Division of Hematology/Oncology and
Bone Marrow and Hematopoietic Cell Transplant Program
Department of Medicine
Tufts Medical Center

# RANDOMIZED PHASE II STUDY OF LYMPHOID TUMOR MICROENVIRONMENTAL TARGETING WITH DUVELISIB (IPI-145) PRIOR TO, AND FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION

Version Date: May 4, 2016

Sponsor-Investigator: Andreas Klein, M.D.

Co-Investigators: Andrew Evens, D.O.
Anita Kumar, M.D.
Kenneth Miller, M.D.
Kellie Sprague, M.D.

Agent: Duvelisib (IPI-145)
IND#



Executive Summary
Long term immunologic memory is maintained through an active program in B- and T-cells that prevents apoptosis through interaction with the microenvironment. Lymphoid malignancies can co-opt this program to avoid apoptosis in the setting of treatment, contributing to chemotherapy resistance. The intracellular kinase PI3k integrates microenvironmental signaling to affect changes in the apoptotic threshold. Targeting PI3k may decrease chemotherapy resistance. In this study, consenting subjects with mature lymphoid malignancy (ie chronic lymphocytic leukemia or lymphoma) who are scheduled to undergo high dose chemotherapy and autologous stem cell transplant will be randomized (2:1) to receive Duvelisib (IPI-145) 25 mg orally vs matched placebo twice daily starting two weeks prior to the start of high dose chemotherapy and continuing until transplant day -6. Following transplant, subjects who do not achieve a complete molecular response are at high risk for failure and will be assigned to receive Duvelisib 25mg twice daily for up to 2 years as maintenance therapy.

**PROTOCOL SIGNATURE PAGE**

Protocol title: Randomized Phase II study of Lymphoid Tumor Microenvironmental Targeting with Duvelisib (IPI-145) Prior to and Following Autologous Stem Cell Transplantation

**VERSION DATE: 06MAR2016**

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the Investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email or fax the completed form to NCCCR and keep a record for your files.

_____ _____

Signature of Investigator Date

_____

Investigator Name (printed)

_____

Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

_____ ❑ Not Submitting to IRB

Expected IRB Approval Date

**PLEASE COMPLETE AND EMAIL/FAX COPY TO NCCCR**

## 2 STUDY OBJECTIVES

### 2.1 Primary Objectives

2.1.1 Determine the molecular complete response rate of duvelisib vs. placebo as chemosensitization at day +42 following high dose chemotherapy for relapsed/refractory or high risk lymphoid malignancy.

2.1.2 Determine the safety and effectiveness in terms of clinical relapse prevention of open label duvelisib daily for two years in patients not achieving molecular complete response following autologous transplant (day +42).

### 2.2 Secondary Objectives

2.2.1 Assess the safety of the addition of duvelisib given twice daily for two weeks and then concurrent with high dose chemotherapy prior to autologous stem cell transplantation.

2.2.2 Assess transplant outcomes including time to neutrophil engraftment, platelet engraftment, tumor response and response duration, comparing duvelisib versus placebo.

2.2.3 Assess the rate of molecular response (conversion from molecularly detectable to undetectable lymphoma) in patients receiving open label duvelisib

2.2.4 Assess the rate of infections due to reactivation of chronic viral infections including cytomegalovirus following HDCT, comparing open label duvelisib to observation

2.2.5 Assess the rate of infections due to opportunistic organisms including pneumocystis jiroveci following HDCT, comparing open label duvelisib to observation

### 2.3 Exploratory Objectives

2.3.1 Determine the extent to which tumor cells are mobilized into the peripheral blood following one and two weeks of study as assessed by peripheral blood flow cytometry and cellular and cell-free tumor DNA, comparing duvelisib versus placebo.

2.3.2 Compare the apoptotic fraction of circulating tumor cells before and after two weeks of study drug and high dose chemotherapy as determined by the proportion of Annexin V staining tumor cells measured by peripheral blood flow cytometry, comparing duvelisib versus placebo.

2.3.3 Assess the kinetics of microenvironmental disruption reflected in tumor cell and DNA release into the peripheral blood following the administration of study drug, comparing duvelisib versus placebo.

2.3.4 For subjects consenting to serial lymph node aspiration, compare the apoptotic potential of tumor cells aspirated from a lymph node before and at intervals after two weeks of study drug as determined by the proportion of Annexin V staining tumor cells.