogenic toxicities of palbociclib. Males or women of childbearing potential may not participate unless they have agreed to use an effective contraceptive method (defined as hormonal contraceptives, intrauterine devices, surgical contraceptives, or condoms).

8. Patients who have uncontrolled infection are not eligible. Patients must have any active infections under control. Fungal disease must have been adequately treated for at least 2 weeks before study entry. Subjects with bacteremia must have documented negative blood cultures prior to study entry.

9. Patients who are candidates for allogeneic transplantation, have a suitable donor, and are willing to undergo transplantation.

10. Patients who are eligible for and willing to receive treatment with tisagenlecleucel.

4.2 Gender/Minority/Pediatric Inclusion for Research

Patients will not be excluded based on gender, race, or economic status. Pediatric patients will not be included in this study. ALL is slightly more common in men with a ratio of 1.2 to 1.0. Accrual will be monitored by the MDG quarterly and if the ratio does not reflect the known incidence a plan to increase recruitment of women will be made.

4.3 Strategies for Recruitment and Retention

Patients will be recruited from the practice of the Medical Oncology Department of the Thomas Jefferson University Hospital. The patients must be 18 years of age or older. Patients who meet eligibility criteria will be invited by their physician to participate in the study. All therapeutic options will be discussed with the patient and the patient's questions will be answered to the

patient's satisfaction. Patients will be asked to read, comment, and ask questions about the study and then sign the informed consent form before study procedures take place.

4.4 Participant Withdrawal

4.4.1 Reasons for Withdrawal

Patients are free to withdraw from participation in the study at any time upon request.

An investigator may terminate a study patient's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The patient meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- The patient does not comply with study medications and procedures
- The physician determines that ongoing participation would be detrimental to the patient
- The patient no longer wishes to participate
- Documented disease progression, unless the investigator (in consultation with the sponsor) deems that continued treatment is appropriate.
- Initiation of a new anti-cancer therapy

4.4.2 Handling of Participant Withdrawals and Participant Discontinuation of Study Intervention

Every attempt will be made to follow patients for data collection, including those patients who are prematurely withdrawn, have disease progression, or withdraw consent.

4.5 Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Insufficient adherence to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.

- Determination of futility.

5 Study Intervention

5.1 Study Product

Palbociclib (Ibrance®)

5.2 Study Product Description

Palbociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways which lead to cellular proliferation.

5.2.1 Acquisition

Palbociclib will be acquired from the manufacturer, Pfizer Inc.

5.2.2 Formulation, Packaging, and Labeling

Ibrance capsules for oral administration contain 125 mg, 100 mg, or 75 mg of palbociclib, a kinase inhibitor. The molecular formula for palbociclib is C24H29N7O2. The molecular weight is 447.54 daltons. The chemical name is 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2 yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one, and its structural formula is: Palbociclib is a yellow to orange powder with pKa of 7.4 (the secondary piperazine nitrogen) and 3.9 (the pyridine nitrogen). At or below pH 4, palbociclib behaves as a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly. Inactive ingredients: Microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule shells. The light orange, light orange/caramel and caramel opaque capsule shells contain gelatin, red iron oxide, yellow iron oxide, and titanium dioxide; and the printing ink contains shellac, titanium dioxide, ammonium hydroxide, propylene glycol and simethicone.

125 mg capsules: opaque hard gelatin capsules, size 0, with caramel cap and body, printed with white ink “Pfizer” on the cap, “PBC 125” on the body.

100 mg capsules: opaque hard gelatin capsules, size 1, with caramel cap and light orange body, printed with white ink “Pfizer” on the cap, “PBC 100” on the body.

75 mg capsules: opaque hard gelatin capsules, size 2, with light orange cap and body, printed with white ink “Pfizer” on the cap, “PBC 75” on the body.

5.2.3 Product Storage and Stability

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

5.3 Dosage, Preparation, and Administration

Patients will begin treatment at assigned dose level. Initial dose level is 100mg. Based on the protocol design, additional patients will be enrolled at either 125mg or 150mg. Patients will receive a daily oral dose of palbociclib.

Palbociclib will be dispensed from the Investigational Drug Service (IDS) at TJU. It will be dispensed in pill bottle(s) containing a full cycle's amount of palbociclib. Patients may start a cycle as an outpatient and may self-administer doses at home. Patients will be asked to bring their pill bottle(s) as well as their pill diary to each visit.

Qualified personnel who are familiar with procedures that minimize undue exposure to them and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in an appropriate environment.

5.4 Dose Modifications and Dosing Delays

Patients who experience a dose limiting toxicity (as defined in section 6.2.1) will stop the study drugs and come off of the trial. The dose cohort level will be de-escalated to 75mg PO daily if dose limiting toxicity occurs in the initial 100mg dose cohort.

Patients who complete the first cycle of maintenance but require treatment to be held up to 4 weeks (after the end of the cycle) to achieve count recovery (as defined below), will have palbociclib resumed with a level -1 dose reduction.

For this study, count recovery is defined as ≥10% cellularity in the bone marrow, neutrophils ≥0.75 x10^9/L, and a platelet count ≥ 75 x 10^9/L.

Dose Escalation Schedule

Dose Level	**Dose***	
	Palbociclib (mg)	***Dexamethasone (mg)***
Level -1	75	20
Level 1	100	20
Level 2	125	20
Level 3	150	20

**Doses are stated as exact dose in units (*e.g.*, mg/m^2, mcg/kg, etc.) rather than as a percentage.*

For patients who remain on maintenance after the first cycle, palbociclib dose modifications will be made as follows:

Hematologic toxicity (except lymphopenia unless associated with clinical events [eg opportunistic infection]), according to Common Toxicity Criteria for Adverse Events Version 4.03:

Neutropenia:

Grade 1 or 2: No dosage adjustment required.

Grade 3:

Day 1 of cycle: Withhold palbociclib therapy and repeat CBC with differential within 1 week. When improved to ≤ grade 2, initiate the next cycle at the same dose. If recovery from grade 3 neutropenia is prolonged (>2 weeks), or for recurrent grade 3 neutropenia on day 1 of subsequent cycles, decrease to next lower dose.

Grade 3 (ANC 500/mm^3 to <1,000/mm^3) plus fever ≥38.5°C and/or infection at any time: Withhold palbociclib treatment until resolved to ≤ grade 2. Resume at the same dose.Grade 4 at any time: Withhold palbociclib treatment until resolved to ≤ grade 2. After resolution, resume at next lower dose.

Anemia:

Grade 1, 2, or 3: No dosage adjustment required

Grade 4: Withhold palbociclib treatment until resolved to ≤ grade 2. After resolution, resume at next lower dose.

Thrombocytopenia:

Grade 1 or 2: No dosage adjustment required.

Grade 3:

Day 1 of cycle: Withhold palbociclib therapy and repeat CBC with differential within 1 week. When improved to ≤ grade 2, initiate the next cycle at the same dose. If recovery from grade 3 thrombocytopenia is prolonged (>2 weeks), or for recurrent grade 3 thrombocytopenia on day 1 of subsequent cycles, decrease to next lower dose.

Grade 4 at any time: Withhold palbociclib treatment until resolved to ≤ grade 2. After resolution, resume at next lower dose.

Nonhematologic toxicity (according to Common Toxicity Criteria for Adverse Events Version 4):

Grade 1 or 2: No dosage adjustment required.

Grade 3 or higher (if persistent despite optimal medical management): Withhold palbociclib until symptoms resolve to ≤ grade 1 or ≤ grade 2 (if toxicity is not a safety risk); after resolution, resume at the next lower dose.

During the maintenance phase, dose reductions of palbociclib may be made as many times as necessary for toxicity to a minimum dose of 75mg daily. Patients may also be changed to a 3 weeks on, 1 week off dosing schedule to minimize toxicity. Any patient who requires palbociclib to be held for >14 days will be considered for discontinuation of the trial.

Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. In vivo, palbociclib is a time-dependent inhibitor of CYP3A. Patients will be screened for concomitant medications that are metabolized by these enzymes, and the possibility of a drug-drug interaction will be considered with dose reduction of concomitant medication, as clinically indicated. Patients taking concomitant medications that are metabolized by these enzymes will not be excluded from the study.

5.5 Study Product

Dexamethasone (Decadron®)

5.6 Study Product Description

Dexamethasone is a synthetic adrenocortical steroid.

5.6.1 Acquisition

Dexamethasone will be billed to patient insurance and handled through the Jefferson outpatient pharmacy.

5.6.2 Formulation, Packaging, and Labeling

Dexamethasone tablets, for oral administration, are supplied in, 0.5 mg and 0.75, mg, 1 mg, 2mg, 4mg and 6 mg tabs. Inactive ingredients are calcium phosphate, lactose, magnesium stearate, and starch. Dexamethasone 0.5 mg also contain D&C Yellow 10 and FD&C Yellow 6. Dexamethasone 0.75 mg also contain FD&C Blue 1.

5.6.3 Product Storage and Stability

Store at controlled room temperature 20° to 25°C (68° to 77°F).

5.7 Dosage, Preparation, and Administration

The dose of dexamethasone will start at 20mg daily and will taper by 4mg each week over the course of induction. During maintenance, patients will receive 20mg of dexamethasone daily for 7 days. Patients will receive a daily oral dose of dexamethasone.

Dexamethasone will be dispensed from a commercial outpatient pharmacy. It will be dispensed in pill bottle(s) containing a full cycle's amount of dexamethasone. Patients may start a cycle as an outpatient and may self-administer doses at home. Patients will be asked to bring their pill bottle as well as their pill diary to each visit.

5.8 Dose Modifications and Dosing Delays

During induction, patients will undergo a planned dexamethasone taper as follows: 20mg of dexamethasone daily from days 1-7, 16mg of dexamethasone daily from days 8-14, 12mg of dexamethasone daily from days 15-21, and 8mg of dexamethasone daily from days 22-28. During maintenance, patients will receive dexamethasone 20mg daily from days 1-7 without a taper.

5.9 Study Product Accountability

The IDS at TJU will be responsible for the storage, management, and distribution of the study drug. Patients will be asked to return unused medication at the end of treatment or at the time of withdrawal from the study.

5.10 Assessing Participant Compliance with Study Product Administration

Patients will be given pill diaries and asked to complete it to assess compliance.

5.11 Concomitant Medications/Treatments

Patients must not have received any investigational medications within 30 days of study entry unless they have exceeded 5 terminal half-lives of the previous study drug used for treatment.

The following list of medications/treatments will be screened for with potential alteration for the concomitant medication (not steroids), but are not exclusionary.

Aminoglutethimide: Aminoglutethimide may diminish adrenal suppression by corticosteroids.

Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (e.g., amphotericin B, diuretics), patients should be observed closely for development of hypokalemia. In addition, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance (see Drug Interactions, Hepatic Enzyme Inducers, Inhibitors and Substrates). NDA 11-664/S-062 Page 7

Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Anticoagulants, oral: Co-administration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Antitubercular drugs: Serum concentrations of isoniazid may be decreased.

Cholestyramine: Cholestyramine may increase the clearance of corticosteroids.

Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Dexamethasone suppression test (DST): False-negative results in the dexamethasone suppression test (DST) in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.

Digitalis glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Ephedrine: Ephedrine may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring an increase in corticosteroid dosage.

Estrogens, including oral contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.

Hepatic Enzyme Inducers, Inhibitors and Substrates: Drugs which induce cytochrome P450 3A4 (CYP 3A4) enzyme activity (e.g., barbiturates, phenytoin, carbamazepine, rifampin) may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased. Drugs which inhibit CYP 3A4 (e.g., ketoconazole, macrolide antibiotics such as erythromycin) have the potential to result in increased plasma concentrations of corticosteroids. Dexamethasone is a moderate inducer of CYP 3A4. Co-administration with other drugs that are metabolized by CYP 3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentration.

Ketoconazole: Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to increased risk of corticosteroid side effects. In addition, ketoconazole alone can inhibit adrenal corticosteroid synthesis and may cause adrenal insufficiency during corticosteroid withdrawal.

Nonsteroidal anti-inflammatory agents (NSAIDS): Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

Phenytoin: In post-marketing experience, there have been reports of both increases and decreases in phenytoin levels with dexamethasone co-administration, leading to alterations in seizure control.

Skin tests: Corticosteroids may suppress reactions to skin tests.

Thalidomide: Co-administration with thalidomide should be employed cautiously, as toxic epidermal necrolysis has been reported with concomitant use.

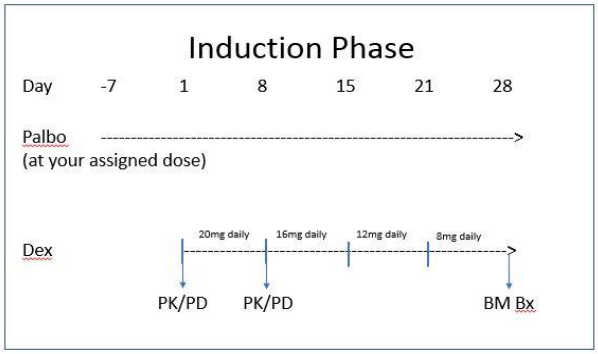
6 Study Schedule

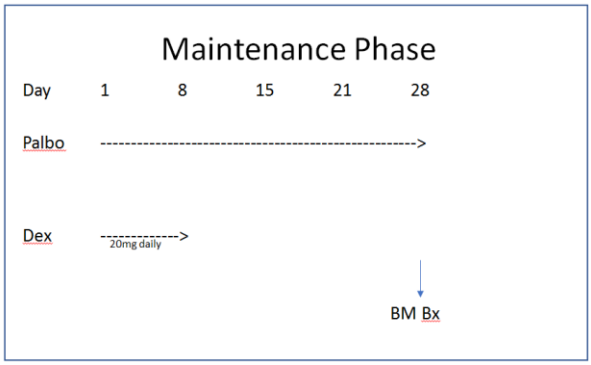
6.1 Enrollment/Baseline

Within the twenty-one days prior to the first dose of palbociclib (day -7), patients will sign the informed consent document and have a medical history taken as well as a physical exam (including neurological exam), vital signs, performance status assessment and review of concomitant medications. Peripheral blood will be drawn for baseline laboratory studies including CBC with differential, complete metabolic panel (CMP), liver function tests, electrolytes, urate, and glucose, as well as a pregnancy test, if applicable. See Schedule of Events in Section 6.2 for more information. During this period, patients may receive cytoreductive treatment with hydroxyurea or steroids at the discretion of the treating physician. Patients who are receiving cytoreductive treatment with steroids must undergo at least a 24 hour washout period prior to their first dose of palbociclib.

Patients will require a bone marrow biopsy and aspirate both for diagnostic purposes and for pharmacodynamic studies. The baseline bone marrow biopsy/aspirate may be substituted with peripheral blood collection for patients with circulating disease only if peripheral blood blasts are >200/μl (WBC x blast percentage >0.2 thousand/uL). Subsequent bone marrow biopsies will be performed at the completion of induction and the completion of cycle 1 of maintenance.

6.2 Treatment Period





*for the purposes of this study, Day 0 and Day +1 are the same during the induction phase

Induction Phase

Mandatory study visits will be conducted during the induction period on the following days:

- Day +1
- Day +8
- Day +28

At each visit, patients will undergo a physical exam, vital signs, and an adverse event assessment. Peripheral blood will be drawn for a CBC with differential, serum chemistry with electrolytes, and liver function tests. On day +1 and day +8 of induction, prior to the administration of dexamethasone and palbociclib, patients will have blood drawn for pharmacokinetics. On day +1 and day +8 of induction, prior to the administration of dexamethasone, patients will also have blood drawn for pharmacodynamic studies. A bone marrow biopsy will performed to assess for response on day +28.

Maintenance Phase

Mandatory study visits will be conducted during the maintenance phase on the following days:

- Day +28

At this visit, patients will undergo a physical exam, vital signs, and an adverse event assessment. Peripheral blood will be drawn for a CBC with differential, serum chemistry with electrolytes, and liver function tests. A bone marrow biopsy will performed to assess for clinical response on day +28.

After the first cycle of maintenance, patients will be monitored with peripheral blood studies every other week. Bone marrow biopsy will only be performed if there is suspicion of relapsed disease.

See Appendix A for the Schedule of Events.

6.2.1 **Dose Escalation Procedures**

Dose Escalation Schedule		
Dose Level	**Dose***	
	Palbociclib (mg)	***Dexamethasone (mg)***
Level -1	75	20
Level 1	100	20
Level 2	125	20
Level 3	150	20
**Doses are stated as exact dose in units (*e.g.*, mg/m^2, mcg/kg, etc.) rather than as a percentage.*		

The dose escalation portion of this study will enroll within each cohort according to a "3+3 design", as explained in the following scheme. Palbociclib will be given as a 1 week lead in alone at the appropriate dose level. This will be followed by 4 weeks of Palbociclib in combination with dexamethasone (induction phase). Patients will receive dexamethasone 20mg daily from days 1-7, 16mg daily from days 8-14, 12mg daily from days 15-21, and 8g daily from days 22-28. Maintenance phase will consist of 1 week of Palbociclib with a dexamethasone 20mg daily followed by 3 weeks of Palbociclib alone. See Section 5.4 for Palbociclib dose modifications/dose levels.

Patients who experience a DLT during the evaluation period as defined below, will stop the study drugs and come off of the trial.

Patients who complete the first cycle of maintenance but require treatment to be held up to 4 weeks to achieve count recovery, will have Palbociclib resumed with a level -1 dose reduction.

The dose escalation portion of this study will follow a traditional 3+3 design, escalating to the next higher dose cohort if 3 patients are treated and no DLTs are observed in the first cycle of therapy. The following will be will be defined as a DLT:

Toxicity	**DLT Criteria***
Hematology	• Marrow aplasia (defined as <10% cellularity with <10% blasts for ≥ 6 weeks not attributable to disease) • Grade 4 neutropenia persisting ≥6 weeks from the start of a cycle that is not attributable to the underlying disease
Cardiac	Any ≥ Grade 3 toxicity
Gastro-intestinal	Any ≥ Grade 3 toxicity except: • Grade 3 nausea, vomiting**, or diarrhea** not requiring total parenteral nutrition (TPN) or tube-feeding
Hepato-biliary	An increase in AST or ALT >3 x ULN and concurrent increase in total bilirubin >2 x ULN (Hy's Law) Any ≥ Grade 3 toxicity except: • Any Grade 3 or 4 liver abnormalities (AST, ALT, or alkaline phosphatase) that resolve to < grade 2 within 72 hours • Grade 3 hyperbilirubinemia that resolves to < grade 2 within 72 hours • Grade 3 indirect hyperbilirubinemia that resolves to < grade 2 within 72 hours
Renal	Any ≥ Grade 3 toxicity
Non-Hematologic	≥ Grade 3, including electrolyte abnormalities, except as noted elsewhere in the table
Exceptions to DLT criteria	• Grade 3 alopecia • Grade 3 fatigue of < 5 days' duration • Grade 3 electrolyte abnormalities that last <72 hours • Infection (including neutropenic fever), unless the investigator determines that the infection or neutropenic fever resulted from the degree or duration of myelosuppression **in the absence of persistent leukemia**

* CTCAE version 5.0 should be used for grading.

** Optimal therapy for vomiting and diarrhea should be based on institutional guidelines with consideration of the prohibited medications listed in these protocol guidelines.

The DLT evaluation period is defined as 35 days (one week lead-in plus Cycle 1). In order to be considered evaluable, the patient needs to take 80% of the doses in the one week lead-in and Cycle 1 (1 cycle=28 days). The 80% completion can be non-consecutive days of dosing with study drug within the one week lead-in and Cycle 1. Any DLT will be followed until resolution.

If one DLT is recorded, then three additional patients will be enrolled into the present cohort. If no further DLTs occur (1 out of 6 DLTs) then the next patient will be enrolled in the next higher cohort. If 2 out of 6 patients have an observed DLT in any given cohort, 3 additional patients will be treated at one dose level lower, and if no additional DLTs are observed, this will be the maximum tolerated dose. If no DLTs are observed in all three cohorts then the expansion phase dose will be cohort 3 for the expansion phase. Toxicities will be graded according to the National Cancer Institute, Common Toxicity Criteria for Adverse Events version 4.0 (NCI CTCAE v5.0). If multiple toxicities are seen, the presence of DLT will be based on the most severe toxicity experience.

Once three patients have enrolled onto the dose cohort and the DLT evaluation period or the third patient has passed, a meeting will be held with the PI and the TJU Medical Monitor to review the safety information. If it is determined safe to open the next dose cohort, a formal letter from the Medical Monitor will be issued. Please see Appendix D for more information.

6.3 End of Treatment Study Procedures

At the end of treatment, patients will be assessed with a history and adverse event assessment.

Patients who receive maintenance therapy and achieve a CR will be assessed at the time of disease progression with a history, adverse event assessment, and bone marrow biopsy to confirm progression.

6.4 Post-treatment/Follow-Up

Patients will be followed every three months for one year after treatment ends for evidence of late toxicity. Follow up visits will either occur as part of routine clinical visits (standard of care) or through review of the patient medical record. Patients who were ineligible for transplant at study entry but achieve a CR and thus become transplant eligible will be followed.

6.5 Withdrawal Visit/Discontinuation of Therapy

If a patient withdraws early or the investigator terminates a patient's participation the following should still be offered to the patient:

- Recording of adverse events

- Recording of physical examination
- Recording of compliance with palbociclib and dexamethasone

7 Study Procedures and Evaluations

7.1 Study Procedures/Evaluations

At enrollment/baseline, each patient will have a medical history. This will include a review of the patient's medical record. A medication history will be obtained. Patients will also undergo a physical exam (including neurological exam), vital signs, and performance status assessment.

7.2 Laboratory Procedures/Evaluations

7.2.1 Clinical Laboratory Evaluations

Laboratory studies will include a CBC with differential, metabolic panel (creatinine, BUN, glucose), magnesium, phosphate, urate, liver function tests (bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase), and a serum or urine pregnancy test, if applicable.

7.2.2 Special Assays or Procedures

Plasma levels of palbociclib for will be determined by a validated assay performed at PPD in Richmond, VA. See Appendix C for full instructions on sample storage, handling, and processing for PK/PD analysis. Palbociclib levels will be obtained **within 1 hour prior** to dosing with dexamethasone and palbociclib on days +1 and +8 of induction.

For analyses of molecular markers of palbociclib and dexamethasone response, we will perform western blots of phospho-RB (using antibodies that recognize CDK4/6 phosphorylation sites on RB) and FOXM1 (CDK4/6 substrate which is stabilized by phosphorylation) on lysates from peripheral blood or bone marrow CD19+ cells (obtained by FACS sorting). We will also assess levels of p21, cyclin E, and CDK2 as markers of cell cycle activity.

As markers of Dexamethasone response, we will assess MYB and BCL2 levels in pre-treatment and post-treatment (palbociclib and dexamethasone combination) CD19+ peripheral blood or bone marrow cells.

For analyses of additional markers of drug response, RNA will be isolated from pre-treatment and post-treatment CD19+ cells and used for gene expression profiles (microarray or RNA-Seq).

7.2.3 Specimen Preparation, Handling, and Storage

Details regarding specimen preparation, handling, and storage for palbociclib PK analysis can be found in Appendix C.

Details regarding specimen preparation, handling, and storage for PD analyses can be found in Appendix C.

7.2.4 Specimen Shipment

Details regarding specimen shipping for palbociclib PK analysis can be found in Appendix C.

8 Evaluation of Safety

Patients will be followed for toxicity for one year after the last dose of the study drugs, or until resolution of serious adverse events, if one is noted.

8.1 Specification of Safety Parameters

8.1.1 Unanticipated Problems

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

UAPs are considered to pose risk to participants or others when they suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

These problems are reported to the IRB and are different from, but linked to, regulatory reporting required by the FDA.

8.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

8.1.3 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred)
- Is disabling or incapacitating
- Results in inpatient hospitalization or prolongation of existing hospitalization

- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant or may require intervention to prevent one of the outcomes listed in this definition.

8.2 Safety Assessment and Follow-Up

Adverse event reporting will begin after study treatment, unless the AE/SAE is caused by a study specific screening procedure, and continue until 30 days (for all AEs and SAEs) after the last dose of study treatment or initiation of a new anti-cancer therapy. At each study visit, the investigator (or designee) will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3 Recording Adverse Events

The following subsections detail what information must be documented for each adverse event occurring during the time period specified in Section 8.2 Safety Assessment and Follow-Up. See section 8.4 for reporting details.

8.3.1 Relationship to Study Intervention

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The following guidelines are used to assess relationship of an event to study intervention:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

8.3.2 Expectedness

The PI is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. Risk information to assess expectedness can be obtained from preclinical studies, the investigator's brochure, published medical literature, the protocol, or the informed consent document.

8.3.3 Severity of Event

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

8.3.4 Intervention

Any intervention implemented to treat the adverse event must be documented for all adverse events.

8.4 Safety Reporting

8.4.1 Reporting to IRB

8.4.1.1 *Unanticipated Problems*

All incidents or events that meet criteria for unanticipated problems (UAPs) as defined in Section 8.1.1 Unanticipated Problems require the creation and completion of an unanticipated problem report form (OHR-20).

UAPs that pose risk to participants or others, and that are not AEs, will be submitted to the IRB on an OHR-20 form via the eazUP system within 10 working days of the investigator becoming aware of the event.

UAPs that do not pose risk to participants or others will be submitted to the IRB at the next continuing review.

8.4.1.2 *Adverse Events*

Grade 1 AEs will be reported to the IRB at continuing review.

Grade 2 AEs will be reported to the IRB at the time of continuing review.

8.4.1.3 *Serious Adverse Events*

SAEs will be reported to the IRB on OHR-10 forms via the electronic reporting system (eSAEy) according to the required time frames described below.

Grade 3-4 AEs that are unexpected and deemed to be at least possibly related to the study will be reported to the IRB within 2 working days of knowledge of the event.

Grade 3-4 AEs that are deemed unrelated to the study will be reported to the IRB within 5 working days.

Grade 5 AEs will be reported to the IRB within one working day of knowledge of the event.

All SAEs will be submitted to the IRB at continuing review, including those that were reported previously.

8.4.2 **Reporting to SKCC DSMC**

All AEs and SAEs, safety and toxicity data, and any corrective actions will be submitted to the DSMC per the frequency described in the SKCC DSMP. The report to the SKCC DSMC will also include any unanticipated problems that in the opinion of the PI should be reported to the DSMC.

All non-hematologic adverse events will be reported to the DSMC.

The only hematologic events which will be considered a DLT/AE/SAE for this study are (i) marrow aplasia (defined as <10% cellularity with <10% blasts for ≥ 6 weeks not attributable to disease) (ii) grade 4 neutropenia persisting ≥6 weeks from the start of a cycle that is not attributable to the underlying disease and this will be reported.

All hematologic grade 5 SAEs will be reported to the DSMC regardless of causality.

For expedited reporting requirements, see table below:

DSMC AE/SAE Reporting Requirements

	Grade 1	Grade 2		Grade 3				Grades 4 and 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I - 48 Hours (Death: 24 Hours) Phase II - 5 working days
Possible Probably Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase I - 48 Hours Phase II - 5 working days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I and Phase II - 48 Hours (Death: 24 Hours)

8.4.3 Reporting to Funding Sponsor

SAEs, as well as all other safety information at the end of the study or as requested by the funding sponsor, will be reported to Pfizer within 24 hours of occurrence by faxing the Pfizer SAE Event Form to the Pfizer US Clinical Trial Department at 1-866-997-8322 (Appendix E).

Serious adverse events and all other safety information as defined below will be collected from day -7 of the lead-in period with palbociclib until 28 days after discontinuation. Safety Information is defined as any information from any source containing information such as:

- Adverse event or suspicion thereof
- Lack of efficacy
- Overdose/incorrect dosage (accidental or intentional)
- Abuse/misuse (e.g., patients sharing medication) even without resulting adverse reaction
- Accidental exposure (e.g., child takes parents medication)
- Medication error
- Withdrawal reactions
- Disease progression/exacerbation of existing disease
- Drug-drug/Drug-food interaction
- Reports of unexpected benefit
- Exposure to drug during pregnancy, where the embryo or fetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure).
- Exposure to drug during lactation (including uneventful)
- Suspected counterfeit product
- Suspected transfer of infectious disease/agent by the medicinal product concerned.
- Product complaint report (any deficiencies related to the identity, quality, labeling, durability, reliability, efficacy, performance of a medicinal product, suspected counterfeit product)
- Pediatric use (if not an approved use)
- Occupational exposure
- Off-label use (if not part of the study design)

8.4.4 Reporting to FDA

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. Pfizer Inc. will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs will be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms will be sent to the FDA at:

MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

9 Study Oversight

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the SKCC's Data and Safety Monitoring Committee (DSMC). The SKCC DSMC operates in compliance with a Data and Safety Monitoring Plan (DSMP) that is approved by the NCI.

10 Clinical Site Monitoring and Auditing

Clinical site monitoring and auditing is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC). The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Appropriate staff will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the SKCC DSMP.

11 Statistical Considerations

11.1 Study Hypotheses

No formal hypotheses will be tested in this Phase I study.

11.2 Analysis Plans

This aim will consist of a Phase I trial of palbociclib to determine the maximum tolerated dose (MTD) of palbociclib when given in combination with dexamethasone. A standard 3+3 dose escalation design will be employed: three dose levels of palbociclib will be explored (100mg, 125mg, 150mg). Patients will be treated in cohorts of size three to six and the dosage will be escalated if the clinical toxicity is acceptable.

Patients who experience a DLT during the evaluation period as defined in section 6.2.1 will stop the study drugs and come off of the trial.

Patients who complete the first cycle of maintenance but require treatment to be held up to 4 weeks to achieve count recovery, will have palbociclib resumed with a level -1 dose reduction. A dose-limiting toxicity (DLT) is defined in the table below:

Toxicity	**DLT Criteria***
Hematology	• Marrow aplasia (defined as <10% cellularity with <10% blasts for ≥ 6 weeks not attributable to disease) • Grade 4 neutropenia persisting ≥6 weeks from the start of a cycle that is not attributable to the underlying disease
Cardiac	Any ≥ Grade 3 toxicity
Gastro-intestinal	Any ≥ Grade 3 toxicity except: • Grade 3 nausea, vomiting**, or diarrhea** not requiring total parenteral nutrition (TPN) or tube-feeding
Hepato-biliary	An increase in AST or ALT >3 x ULN and concurrent increase in total bilirubin >2 x ULN (Hy's Law) Any ≥ Grade 3 toxicity except: • Any Grade 3 or 4 liver abnormalities (AST, ALT, or alkaline phosphatase) that resolve to < grade 2 within 72 hours • Grade 3 hyperbilirubinemia that resolves to < grade 2 within 72 hours • Grade 3 indirect hyperbilirubinemia that resolves to < grade 2 within 72 hours
Renal	Any ≥ Grade 3 toxicity
Non-Hematologic	≥ Grade 3, except as noted elsewhere in the table
Exceptions to DLT criteria	• Grade 3 alopecia • Grade 3 fatigue of < 5 days' duration • Grade 3 electrolyte abnormalities that last <72 hours • Infection, unless the investigator determines that the infection resulted from the degree or duration of myelosuppression in the absence of persistent leukemia

* CTCAE version 5.0 should be used for grading.

** Optimal therapy for vomiting and diarrhea should be based on institutional guidelines with consideration of the prohibited medications listed in these protocol guidelines.

The design is constructed to reduce the chance of escalating the dose when the probability of DLT is high, and increase the chance of escalating the dose when the probability of DLT is low. The maximum tolerated dose (MTD) is defined as the highest dose level where a DLT occurs in at most one out of six patients treated. The escalation scheme is as follows:

(1) If none of the initial three patients in a cohort experiences a DLT, then a new cohort of three patients will be treated at the next higher dose level.

(2) If one of the three patients in a cohort experiences a DLT, then up to three additional patients will be treated at the same dose. Escalation will continue if only one of six patients experiences DLT.

(3) If two or more patients in a cohort experience DLT, then the MTD will have been exceeded, and no further dose escalation will occur. The previous dose level will be considered the MTD.

(4) If only three patients were treated at a dose level under consideration as the MTD, then up to three additional patients will be accrued. If no more than one of the six patients at that dose level experience a DLT, then that dose level will be confirmed as the MTD. If two or more patients in that cohort experience DLT, then the previous dose level will be studied in the same fashion.

The MTD is defined as the highest dose studied for which the observed incidence of DLT is less than 33%. Frequencies of toxicities will be tabulated according to the NCI Common Toxicity Criteria. Patients will be continued to be followed for one year for evidence of late toxicity.

Table 1.1 below gives the probabilities of dose escalation based on true DLT risk in the 3+3 design.

	True DLT rate								
	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of escalation	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.01	0.001

All patients treated with at least one dose will be included in the safety analysis.

Response criteria for the study are defined as follows:

Response Criteria
Complete Remission (CR)
No lymphoblasts in the bone marrow
Absolute neutrophil count ≥0.75 x10^9/L

Platelet count ≥75 x 10^9 /L

Complete Remission with Incomplete Hematologic Recovery (CRi)
<5% lymphoblasts in the bone marrow

Partial Remission (PR)
All criteria for CR are satisfied except there are between 5% and 25% lymphoblasts in the bone marrow

Stable Disease (SD)
Failure to achieve at least a PR, but with no evidence of progression as defined as an increase of peripheral blood or bone marrow blasts of more than 10% from nadir during study.

Progressive Disease (PD)
For patients with < 5% blasts at baseline, there must be an increase to ≥ 10% blasts.
For patients with 5% to 10% blasts at baseline, there must be a ≥ 50% increase to > 10% blasts.
For patients with 10% to 20% blasts at baseline, there must be a ≥ 50% increase to ≥ 20% blasts.

Response rate defined as the proportion of patients who achieve a CR, CRi, PR, or SD response will be estimated along with a 95% confidence interval.

11.3 Sample Size Considerations

This traditional 3+3 dose escalation study will include a minimum of 4 and a maximum of 24 participants. The minimum sample size of 4 would be achieved if ≥ 2 patients out of the first 3 patients have a DLT at dose levels 1 and -1. The maximum sample size of 18 would be achieved if 6 patients are enrolled at dose levels -1 through 3 (100 mg, 125mg, 150mg, 175mg). The anticipated sample size is 12-18.

11.3.1 Replacement Policy

Patients need to take 80% of doses in the one week lead-in and Cycle 1 to be evaluable for DLTs. The 80% completion can be non-consecutive days of dosing with study drug within the one week lead-in and Cycle. If a patient is not considered evaluable for DLTs, they must be replaced for the purposes of dose escalation.

11.3.2 Accrual Estimates

We estimate that we will be able to complete accrual within 42 months.

11.4 Exploratory Analysis

Analysis of exploratory endpoints will be descriptive with continuous variables summarized using means, medians, standard deviations, and ranges, and categorical variables summarized using frequencies and percentages. The analyses will occur at the conclusion of the trial.

Plasma levels of palbociclib will be determined on days 1 and 8 of induction and changes will be summarized by dose level. Phospho-RB and FOXM1 will be assessed by Western blot at days 1 and 8 of induction. MYB, BCL2, p21, CDK2, cyclin E, S-Phase, Annexin, V/Caspase 3 will be assessed by gene expression profiles (microarray or RNA-Seq) on days 1 and 8 of induction.

12 Source Documents and Access to Source Data/Documents

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of participant information. Study staff will permit authorized representatives of SKCC and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

13 Quality Control and Quality Assurance

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of participant information. Study staff will permit authorized representatives of SKCC and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

14 Ethics/Protection of Human Participants

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

14.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

14.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

14.4 Exclusion of Women, Minorities, and Children (Special Populations)

Individuals age 18 years or older will not be excluded based on gender, race or economic status.

14.5 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

14.6 Future Use of Stored Specimens and Other Identifiable Data

No residual specimens will be maintained after the study is complete.

15 Data Handling and Record Keeping

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents must be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

15.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

15.2 Data Capture Methods

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

15.3 Types of Data

Safety, laboratory (clinical, pharmacokinetic, and pharmacodynamic), and outcome data will be recorded. Accrual data will be recorded and will be monitored quarterly by the MDG.

15.4 Study Records Retention

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

Study documents must be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

15.5 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to the IRB and other regulatory bodies according to their requirements

16 Study Finances

16.1 Funding Source

This study will be funded by Pfizer, Inc and Thomas Jefferson University.

16.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

16.3 Participant Stipends or Payments

Participants will not receive payment for participation in the study.

17 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or

concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

18 **Literature References**

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4. Gökbuget, N., et al., *Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation.* Blood, 2012. **120**(10): p. 2032-2041.
5. Oriol, A., et al., *Outcome after relapse of acute lymphoblastic leukemia in adult patients included in four consecutive risk-adapted trials by the PETHEMA Study Group.* Haematologica, 2010. **95**(4): p. 589-596.
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7. Jain, N., et al., *Ph-like acute lymphoblastic leukemia: a high-risk subtype in adults.* Blood, 2017. **129**(5): p. 572-581.
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9. O'Rourke, J.P. and S.A. Ness, *Alternative RNA Splicing Produces Multiple Forms of c-Myb with Unique Transcriptional Activities.* Molecular and Cellular Biology, 2008. **28**(6): p. 2091-2101.
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12. Sarvaiya, P.J., et al., *Role of c-Myb in the survival of pre B-cell acute lymphoblastic leukemia and leukemogenesis.* American Journal of Hematology, 2012. **87**(10): p. 969-976.
13. Inaba, H. and C.-H. Pui, *Glucocorticoid use in acute lymphoblastic leukemia: comparison of prednisone and dexamethasone.* The Lancet Oncology, 2010. **11**(11): p. 1096-1106.
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15. Jing, D., et al., *Opposing regulation of BIM and BCL2 controls glucocorticoid-induced apoptosis of pediatric acute lymphoblastic leukemia cells.* Blood, 2015. **125**(2): p. 273-283.

Appendices

The following documents are officially affiliated with the protocol and will be submitted to the IRB as a part of the protocol. As such, changes to these items require a protocol amendment.

Appendix A: Schedule of Events

Appendix B: ECOG Performance Status

Appendix C: Sample Handling, Processing, and Storage Instructions

Appendix D: Requesting a Dose Escalation/Expansion Approval

APPENDIX A: SCHEDULE OF EVENTS

	Baseline	Induction Day+1	Induction Day +4[10]	Induction Day +8	Induction Day +12[10]	Induction Days +14 and +21[10]	Induction Day +28[10]	Maintenance Cycle 1 (weekly)	Maintenance Day +28[10] *	Maintenance Cycles 2-6 (every other week)[11]	Follow-up[7,8]
Informed Consent	X[1]										
Medical/Oncologic History	X[1]										X
Physical Examination (including neurological exam)	X[1]	X		X			X		X		
Vital Signs	X[1]	X		X			X		X		
Performance Status	X[1]										
Review of concomitant medications	X[1]	X		X			X		X		X
Adverse Event Assessment		X		X			X		X		X[6]
Laboratory Studies											
CBC with differential	X[1]	X	X	X	X	X	X	X	X	X	
Serum Chemistry, Electrolytes	X[1,7]	X[7]	X	X[7]	X	X	X[7]	X	X[7]	X	
Liver Function Tests	X[1]	X	X	X	X	X	X	X	X	X	
Pregnancy test	X[1,2]										
Pharmacokinetics		X[3]		X[3]							
Pharmacodynamics	X[3]	X[3]		X[3]							
Tests & Studies											
Bone Marrow Biopsy/Aspirate[9]	X[1,4]						X		X		X[5]
Investigational Agent											
Pill Diary Given to Patient	X[1]										

Note: Palbociclib will be given with a one week lead-in starting on Day -7 to Day -1.
*Patients who continue treatment for multiple cycles will have the maintenance Day +28 procedures repeated for each cycle.

1. To be done within twenty-one days prior to first dose of study drug unless otherwise indicated (with exception to the bone marrow biopsy/aspirate which is required at any time prior to study treatment). Informed consent, baseline procedures, and confirmed eligibility must be completed prior to the one week lead in with Palbociclib (starting on Day -7)
2. Only perform for females of child bearing potential (serum or urine)
3. Blood to be drawn prior to administration of palbociclib and dexamethasone on day +1, and day +8. PK samples will be one tube of 3-4mL. PD samples are 10mL each.
4. The bone marrow aspirate may be replaced by 20 mLs of peripheral blood if the patient has a peripheral leukemic blast count ≥200/μl.
5. In patients who attain a CR, a bone marrow should ONLY be performed after cycle 1 maintenance if there is a suspicion/evidence of relapse based on peripheral blood studies or other clinical indications during the follow up period.
6. All AEs will be followed until resolution. Patients will be monitored for AEs for 30 daysafter the end of therapy or until initiation of a new anti-cancer therapy.
7. Serum chemistry and electrolytes labs should include: creatinine, BUN, glucose, magnesium, phosphate, and urate. Liver function labs should include: bilirubin, SGOT (AST), SGPT (ALT), alkaline phosphatase.
8. Patients will be followed for disease status until relapse/progression
9. Correlative studies will be performed by the Calabretta laboratory on peripheral blood or bone marrow.
10. Labs and bone marrow biopsy/aspirate may be performed ±2 days from the desired study day.
11. Patients who remain on maintenance for >6 months may have labs checked monthly.

APPENDIX B: ECOG PERFORMANCE STATUS

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.:*Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

APPENDIX C: SAMPLE HANDLING, PROCESSING, and STORAGE INSTRUCTIONS FOR PK and PD SAMPLES

Suggested Sample Handling, Processing and Storage Instructions for Palbociclib (PD-0332991):

Pharmacokinetics of Palbociclib

- Blood samples (3 or 4 mL, depending on the availability of the blood collection tube) to provide a minimum of 1.0 mL of plasma for pharmacokinetic analysis of Palbociclib will be collected into appropriately labeled[1] tubes containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) per time point.

- 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 -20°C within 1 hour of collection.

- To process the blood samples to plasma, centrifuge the blood samples in a refrigerated centrifuge at approximately 4 °C 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 -20°C until shipment. If a -20°C freezer is not available at the site the samples may be stored at -80°C. Palbociclib is stable at -20°C and -80°C for 439 days in frozen K_2EDTA plasma.

- Ship the frozen samples on dry ice to the contract bioanalytical laboratory.

[1] All information added to the labels should be written with an indelible marker; water-based inks will smear during thawing, making the label unreadable rendering the written information useless. Labels should be affixed only to DRY surfaces.

Labels should contain, at a minimum, the following information:
-Protocol # or Pfizer IIR Tracking #
-Investigator Name
-Subject ID
-Sample Matrix (e.g. plasma)
-Analyte (e.g. palbociclib)
-Visit (e.g. C1D15)
-Nominal Sampling Time (e.g. 1Hr)

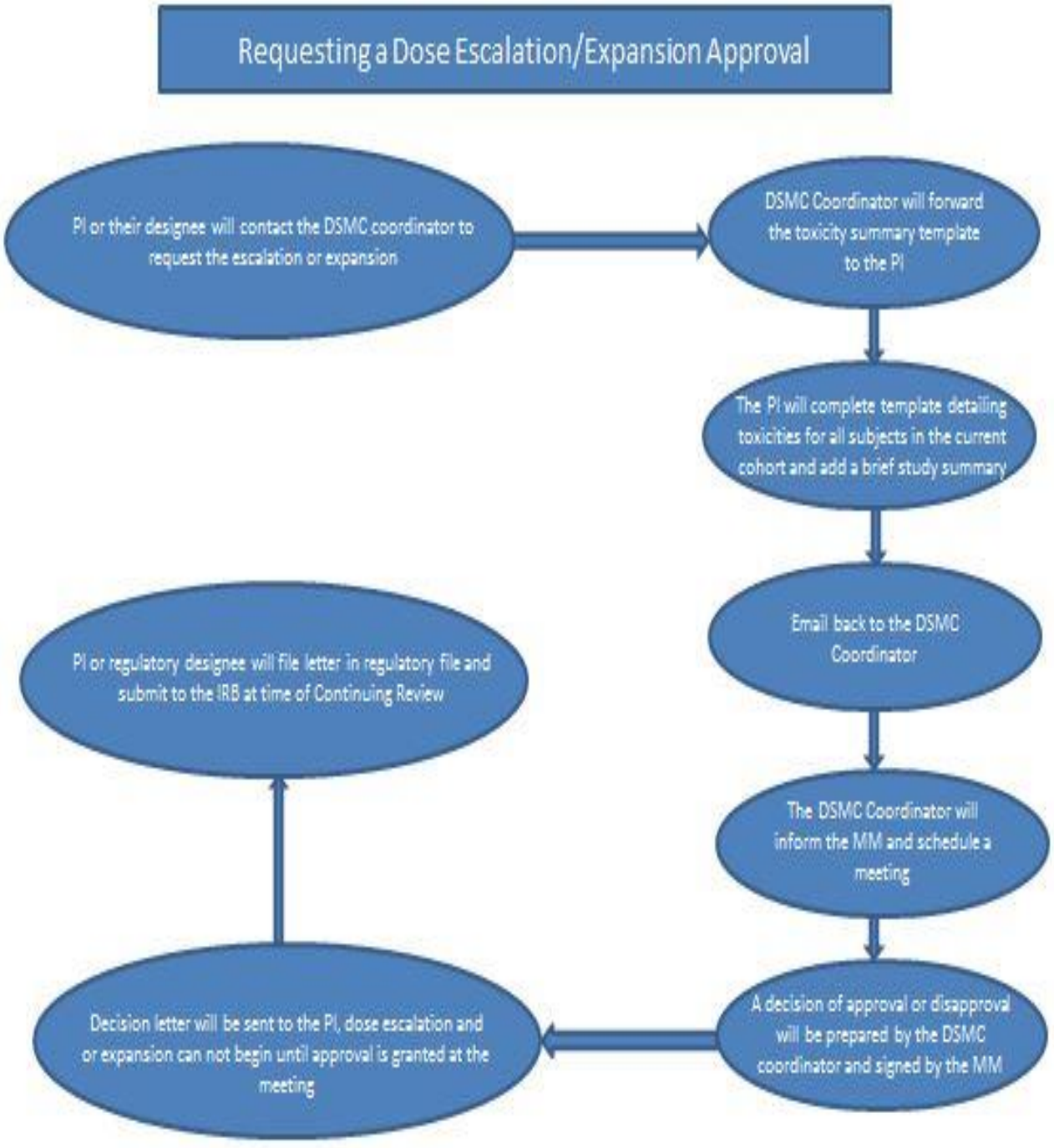
Sample Shipment
Contract bioanalytical laboratory contact and shipping address will be provided at a later date by email.

Laboratory Address: PPD Inc 2244 Dabney Road
Richmond, VA 23230-3323 United States

Suggested Sampling, Handling, Processing, and Storage Information for PD Analyses

Pre-treatment and post-treatment peripheral blood and/or bone marrow samples (10 mL/each) will be collected in heparinized 10-ml green-top tubes and transported in ice to Dr. Calabretta's laboratory (Bluemle Building room 630). Samples will be immediately processed by removing red blood cells using an Ammonium Chloride solution (Stem Cell Technology). Then, mononuclear cells will be purified through Ficoll Hypaque centrifugation and subjected to FACS-sorting to isolate CD19+ B-cells. From these cells, we will obtain whole lysates for western blot analyses and total RNA for gene expression profiles (microarrays or RNA-Seq). Cell lysates and RNAs will be stored at -70 degrees. We anticipate that we will obtain enough cells (ideally, 5-10 x 10^6 cells/sample) to extract proteins and RNA. If the number of CD19+ cells is insufficient, we will give priority to the preparation of whole cell lysates for western blot analyses of palbociclib and dexamethasone response biomarkers.

Appendix D: Requesting a Dose Escalation/Expansion Approval



Appendix E: Pfizer SAE Report Form

Investigator-Initiated Research or Clinical Research Collaboration
Interventional Study Serious Adverse Event Report Form

For Pfizer internal use only

AER # (insert when known)	Local #	Date Reported to Pfizer
		___-_____-____

PROTOCOL # SUBJECT #

Protocol Title: A Phase I Trial of Palbociclib in Combination with Dexamethasone in Relapsed or Refractory Adult B-Cell Acute Lymphoblastic Leukemia (ALL)

☐ Initial Report ☐ Follow Up Report **Country where event occurred:**

Patient Data Date of Birth DD-MMM-YYYY ☐ Male ☐ Female Height: ☐ in ☐ cm Weight: ☐ lb ☐ kg

Patient's Race:
☐ Asian ☐ Black or African American ☐ Native Hawaiian or other Pacific Islander ☐ American Indian or Alaska Native
☐ White ☐ Unknown ☐ Cannot ask per local regulations, Other (specify):

Patient's Ethnicity: ☐ Hispanic or Latino ☐ Not Hispanic or Latino ☐ Unknown

If patient has died: Date of Death DD-MMM-YYYY Cause(s) of Death Determined by Autopsy: Y ☐ N ☐ Unknown ☐
If yes, what was the autopsy determined cause of Death:

Patient History ☐ None ☐ Unknown *Provide relevant medical history below. Include other illnesses present at time of event and pre-existing medical conditions. If additional space is necessary, use additional copies of this page.*

Illness (specify)	Onset Date	Stop Date	Check box if Ongoing	Pertinent Details *Include surgical procedures and dates*
	--	--	☐	
	--	--	☐	
	--	--	☐	
	--	--	☐	

Study Drug (Trade and Generic), Formulation, Route, Indication	Check box if Pfizer Drug	Dose	Units	Frequency	Start Date	Stop Date	Check box if Ongoing
	☐				--	--	☐
	☐				--	--	☐
	☐				--	--	☐
	☐				--	--	☐

Concomitant Drugs ☐ None ☐ Unknown *List below concomitant drugs taken within two weeks before the event onset. Exclude all drugs only administered more than two weeks before the event, and any drug used to treat the event or taken after event onset. If additional space is necessary, use additional copies of this page.*

Drug Name (Trade and Generic)	Reason for Use	Route	Start Date	Stop Date	Check box if Ongoing
			--	--	☐
			--	--	☐
			--	--	☐
			--	--	☐

Relevant Tests *List only relevant confirmatory test results for adverse event(s), for example, from blood tests, diagnostic imaging. If additional space is necessary, use additional copies of this page.*

Test	Date	Result	Units	Normal Range Low	Normal Range High	Comments
	--					
	--					
	--					
	--					

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Investigator-Initiated Research or Clinical Research Collaboration
Interventional Study Serious Adverse Event Report Form

For Pfizer internal use only

AER # (insert when known)	Local #	Date Reported to Pfizer

PROTOCOL # SUBJECT #

ADVERSE EVENTS *(if more than two, use additional copies of this page)*
Specify diagnosis if known, rather than symptoms or signs

Serious Adverse Event Term	**Serious Adverse Event Term**
Onset Date:	Onset Date:
Seriousness Criteria (Check all that apply): ☐ Resulted in death ☐ Life-threatening ☐ Hospitalization/Prolongation of hospitalization ☐ Persistent/Significant disability/incapacity ☐ Congenital anomaly/Birth defect ☐ Important medical event	**Seriousness Criteria (Check all that apply):** ☐ Resulted in death ☐ Life-threatening ☐ Hospitalization/Prolongation of hospitalization ☐ Persistent/Significant disability/incapacity ☐ Congenital anomaly/Birth defect ☐ Important medical event
Status at date of report or at death: ☐ Recovered } Date of ☐ Recovered with sequelae } Recovery: ☐ Recovering ☐ Not Recovered ☐ Unknown	**Status at date of report or at death:** ☐ Recovered } Date of ☐ Recovered with sequelae } Recovery: ☐ Recovering ☐ Not Recovered ☐ Unknown
Is there a reasonable possibility that the event is related to Study Drug? (specify): ☐ Yes ☐ No ☐ Yes ☐ No	**Is there a reasonable possibility that the event is related to Study Drug? (specify):** ☐ Yes ☐ No ☐ Yes ☐ No
Is there a reasonable possibility that the event is related to Concomitant Drug? (specify): ☐ Yes ☐ No ☐ Yes ☐ No	**Is there a reasonable possibility that the event is related to Concomitant Drug? (specify):** ☐ Yes ☐ No ☐ Yes ☐ No
Last Action Taken in Response to Event(s); specify drug name:	**Last Action Taken in Response to Event(s); specify drug name:**
☐ Withdrawn (temporarily or permanently, or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Withdrawn (temporarily or permanently or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable
☐ Withdrawn (temporarily or permanently, or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Withdrawn (temporarily or permanently or delayed) ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable
Did an SAE recur with re-administration of drug? ☐ Yes ☐ No ☐ Unknown ☐ Not Applicable If yes, which drug?:	Did an SAE recur with re-administration of drug? ☐ Yes ☐ No ☐ Unknown ☐ Not Applicable If yes, which drug?:

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Interventional Study Serious Adverse Event Report Form

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AER # (insert when known)									

Local #	Date Reported to Pfizer
	-- --- ---

PROTOCOL # SUBJECT #

Event Narrative

Provide any information regarding the circumstances, sequence, diagnosis and treatment of the event(s) not otherwise reported on this form. If additional space is necessary, use additional copies of this page.

Report Comments:

Report:

First Name	Last Name (Please PRINT)		Date: DD-MMM-YYYY
Address: 1015 Chestnut Street, 7th Floor (Street)	Philadelphia/PA (City / State)	19107 (Zip Code)	USA (Country)

Telephone: Fax: 215-923-9974 Email:

Investigator/Designee Name: **Investigator/Designee Signature:**

Investigator/Designee Awareness Date: DD-MMM-YYYY

Report this form to Pfizer within 24 hours of awareness or immediately in case of death and life-threatening SAEs.

RECORD ALL PERTINENT INFORMATION ON THE FORM. DO NOT ATTACH SOURCE DOCUMENTS.

Pfizer	REPORTABLE EVENT FAX COVER SHEET (US)	

Use this fax cover sheet to fax a reportable event for investigator-initiated research studies

Include with this form the completed Pfizer investigator-initiated research (IIR) serious adverse event (SAE) form, MedWatch Form FDA 3500A-Mandatory Reporting, which can be obtained from the FDA website: www.fda.gov/medwatch/getforms.htm, or other Pfizer agreed-upon form for SAE reporting. If you are using the MedWatch Form to report, the following information should be included in block 5 of the adverse events section:

- The complete clinical course of the patient receiving Pfizer drug
- The causality assessment for each reportable event
- The action taken for each study drug and for each reportable event
- The outcome for each reportable event

This cover sheet MUST be provided with each completed SAE form.

Do not substitute forms/reports or submit additional documentation (such as source documentation) other than what is required.

Do not fax these forms to any additional fax numbers other than the one listed below.

TO:	*Pfizer U.S. Clinical Trial Department*	
FAX:	*1-866-997-8322*	
FROM:		DATE:
TELEPHONE:		FAX:
NUMBER OF PAGES:		
PRODUCT	~~Palbociclib~~	
PFIZER REFERENCE NUMBER	WI227561	EXTERNAL REFERENCE NUMBER
STUDY TITLE	A Phase I Trial of ~~Palbociclib~~ in Combination with Dexamethasone in Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL)	
PATIENT NUMBER		
INVESTIGATOR	Margaret Kasner	

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