Open Label Phase 2 Single Agent Study of LCL-161 in Patients with Primary Myelofibrosis (PMF), Post-Polycythemia Vera Myelofibrosis (Post-PV MF), or Post-Essential Thrombocytosis Myelofibrosis (Post-ET MF)

Novartis Study #:	**CLCL161AUS02T**
MDACC Protocol #:	**2013-0612**
Investigator Name:	**Naveen Pemmaraju, MD**
	Assistant Professor, Dept of Leukemia, MD Anderson
Investigator Contact Information:	**T: 713-792-4956,**
	npemmaraju@mdanderson.org
	MD Anderson Cancer Center
	Unit 428
	PO BOX 301402
	Houston, TX 77230-1402
Co-Investigator:	**Srdan Verstovsek, MD, PhD**
	Professor, Dept of Leukemia, MD Anderson

Amendment 10

July 9, 2019

Table of contents

List of abbreviations

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
ALT	Alanine aminotransferase/serum glutamic pyruvic transaminase/SGPT
AST	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase/SGOT
AUC	Area under the plasma concentration-time curve
CL/F	Systemic clearance (where F is the fraction of the dose absorbed)
CL/F	Apparent oral clearance
Cmax	Maximum (peak) concentration of drug
CNS	Central nervous system
DLT	Dose limiting toxicity
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
GLP	Good laboratory practice
Hr	Hour
IAP	Inhibitor of Apoptosis proteins
IC_{50}	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MTD	Maximum tolerated dose
PD	Pharmacodynamics
PK	Pharmacokinetics
QD	Once daily
REB	Research Ethics Board
SAE	Serious Adverse Event

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cycle	Number and timing or recommended repetitions of therapy are usually expressed as number of days (eg: q28 days)
Enrollment/Enrolled	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug.”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/healthy volunteer who enrolls in the study
Phase	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatments

Primary myelofibrosis (PMF) is a rare hematologic malignancy (approximately 0.4-1.3 cases per 100,000 people in United States/Australia/Europe). PMF is one of the three classical BCR/ABL negative myeloproliferative neoplasms (MPN), along with essential thrombocytosis (ET) and polycythemia vera (PV) Initially postulated as an MPN in the 1950's by William Dameshek, PMF is now recognized as a clonal hematopoietic stem cell disorder in which 50% of patients have a constitutively activated mutation in the Janus kinase (JAK)2 gene, most commonly at V617F. Patients with ET and PV can acquire over time features of myelofibrosis, then called Post-Polycythemia Vera Myelofibrosis (Post-PV MF), or Post-Essential Thrombocytosis Myelofibrosis (Post-ET MF).

The primary pathogenic mechanism in MF is the unchecked proliferation of a pluripotent stem cell clone that leads to ineffective erythropoiesis, dysplastic-megakaryocyte hyperplasia, and an increase in the ratio of immature granulocytes to total granulocytes. This clonal myeloproliferation is characteristically accompanied by reactive myelofibrosis (bone marrow fibrosis) and by extramedullary hematopoiesis in the spleen or in multiple organs. The diagnosis is often suspected when teardrop-shaped red cells and myeloid precursors are detected in the peripheral blood. The typical clinical features include marked splenomegaly, progressive anemia, and constitutional symptoms. The terms "myeloid metaplasia" and "extramedullary hematopoiesis" are used interchangeably to describe a pathologic process of ectopic hematopoietic activity that may occur in any organ system but that affects primarily the liver and spleen.

At the molecular level, a JAK2 tyrosine kinase mutation (JAK2V617F) can be demonstrated in MF in approximately half of patients, with most being homozygous for such mutation. To date, however, many other mutations have been discovered in patients with MPN (up to 20 at last count), sometimes few present in a single patient, in different cell clones. What has become clear over last two years is the relationship between dysregulated JAK-STAT (signal transducer and activator of transcription) signaling and the signs and symptoms of MPNs. The understanding of dysregulated JAK-STAT activity in MPNs as the basic pathophysiologic abnormality in practically all patients with MPNs has led to the clinical development of several JAK2 inhibitors.

Adverse prognostic factors for survival include older age and anemia (hemoglobin < 10 gm/dL). The etiology for the latter finding is usually multifactorial and related both to marrow failure and hypersplenism. Poor prognosis has also been correlated with leukocytosis, leukopenia, circulating blasts, increased numbers of granulocyte precursors, thrombocytopenia, abnormal karyotype, and hypercatabolic symptoms. The course of the disease is highly variable. Median survival from time of diagnosis ranges from 3 to 6 years; survival rates are 68% at 2 and 40% at 5 years. The usual causes of death are progressive marrow failure, body wasting, transformation into acute myeloid leukemia, and/or portal hypertension.

Treatment of PMF

Patients with acceptable quality of life and no threatening hematologic abnormalities, such as erythrocytosis or thrombocytosis, are customarily observed without any therapy. Hydroxyurea is the most commonly used agent in the proliferative phases of the disease. Interferon-alpha had yielded hematologic responses and reductions in splenomegaly in 30% to 50% of subjects, especially those in a proliferative phase; however, conventional interferon-alpha therapy is frequently poorly tolerated. Therapies aimed at improving the anemia found in patients with MF include androgens and/or erythropoietin. Splenectomy and/or splenic irradiation have been used to manage symptomatic splenomegaly. Splenectomy has been associated with risk of leukemic transformation in some series, and splenic irradiation can result in severe myelosuppression. Benefit to a subset of subjects has been demonstrated for both allogeneic SCT and several novel drugs, including the thalidomide-derived immunomodulatory analogs known as immunomodulatory drugs (IMiDs; i.e. lenalidomide, pomalidomide).

Several JAK2 (or JAK1/JAK2) inhibitors are currently in clinical trials for MF. Ruxolitinib (formerly INCB018424; Incyte Corporation, Wilmington, DE, USA) recently became the first FDA-approved drug for the treatment of MF. Ruxolitinib is a potent and selective JAK1- and JAK2-inhibitor. Treatment with ruxolitinib is associated with a dramatic decrease in circulating levels of proinflammatory cytokines, IL-6, and tumor necrosis factor (TNF)-α, which have been implicated in the pathogenesis of MPNs. Proinflammatory cytokines are known to be at very high levels in MF and to contribute to the disease pathogenesis. Primary benefit of ruxolitinib in MF is significant decrease in organomegaly (splenomegaly and hepatomegaly) and significant improvement in quality of life and the therapy controls debilitating MF-related systemic symptoms, improves patients ability to walk, and patients gain weight. It does not improve anemia, and it does not improve the bone marrow fibrosis.

1.2 Overview of LCL161 and apoptosis

LCL161 is a biostable, cell-permeable, small molecular weight SMAC-mimetic compound. It is an orally bioavailable pan-IAP inhibitor that demonstrates anti-tumor efficacy as a single agent in a small subset of cell lines, and in many more cell lines and xenograft models when given in combination with paclitaxel.

Apoptosis, or programmed cell death, plays a critical role in regulating cell number and eliminating stressed or damaged cells from normal tissues and provides a major barrier to the development and progression of human cancer. Cancer cells have evolved mechanisms to ensure their survival, often including ways to avoid activation of apoptosis. Many commonly used antineoplastic therapies rely on overriding these mechanisms to trigger apoptosis.

Apoptosis signaling networks are classified as either intrinsic and mediated by cellular stress and mitochondrial permeability, or extrinsic and mediated by death receptor-ligand interactions (Ashkenazi and Dixit 1998, Green and Reed 1998). Both pathways ultimately converge on caspases, the enzymatic mediators of cell destruction. One class of negative regulatory molecules is the Inhibitor of Apoptosis (IAPs) proteins (Tamm et al 2000,

Hofmann 2002, Krajewska et al 2003, Shiraki et al 2003, Tamm et al 2004). The ability of IAP proteins to buffer an apoptotic signal is regulated by SMAC/Diablo (Second mitochondrial activator of cytochrome *c*), a mitochondrial protein (Du et al 2000, Verhagen et al 2000). SMAC is released from mitochondria upon activation of the intrinsic apoptotic pathway, and it's binding to IAPs promotes apoptosis. The observation that short SMAC-derived peptides could inhibit the caspase 9-XIAP interaction *in vitro* hinted at a therapeutic utility for SMAC (Chai et al 2000). Agents that, like SMAC, could disengage IAPs from caspases may potentially sensitize cancer cells to apoptotic stimuli.

SMAC-mimetic agents developed by multiple groups have expanded our understanding of the roles of IAPs in cells, and have demonstrated activity as single agents in a subset of tumor cell lines (Li et al 2004, Gaither et al 2007, Varfolomeev et al 2007, Vince et al 2007). Analysis of the basis for the single agent activity has revealed the role of the cIAP1 and cIAP2 proteins as E3 ligases that modify the function of multiple proteins in the TNF/death receptor signaling cascade to control NF-κB activity. Treatment with SMAC-mimetic compounds disrupts signaling by stimulating auto-ubiquitination and degradation of cIAP1 and in the presence of TNFα, this promotes formation of a death-inducing signaling complex and apoptosis (Gyrd-Hansen and Meier 2010; Wu et al 2007).

1.2.1 Preclinical experience

In vitro pharmacology

LCL161 binds with high affinity to XIAP, cIAP1, and cIAP2 through their BIR3 domains. LCL161 binding to cIAP1 causes cIAP1 autoubiquitination and degradation of cIAP1 and cIAP2 by the proteosome in a dose-dependent manner. Loss of cIAP1 occurs rapidly (within 30 minutes) in both sensitive and insensitive cell lines. Since this phenomenon is also observed in human PBMCs, the measurement of cIAP1 protein levels is a useful pharmacodynamic biomarker. The binding of LCL161 to XIAP interferes with XIAP's ability to interact with and repress caspase 9, but does not impact XIAP protein levels.

LCL161 exhibits single agent cellular activity with an $IC_{50} < 1$ μM in ~5% of tumor cell lines representing a wide range of tumor histotypes. Single agent sensitive lines include, but are not limited, to SKOV-3 (ovarian), MDA-MB-231, EVSA-T and UACC732 (breast), HCC44 (lung, adenocarcinoma), Kym-1 (sarcoma), REh, HSB-2 and CCRF-CEM (ALL). SKOV-3 and MDA-MB-231 are among the most sensitive with IC_{50}s in the 10 nM range. The basis for single agent activity is related to baseline and compound-induced NF-κB and TNF-α expression levels, but expression levels alone are insufficient to predict single agent activity (Gaither 2007, Petersen 2007, Varfolomeev 2007, Vince 2007).

In vivo pharmacology

Since the MDA-MB-231 human breast cell line was highly sensitive to LCL161 *in vitro*, the single agent activity of LCL161 was assessed in an MDA-MB-231-based orthotopic nude mouse xenograft model. LCL161 demonstrated dose-dependent anti-tumor activity corresponding to a tumor over control (T/C) value of 24% and 9% for the two doses tested (28.9 mg/kg PO, BID and 57.8 mg/kg PO BID, respectively, $p < 0.05$). LCL161 dosed at 10.8 mg/kg PO BID had no significant anti-tumor effect, corresponding to T/C value of 48% ($p > 0.05$). For comparison, the positive reference compound paclitaxel, dosed at a maximum

tolerated dose of 12.5 mg/kg, iv, 2x/week, resulted in a T/C value of 19% at study termination ($p < 0.05$).

Plasma and tumor exposure assessed at study termination were dose proportional over the tested range. The tumor-to-plasma ratios of LCL161 were approximately 1-2 fold in all three dose groups. The doses of LCL161 resulting in single agent anti-tumor activity, i.e., T/C values of 24% and 9%, provided estimated plasma $AUC_{0\text{-}24h}$ of approximately 18,600 nM.h (9,300 ng.h/mL) and 25,000 nM.h (12,500 ng.h/mL), respectively.

1.2.2 Animal pharmacokinetics and drug metabolism

The pharmacokinetics of LCL161 was investigated in the rat, dog, and monkey. LCL161 is rapidly and extensively absorbed in all animal species tested after an oral dose. The compound has a low to moderate plasma clearance and a moderate to high volume of distribution at steady state, indicating wide tissue distribution. LCL161 is highly bound to plasma protein across all species examined with saturable plasma protein binding at high concentrations. Results from the rat ADME study demonstrated that [^{14}C]LCL161 is mainly excreted into feces, with minor renal excretion (~21%), and this was confirmed in orally dosed, bile duct cannulated animals. The major metabolic pathway for LCL161 based on *in vitro* studies in human hepatocytes involves cytosolic NADPH-dependent carbonyl reductase(s) (~60%), while a minor pathway exists for oxidative metabolism (~40%) by CYP2C8 and by CYP3A4. No unique, major metabolites were identified in human hepatocytes. LCL161 is a P-glycoprotein (P-gp) substrate, which may affect the distribution of LCL161 to tissues expressing this efflux transporter (e.g., brain).

With respect to potential drug-drug interactions (DDI), *in vitro* data suggested that there is a high risk for clinically relevant CYP3A4/5 time-dependent inhibition ($K_I \sim 0.8$ μM) and a clinical drug-drug interaction study with midazolam (CLCL161A2105) confirmed this finding in vivo. LCL161 is also a reversible CYP2B6 inhibitor (Ki ~ 0.2 μM) based on in vitro data; the clinical relevance has not been confirmed in vivo.

1.2.3 Animal toxicology

Safety pharmacology studies demonstrated that LCL161 had no significant effects on the function of the central nervous system (CNS), cardiovascular and respiratory systems. It is also considered non-genotoxic, as shown by the results of *in vitro* genetic toxicology studies.

In the general toxicology studies, LCL161 was administered to rats and monkeys by oral (gavage) for up to 4-weeks with once daily dosing. The doses for the 4-week rat study were: 0 (control), 3, 10 and 20 mg/kg/day, and the doses for the 4-week monkey study were 0 (control), 10, 30 and 45 mg/kg/day. The following are considered the main target organs of toxicity: lymphoid hyperplasia and general inflammation in both rats and monkeys and bone/joint lesions in rats only. The STD_{10} in the rat was determined to be 10 mg/kg/day, with steady-state systemic exposure ($AUC_{0\text{-}24h}$) of 19,800 ng.hr/mL (males and females combined), and the highest non-severely toxic dose (HNSTD) in monkeys was 30 mg/kg (360 mg/m^2, males and females combined). General inflammation was the most prominent finding in the daily dosed toxicology studies. In rats, inflammatory changes were observed in mesenteric and mandibular lymph nodes, the spleen, the skin, bone/joints, bone marrow, serosa/adventitia of thoracic, abdominal and subcutaneous organs/tissues, lungs, gastrointestinal (GI) tract and liver. In general, the lesions were dose dependent and fully reversed, or showed a tendency

towards reversibility upon drug withdrawal. Clinical pathology changes in rats were also indicative of inflammation, including decreases in lymphocytes and eosinophils, increases in neutrophils and monocytes, and abnormal neutrophil and lymphocyte morphology. In monkeys, evidence of inflammation was observed in the kidney, liver, lacrimal gland, salivary gland, lungs and stomach. The inflammation in the monkeys was reversed after a 4-week recovery period. Clinical pathology changes were also indicative of inflammation, including increases in peripheral leukocyte counts, increased fibrinogen and C-reactive proteins, and increased bone marrow myeloid: erythroid ratios, although the degree of clinical pathology findings was generally minor. Cytokine analysis identified sporadic increases in serum concentrations of IL-1 beta, IL-2, IL-6, TNF-α, and GM-CSF.

General inflammation is believed to be related to LCL161's mechanism of action. Inhibition of IAPs leads to activation of the NF-κB pathway and to the increased production of inflammatory cytokines such as TNF-α in tumors. While TNF-α has not been demonstrated to be responsible for the inflammation observed in animals, other cytokines including GRO-KC (a rat-specific analog of IL-8) and MCP-1 have been characterized. Based on the understanding of the mechanism of action and on preclinical data, the inflammation is reversible upon discontinuation of drug.

Based on the dose limiting toxicity for LCL161 of generalized inflammation, it was of interest to evaluate the impact on the *in vivo* safety profile of combining LCL161 with an anti-inflammatory corticosteroid. Dexamethasone, selected as the corticosteroid due to its common use in rodents, was assessed in three contexts. First, 0.3 mg/kg/day of dexamethasone (modeled from 20 mg of dexamethasone in humans daily) was administered to rats prior to LCL161 and in combination with each LCL161 dose over a 2-week period. In this study, steroids in combination with LCL161 were able to prevent the majority of the inflammatory findings. In a second experiment, dexamethasone dosing was not started until LCL161- mediated inflammation had been allowed to fully develop in rats, and it was then given at 0.1 mg/kg daily for 5 days (modeled from 40 mg of prednisone in humans daily). In this context, dexamethasone suppressed the inflammation and bone changes. A 5-day drug holiday without the administration of dexamethasone also diminished inflammation and bone changes significantly, but not to the same degree as treatment with dexamethasone. In a third experiment designed to test whether treatment with dexamethasone impaired tumor killing, dexamethasone at 0.5 mg/kg/week was administered as a pre-dose (modeled from 3 mg dexamethasone in humans as a pre-dose) with 150 mg/kg of LCL161 given weekly to tumor-bearing mice (MDA-231 xenograft). In this study, steroids did not antagonize the anti-tumor activity of LCL161 (see Investigator's Brochure).

Lymphoid hyperplasia is consistently observed in animal studies with daily doses. In rats and monkeys, enlarged spleen and lymph nodes and microscopic evidence of lymphoid hyperplasia was observed. The spleen appears to be the most sensitive organ for LCL161 induced lymphoid proliferative changes, and lymphoid hyperplasia was observed in spleen at all doses in the rat and monkey 4-week GLP studies. Hyperplastic changes of lymph nodes were also observed in multiple organs/tissues in rat and monkeys - often at higher doses. Lymphoid hyperplasia in spleen and lymph nodes were at least partially reversible in the 4-week studies, though 4 weeks may not be long enough for complete recovery for lymphoid hyperplasia.

Effects on bone/joints were observed in toxicology studies with daily dosing in rats, but not in monkeys. The findings include: mesenchymal proliferation, outgrowth of mesenchymal tissues with destruction of cortical bone, periosteal proliferation, new bone formation, decrease in trabecular bone, growth plate thickening and/or disorganization of trabecular bone adjacent to growth plate. Articular findings include inflammation, fibroplasias, and/or necrosis of periarticular soft tissue and exudation in the articular cavity. The findings were dose-dependent. The bone findings were partially reversed during recovery, though it is unlikely that a 4- to 6-week recovery period is long enough for bone findings. It is not certain if the bone/joint findings are secondary to inflammation, or a direct effect, or both. It is suspected that the bone findings in rats are confounded by the continued presence of open epiphyses and high bone turnover rates. However, due to the lower exposures obtained in the monkey toxicology studies, these bone findings cannot be characterized as species-specific. Final data from the ongoing first-in-human trial suggest that LCL161 does not have clinically significant effects on bone turn over (see Investigator's Brochure).

1.2.4 Biomarkers

Preclinical and clinical biomarker data from the first-in-human trial (CLCL161A2101) with LCL161 given as a single agent on a once-weekly schedule were used to select the biomarkers employed in this trial to explore the relationship between pharmacokinetics/ pharmacodynamics, efficacy, target modulation, molecular response, and immune modulation. Preclinical studies in MDA-MB-231 breast cancer cells treated with LCL161 *in vitro* demonstrated that cIAP1 is degraded within 30 minutes of drug treatment. In mouse studies, maximal degradation of cIAP1 in MDA-MB-231 tumor tissue occurred approximately 6 hours following PO administration of LCL161. Analysis of clinical data from the CLCL161A2101 trial suggest that cIAP1 is degraded in PBMCs within 2 hours of LCL161 dosing, and variably recovers around 72 hours after dosing.

The downstream impact of cIAP1 degradation is proteolytic activation of caspase-3 in sensitive models, which induces apoptosis.

In addition to the activation of apoptosis, preclinical studies have also demonstrated that the degradation of cIAP1 leads to the transient activation of NF-κB. In LCL161-sensitive cell lines, NF-κB activation led to the production of TNF-α, which is weakly correlated with anti-tumor activity. Independent of the anti-tumor activity, preclinical studies have also shown that NF-κB activation plus antigen stimulation activates immune cells and stimulates the release of numerous cytokines into the circulation. These effects of LCL161 could underlie the inflammation observed with chronic dosing in rats and monkeys and to the cytokine release syndrome observed in patients, described below.

1.2.5.1 Human clinical experience

Two clinical trials with LCL161 have been completed and final data are available (Investigator's Brochure). Two clinical trials with LCL161 are ongoing.

1.2.5.2 CLCL161A2101, a first-in-human clinical trial

CLCL161A2101 was a phase 1 dose escalation study designed to identify the maximum tolerated dose (MTD), safety and tolerability of LCL161 when given as a single oral dose once each week, and to seek preliminary evidence of activity.

A total of 53 patients with advanced solid tumors (relapsed or refractory) were enrolled, and patients received oral LCL161 on Days 1, 8, and 15 of every 21-day cycle at doses ranging from 10-3000 mg.

Clinical safety and tolerability

The most common adverse events of any CTCAE grade observed that were suspected to be related to LCL161 included fatigue, nausea and vomiting. In general these toxicities were manageable and severe toxicity was unusual. Eight patients (15%) experienced grade 3 or 4 toxicities that were considered to be related to LCL161. Three patients (5.6%) experienced DLTs (one each at doses of 1800 mg, 2100 mg and 3000mg). All DLTs were a clinical syndrome of cytokine release (CRS) that is consistent with the mechanism of action of LCL161 and that variably included vomiting, diarrhea, fever, flushing or pruritic rash, and in the most severe cases symptomatic hypotension. Symptoms occurred on the day of dosing within hours of having received LCL161. Two patients experienced grade 3 CRS (one each at 1800 and 2100 mg), both of whom recovered within 24 hours of the development of symptoms. One patient (at 3000 mg) developed significant hypotension with grade 4 cytokine release syndrome. The severe hypotension experienced by this patient was unusual and may have been complicated by concomitant administration of three anti-hypertensive medications including amlodipine, which is metabolized by CYP3A4. In the 1800 mg dose group one patient (4%) among 24 developed grade 3 CRS as a DLT; this dose was selected as the dose recommended for further study.

Laboratory abnormalities including hematological toxicity was uncommon. The most common severe hematological abnormality was lymphopenia, which occurred in 8 patients (15%), followed by anemia in 5 patients (9%) and grade 4 thrombocytopenia in 1 patient (1.8%). No severe or life threatening hematologic abnormalities were reported for WBC or absolute neutrophils (neutropenia). Neuropathy or pneumonitis was not reported as a new adverse event.

Clinical pharmacokinetics

LCL161 was rapidly absorbed after a single oral dose of a tablet formulation, with peak plasma concentrations occurring between 1.0 and 6.2 hours. LCL161 exhibited variable PK, with a large apparent volume of distribution (Vz/F) ranging from 190-1689 L, a moderate apparent total body clearance (CL/F) ranging from 13-151 L/h, and a terminal elimination half-life (T1/2) ranging from 4.4-15.5 hours. LCL161 C_{max} and AUC_{inf} generally increased with increasing doses; however, a slightly less than proportional increase was observed. Substantial inter-patient variability was observed in LCL161 PK at the RDE of 1800 mg with the percent coefficient of variation of 78% for C_{max} and 84% for $AUC_{(0\text{-}inf)}$. There was no accumulation in LCL161 plasma C_{max} or $AUC_{(0\text{-}6)}$ from Day 1 to Day 8 and no evidence for time-dependent effects on PK following weekly oral administration of LCL161.

Clinical pharmacodynamics

This study provided evidence that LCL161 is pharmacodynamically active at tolerable doses investigated in patients. The principal marker of pharmacodynamic activity was degradation of cIAP1. Target degradation was observed in all paired tumor biopsies obtained prior to and following a single dose of LCL161, including one case at 900 mg and five cases at 1800 mg. cIAP1 degradation was also observed in some paired skin biopsies at doses ≤160 mg and in

22 of 24 the samples at doses ≥320 mg. cIAP1 depletion in skin was consistently evident 24 hours after LCL161 dosing. The evidence of pharmacodynamic activity (cIAP1 degradation) at doses ≥320 mg suggests that 1800 mg, the dose chosen for further study, is well above that required for target inhibition. The time course of degradation and recovery of cIAP1 protein levels after a single weekly dose of LCL161 was characterized in PBMCs. The data demonstrated that cIAP1 is rapidly degraded within 2 hours of treatment with LCL161 and suggested that protein levels begin to recover in most patients approximately 72 hours after dosing.

Clinical efficacy

No evidence of anti-tumor activity was identified in this unselected population, which is consistent with the preclinical data that suggest a small proportion of malignant cell lines are sensitive to LCL161 as a single agent.

For more information, refer to the [Investigator's Brochure].

1.2.5.3 CLCL161A2105, a drug-drug interaction study with midazolam

To evaluate the clinical risk of CYP3A4/5 inhibition by LCL16, the clinical drug-drug interaction (DDI) study CLCL161A2105 was conducted in 16 healthy patients. This study evaluated the effect of a single 600 mg dose of LCL161 on the PK of the sensitive CYP3A probe substrate, midazolam. The study was also designed to evaluate the time-course of CYP3A4/5 recovery with repeat, single oral doses of midazolam (2 mg) given 3 and 7 days after LCL161. This study had no accompanying pharmacodynamic or efficacy endpoints.

Clinical safety and tolerability

Among the 16 healthy patients treated with LCL161 and midazolam, one patient developed possible grade 1 CRS characterized by transient fever and neutrophilia approximately 12 hours after dosing.

Clinical pharmacokinetics

LCL161 exhibited rapid absorption in healthy patients with a Tmax ranging from 1.0-4.0 hours and a T1/2 ranging from 4.5-7.6 hours. A strong drug interaction was observed when LCL161 and midazolam were dosed on the same day: midazolam Cmax was increased 3-fold and AUC(0-inf) was increased 9-fold. The drug interaction was transient, however. CYP3A4/5 enzyme activity was greater 3 days after the single dose of LCL161 compared to baseline, with midazolam Cmax and AUC(0-inf) decreased by approximately 30%. Enzyme activity completely returned to baseline levels within 7 days of dosing.

Based upon the preclinical and clinical data from this DDI study, caution should be used for patients receiving LCL161 who are taking medications that are substrates for CYP3A4/5.

For more information, refer to the [Investigator's Brochure].

1.2.5.4 CLCL161A2104: A combination study with weekly paclitaxel

CLCL161A2104 is an ongoing phase Ib dose-escalation study of LCL161 with paclitaxel in which patients are treated with a fixed, standard dose of paclitaxel (80 mg/m2 IV once

weekly) followed immediately by oral LCL161 once weekly at doses ranging from 600 mg to the RDE (recommended dose for expansion) of 1800 mg. The objectives of the study are to define the MTD, safety, tolerability, pharmacokinetics and pharmacodynamics of LCL161 in combination with paclitaxel. Eligible patients are aged ≥18 years, with advanced solid tumors that have progressed despite the use of standard therapies or for which no effective therapies are available.

Clinical safety and tolerability

As of July 31st, 2012, preliminary AE data are available from 52 patients receiving treatment with LCL161 + paclitaxel; 600 mg LCL161 (n=3), 1200 mg LCL161 (n=5), 1500 mg LCL161 (n=5), and 1800 mg LCL161 (n=39). The most common AE regardless of relationship to LCL161 is anemia of any grade, occurring in 32 out of 52 (62%) patients. Other common AEs (greater than 10%) include diarrhea (58%); asthenia and nausea (48%); neutropenia (44%); pyrexia (37%); fatigue (33%); alopecia and constipation (31%); decreased appetite (29%); vomiting (25%); mucosal inflammation (23%); dyspnea, rash, and peripheral neuropathy (21%); abdominal pain (19%); dysgeusia (17%); peripheral oedema (15%); cough, dyspepsia, myalgia, peripheral sensory neuropathy, urinary tract infection (13%); dizziness, febrile neutropenia, headache, neutrophil count decreased, pruritus, and respiratory tract infection (12%).

Neutropenia was the most common Grade 3 and Grade 4 adverse event (17% and 19% respectively). Ten of the 52 (19%) patients experienced Grade 3 anemia; no Grade 4 anemia was reported.

Two patients (600 mg and 1800 mg) experienced a Grade 1 CRS. The incidence and severity of CRS is lower than that observed in patients treated with LCL161 as a single agent. This is consistent with the preclinical and extensive clinical experience with dexamethasone as a suppressant of cytokine release and inflammation. Dexamethasone is being given to all patients on the CLCL161A2104 study as a premedication to prevent hypersensitivity reactions to paclitaxel. To inhibit clinically significant CRS, dexamethasone is generally being continued for all patients at a dose of 4 mg prior to paclitaxel infusion.

As of August 10th, 2012, 28 patients (54%) experienced SAEs. Three cases were suspected to be related to treatment with LCL161, including two cases of non-infectious pneumonitis and one case of asymptomatic ALT elevation; all three recovered fully. No deaths have occurred that were considered related to LCL161.

Overall, five patients have developed non-infectious pneumonitis among 55 patients evaluable for this toxicity. Three patients experienced grade 3 pneumonitis and two patients experienced grade 2 pneumonitis; two patients experienced pneumonitis as a serious adverse event. One patient with grade 3 pneumonitis had twice received palliative radiation to the chest wall, most recently ten weeks prior to treatment with paclitaxel and LCL161. This patient developed radiation pneumonitis in the radiation field as an SAE. All cases have occurred at a single geographic location at which 25 of the 55 patients have been treated. All five patients responded promptly to treatment with corticosteroids and recovered fully. Of the three initial cases reported, two were rechallenged with LCL161 and paclitaxel. Both patients weaned off corticosteroids and remain on treatment. After at least six additional cycles of study treatment each, neither patient has had a recurrence of pneumonitis. The third patient withdrew consent. Pneumonitis did not occur as a toxicity of LCL161 as a single agent on the CLCL161A2101 study (section 1.2.2.1.1). Radiation pneumonitis as a toxicity of paclitaxel is listed on the drug label; nonetheless the incidence of pneumonitis observed in this study is higher than expected.

Clinical pharmacokinetics

Preliminary noncompartmental PK analysis was conducted on data from patients with full PK sampling (n=32) indicates LCL161 Cmax and AUCinf did not increase with increasing doses from 600 to 1800 mg. The lack of increase in exposure with increasing LCL161 doses is consistent with the first-in-human study where dose proportionality could not be definitively claimed due to the small sample sizes and the large inter-patient variability. Based on preliminary analysis, co-administration of paclitaxel and LCL161 does not appear to result in a PK interaction. At the 1800 mg dose level, the median LCL161 Cmax and AUCinf were comparable to values observed following single agent LCL161. Paclitaxel plasma PK parameters were unaffected by increasing doses of LCL161 and were consistent with published data for weekly paclitaxel dosed at 80 mg/m2 as a 1 hour infusion (Campone et al 2009; Ready et al 2007), indicating LCL161 has no effect on the PK of paclitaxel.

Clinical efficacy

Among the 45 patients, 11 have confirmed PRs to study treatment.

For more information, refer to the [Investigator's Brochure].

1.2.5.4 CLCL161A2201: neoadjuvant, randomized weekly paclitaxel with or without LCL161

CLCL161A2201 is an ongoing phase II open-label, neoadjuvant, randomized study of weekly paclitaxel with or without LCL161 in patients with triple negative breast cancer. Following a screening period to determine eligibility, patients will be randomized to either paclitaxel 80 mg/m2 IV given weekly (the control arm) or paclitaxel 80 mg/m2 IV weekly immediately followed by LCL161 1800 mg PO once weekly (the experimental arm). Treatment will be administered each week for 12 weeks (4 cycles). The length of each treatment cycle is 21 days. The objectives of this trial are to assess whether adding LCL161 to weekly paclitaxel enhances the efficacy of paclitaxel in women with triple negative breast cancer that are positive for the gene expression signature.

1.3 Study purpose/rationale

Multiple groups have demonstrated that targeting of inhibition of apoptosis pathways and use of Smac mimetics represents a novel therapeutic approach for patients with myeloid malignancies (Fulda S , Nat Rev Drug Discov 2012;11:109-124). Carter et al (Blood 2010 Jan 14;115(2):306-14) demonstrated that inhibition of X-linked inhibitor of apoptosis protein (XIAP) leads to enhancement of apoptosis signaling pathways in AML by release of Smac from the mitochondria and leading to expression of the caspase pathway. Katragadda et al (Katragadda, Expert Opin Investig Drugs 2013 May;22(5):663-70) discuss an antisense oligonucleotide to (XIAP), that has shown evidence of anti-leukemic activity in AML and the authors suggest exploration of Smac mimetics and targeting of other inhibitors of apoptosis(IAPs) to be valid therapeutic considerations in AML and myeloid malignancies .

In pre-clinical work in the area of Smac mimetics, Carter et al (Carter, personal communication and in press) have recently demonstrated synergistic targeting of AML stem/progenitor cells with a novel IAP antagonist , birinapant (a different Smac mimetic compound), in combination with hypomethyaltor agent as Phase Ib/2a clinical trial (2013-0141, Dr Gautam Borthakur, PI, Dept of Leukemia). Based on this group's work, it has been shown that birinipant leads to induced death receptor /caspase-mediated apoptosis in AML cells. With this background, a clinical trial in our group has recently been opened for accrual with the Smac mimetic birinipant, with addition of hypomethylator agent, for patients with myelodysplastic syndrome (MDS) after failure to standard hypomethylator alone frontline therapy.

TNF-α has been previously shown to be involved in the clonal evolution to leukemia in Fanconi anemia in animal model systems. Based on the work by Fleishman and colleagues (Blood 2011), researchers have confirmed the overexpression of TNF-α, a pro-inflammatory cytokine, in PMF patients. The authors demonstrate that TNF-α plays a critical part in the promotion of clonal dominance of MPN cells expressing JAK2V617F mutation. Indeed, JAK2V617F allele level is correlated with TNF-α mRNA expression levels, which indicates that JAK2V617F leads to up-regulation of TNF-α mRNA.

Therefore on the basis of preclinical data suggesting overexpression of TNF-α as a central mediator of clonal dominance of JAK2V617F expressing MPN cells, and the inhibition of LCL161 of tumor activity via inhibition of IAPs in high TNF-α expressing tumor models, we propose an open label, phase 2 single agent clinical trial of LCL161 in PMF patients including post-PV and post-ET MF patients.

2 Objectives and endpoints

Primary Objectives

To determine the efficacy of LCL161 as therapy for PMF, post-PV MF and post-ET MF.

To determine the objective response which is defined as CR (complete remission) + PR (partial remission) + CI (clinical improvement) after three cycles of treatment. It will be categorized according to the International Working Group (IWG) consensus criteria for

myelofibrosis (Blood. 2013 Aug 22;122(8):1395-8. doi: 10.1182/blood-2013-03-488098. Epub 2013 Jul 9).

Secondary Objectives

To determine the safety of LCL161 as therapy for PMF, post-PV MF and post-ET MF.

To determine time to response and response duration

To assess changes in symptom burden as assessed by Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF TSS) and M. D. Anderson Symptom Inventory (MDASI) questionnaires.

Exploratory Objectives

Samples will be collected during the course of the study to assess the mechanisms of action of LCL161 in patients with MF. These studies will include the analysis of cIAP1, XIAP, and PARP protein levels which will be determined by western blot (actin as loading control) and will be measured at baseline and at beginning of each cycle for first 3 cycles and at end of study.

3 Investigational plan

Overview of Study Design

This is a phase 2, non-randomized, prospective, open-label study to determine the efficacy and safety of LCL161 in subjects with PMF and post ET/PV MF. Potential subjects will be screened for participation in the study. In general, screening assessments will include review of past medical history and transfusion history, review of current medication and prior MF-directed therapies, complete physical exam and vital signs, including spleen and liver measurements, ECOG performance status assessment, complete blood count (CBC) with differential, serum chemistries, 12-lead ECG, pregnancy test, bone marrow biopsy and aspirate (including cytogenetics), as well as testing for JAK2 mutation (by quantitative polymerase chain reaction [PCR]), and PCR or fluorescent in situ hybridization (FISH) for *BCR-ABL1*, if not previously done.

Twenty-eight days (4 weeks) will be considered one cycle of therapy. Subjects will remain on study treatment, in the absence of disease progression or toxicity warranting discontinuation of therapy, as long as there is evidence of clinical benefit, as judged by the treating physician. Dose reduction is allowed in case of intolerance; guidelines for drug dose decrease or interruption will be provided.

Study assessments and serial measurements of safety and efficacy will be performed. All scheduled visits will have a ±5-day window. Study visits at MD Anderson Cancer Center will occur at minimum (more often if judged necessary by the treating physician) for the initial dose of LCL161 –then at the start of cycles 2, 3, 4, 7 and 10, and then every 6 cycles (cycle 16, 22 etc.) thereafter while participating in the study.

Only patients who have been on study for at least 3 cycles, and on a stable dose of LCL161 for at least 2 cycles without grade 3-4 toxicity, will be allowed to extend their visits to M.D. Anderson to every 3 cycles. Bone marrow biopsy sample will be collected before therapy, Cycle 4 Day 1, and then every 3-6 cycles at the discretion of the treating physician. All planned study visits should occur whether or not the study drug has been interrupted for an adverse event. The patient will be contacted by the principal investigator or research staff 30 days after discontinuation of protocol +/-5 days to assess for AE's. All treatment decisions related to study drug are to be made by treating physician at MD Anderson and discussed with principal investigator.

Females of childbearing potential (FCBP) and males participating in the study must agree to use a reliable form of contraception or to practice complete abstinence from heterosexual intercourse while participating in the study and for at least 90 days after discontinuation from the study. If pregnancy or a positive pregnancy test does occur in a study subject, treatment with the study drug must be immediately discontinued.

4 Population

This is a phase 2, prospective, open-label study to determine the efficacy and safety of LCL161 in subjects with PMF and post ET/PV MF.

4.1 Inclusion criteria

The investigator or his/her designee must ensure that all patients offered enrollment in this study meet the inclusion and exclusion criteria outlined below.

Patients eligible for inclusion in this study have to meet **all** of the following criteria:

1. Patients must provide written informed consent.
2. Age 18 years or older.
3. Willing and able to comply with scheduled visits, treatment plan and laboratory tests
4. Patient is able to swallow and retain oral medication
5. Must be diagnosed with treatment requiring PMF or post ET/PV MF with intermediate-1, intermediate -2 or high risk disease according to the IWG prognostic scoring system, or if with low risk disease then with symptomatic splenomegaly that is ≥5 cm below left costal margin by physical exam.
6. Patients who are not candidates for, intolerant, or relapsed/refractory to Ruxolitinib
7. ECOG performance status 0-2
8. Required baseline laboratory status:
   - Absolute neutrophil count (ANC) ≥ 0.5 x 10^9/L (1500/mm^3)
   - Serum direct bilirubin ≤ 2.0 x ULN (upper limit of normal)
   - AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN, except for patients with MF involvement of the liver who must have AST and ALT ≤ 5 x ULN
   - Serum creatinine ≤ 1.5 x ULN
9. Treatment-related toxicities from prior therapies must have resolved to Grade ≤ 1

10. At least 2 weeks from prior MF-directed treatment (till the start of study drug)

4.2 Exclusion criteria

Patients eligible for this study must not meet **any** of the following criteria:

1. Any concurrent severe and/or uncontrolled medical conditions that could increase the patient's risk for toxicity while in the study or that could confound discrimination between disease- and study treatment-related toxicities.
2. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
   - History or presence of ventricular tachyarrhythmia
   - Presence of unstable atrial fibrillation (ventricular response > 100 bpm); Patients with stable atrial fibrillation are eligible, provided they do not meet any of the other cardiac exclusion criteria.
   - Clinically significant resting bradycardia (< 50 bpm)
   - Angina pectoris or acute myocardial infarction ≤ 3 months prior to starting study drug
   - Other clinically significant heart disease (e.g., symptomatic congestive heart failure; uncontrolled arrhythmia or hypertension; history of labile hypertension or poor compliance with an antihypertensive regimen)
3. Patients who are currently receiving chronic (>14 days) treatment with corticosteroids at a dose ≥ 10 mg of prednisone (or its glucocorticoid equivalent) per day, or any other chronic immunosuppressive treatment that cannot be discontinued prior to starting study drug
4. Patients who are currently receiving treatment with agents that are metabolized solely through CYP3A4/5 and have a narrow therapeutic index or are strong CYP2C8 inhibitors; or are receiving treatment with agents that carry a risk for QT prolongation and are CYP3A substrates.
5. Patients with impairment of GI function or GI disease that may significantly alter the absorption of LCL161 as per physicians opinion
6. Pregnant or breast feeding (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive β-HCG laboratory test.
7. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 90 days after study treatment. Highly effective contraception methods include:
   - Total abstinence or
   - Male partner or female sterilization or
   - Combination of any two of the following (a+b or a+c, or b+c):
     a. Use of oral, injected or implanted hormonal methods of contraception
     b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
     c. Barrier methods of contraception: condom for male partner or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

   Note: Postmenopausal women are allowed to participate in this study. Women are considered post-menopausal and not of child bearing potential if they have had 12 months

of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of asomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, a woman is considered to be of not child bearing potential only when her reproductive status has been confirmed by follow-up hormone level assessment.

8. Sexually active males must use a condom during intercourse while taking the drug and for 3 months after stopping study drug and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid

5 Treatment

5.1 Treating the patient

The investigator needs to instruct the patient to take the study drug as per protocol. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded appropriately.

Labs (chemistry and hematology) will be performed per visit evaluation schedule and as needed if clinically indicated and at the discretion of the PI and treating physician.

5.1.1 Administration

Table Treatment and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose Level	Dose	Frequency and/or regimen
LCL161	Tablets for oral use	-4	300 mg	Weekly
		-3	600 mg	
		-2	900 mg	
		-1	1200 mg	
		0	1500 mg	

LCL161 will be dosed on a flat milligram per dose scale. LCL161 tablets will be administered orally on a weekly schedule, every 7 days (+/- 3 days). Responsible site personnel will ensure that the appropriate dose of study drug is administered at the clinic for the initial dose and will provide the patient with the correct amount of LCL161 for subsequent dosing at home. Patients will be instructed to return unused LCL161 study drug to the site at each visit. Study visits at MD Anderson Cancer Center will occur at minimum at the start of cycles 1, 2, 3, 4, 7, and 10, and then every 6 months thereafter while participating in the study.

Patients will be given LCL161 at a flat milligram per dose scale of 1500 mg weekly.

LCL161 administration

Due to the unknown effect of food on its absorption, patients should be instructed to fast for 2 hours prior to taking LCL161 and 2 hours after. Light meals (e.g. cereal, toast and jam for breakfast) and/or liquids (e.g. milk, non-citrus juice) can be taken outside of the fasting periods on days of LCL161 dosing.

- For example, if a light meal was completed at 08:00 am, then study drug administration should begin at 10:00 am and the next meal could begin at 12:00 pm. Water and regularly prescribed medications are allowed during the fasting periods.

If vomiting occurs during the course of the treatment, no re-dosing of LCL161 is allowed before the next scheduled dose.

Due to a theoretical potential for LCL161 sensitizing skin to toxicity from UV exposure, patients should be instructed to refrain from excessive sun exposure and other forms of UV radiation (e.g., tanning beds) while taking LCL161.

The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded appropriately.

the first dose of LCL161 be administered in the clinic under the supervision of the investigator, treating physician, or clinic staff. Dexamethasone administration will be optional for first dose and for subsequent doses at discretion of treating physician and PI. For at home dosing, patients must be provided with appropriate patient education to ensure awareness of recognizing symptoms of cytokine release syndrome, and an informed action plan in the event of CRS onset. Patients must also be provided with adequate supply of dexamethasone in the event of cytokine release syndrome occurrence.

5.1.1.2 Known undesirable effects of LCL161

See Section 1.2.2.1 and the Investigator's Brochure. The most common toxicities of LCL161 are diarrhea, asthenia and rash; grade 3 and 4 toxicity is rare. Diarrhea is common, typically as one or two loose stools within hours of taking LCL161. A complex of symptoms consistent with cytokine release syndrome (CRS) was the principle dose limiting toxicity for patients treated in the first in human study, where use of concomitant dexamethasone was prohibited. The symptoms of CRS variably included fever, flushing/rash, diarrhea, vomiting, asthenia and in the most severe cases, hypotension. Clinically significant CRS has not been reported to date on the ongoing study with paclitaxel + LCL161, where dexamethasone is used as a premedication for paclitaxel. Two principal toxicities characteristic of paclitaxel, neutropenia and peripheral neuropathy, have not generally been observed with LCL161, suggesting that it does not cause these toxicities. Pneumonitis, a toxicity observed for some patients treated with LCL161 + paclitaxel, was not observed in patients treated with LCL161 as a single agent.

5.1.1.3 Ancillary treatments for LCL161

Cytokine release syndrome

Cytokine release syndrome variably includes signs of flushing or pruritic rash, fever, diarrhea, asthenia/extreme weakness, and in more severe cases, symptomatic hypotension. The symptoms have typically occurred within twelve hours of LCL161 administration, and if they occur then consideration should be given to increased monitoring/hospitalization, IV fluids, IV dexamethasone, and H1/ H2 receptor antagonists.

For at home dosing of study drug after the initial dose, patients must be provided with adequate supply of dexamethasone along with instruction on self-administration. Adequate education on how to recognize the symptoms of cytokine release syndrome should be provided

to patients at every cycle. Should CRS onset symptoms occur, patients should be instructed on how to manage the symptoms and to contact the investigator.

Medications metabolized by CYP3A4/5

Results from the clinical DDI study with midazolam CLCL161A2105 showed that LCL161 is a potent time-dependent inhibitor of CYP3A4 activity. For patients taking medications metabolized by CYP3A4/5 and where increased exposure to these medications may put the patient at risk, the medication may be withheld on the day of LCL161 dosing and resumed on the following day. This could include, for example, blood pressure medications metabolized primarily by CYP3A4/5. High levels of anti-hypertensive medication after LCL161 dosing could exacerbate clinical symptoms of hypotension for patients who develop CRS. The risk of CRS appears to be limited to the day of LCL161 dosing and CYP enzyme activity returns quickly.

Rash

Preclinical data indicate that LCL161 induces apoptosis of basal and suprabasal epidermal cells. Rash, often described as acneiform and sometimes associated with pruritus or some peeling, has been observed in patients treated with LCL161. Symptomatic treatment with topical agents may include steroids.

Anti-emetics

Patients may be treated prophylactically with anti-5-HT3-emetics.

Anti-diarrheals

Patients should have medication available in case LCL161-induced diarrhea occurs. The commonly used anti-diarrheal medication loperamide is metabolized by CYP2C8 and CYP3A4, and based upon DDI studies performed to date, LCL161 may affect the metabolism of loperamide. However, extensive clinical experience with loperamide has demonstrated a wide safety margin for dosing, with very few serious consequences of overdosing. Nonetheless, caution should be used and patients taking LCL161 should be made aware of the risk of constipation.

Pneumonitis

All patients reporting respiratory symptoms should be evaluated for possible infectious causes and for non-infectious pneumonitis. Such symptoms might include cough, dyspnea and fever, hypoxia can occur in the more severe cases hypoxia. Radiographic confirmation and an appropriate evaluation for infectious causes are required for those patients in whom a diagnosis of pneumonitis is being considered. Bronchoscopy and pulmonary function testing may be helpful in evaluating the causes and severity of lung disease. Initial treatment for pneumonitis should include prednisone at 1 mg/kg/day or similar corticosteroid to be tapered as symptoms resolve.

5.1.2 Dosing and treatment schedule

Twenty-eight days (4 weeks) will be considered one cycle of therapy. Subjects will remain on study treatment, in the absence of disease progression or toxicity warranting discontinuation of therapy, as long as there is evidence of clinical benefit, as judged by the treating physician. Dose reduction is allowed in case of intolerance; guidelines for drug dose decrease or interruption will be provided.

5.1.3 Definitions of dose limiting toxicities (DLTs)

DLT will be defined as an AE or abnormal laboratory value related to study treatment (i.e., assessed as unrelated to disease, intercurrent illness, or concomitant medications), including those AEs and abnormal laboratory values that result in a failure to meet the criteria for re-treatment. If at any time during the study a patient experiences a DLT, the study treatment must be stopped and the toxicity(ies) in question must be followed until resolution or stabilization. If treatment is to be resumed administration must be resumed at a lower dose.

Prior to advancing/changing dose levels a cohort summary must be completed and submitted to the IND Office/Medical Monitor.

Table 5-1 Criteria for defining dose-limiting toxicities (DLTs)

Toxicity	Criteria
Hematology	Febrile neutropenia (ANC, including bands, of < 1.0 x 10^9/L (1000/mm^3) and fever of ≥38.5°C) Grade 4 thrombocytopenia or anemia or neutropenia without fever
Neurotoxicity	≥ Grade 3 peripheral motor neuropathy or ≥ Grade 3 peripheral sensory neuropathy
Gastrointestinal	≥ Grade 3 vomiting or nausea despite the optimal use of anti-emetics ≥ Grade 3 diarrhea despite the use of optimal anti-diarrheal treatments
Fatigue	Grade 3 or higher
Renal	Serum creatinine 2.0 X ULN to 3.0 X ULN for > 7 consecutive days CTCAE grade ≥ 3 serum creatinine
Hepatic*	Direct Bilirubin ≥ 3.0 x ULN Direct Bilirubin 2.0-3.0 x ULN and ≥ Grade 2 ALT AST or ALT ≥ Grade 3 or > 5 x ULN for > 2 weeks for patients with involvement of liver with myelofibrosis at baseline
Allergic	≥Grade 2 hypersensitivity reaction despite optimal use of prophylaxis
Dermatologic/ Skin	Any grade ≥ 2 skin toxicity resulting in a > 72 hour delay in, or interruption of LCL161 treatment; any CTCAE grade ≥ 3
Other adverse events not listed above	Non-hematologic toxicities of ≥ Grade 3 Any adverse event that requires a dose reduction as determined by the investigator

5.1.4 Follow-up for toxicities

Patients who experience study treatment-related toxicity must be evaluated at least once a week until resolution of the toxicity in question to Grade 1, to the patient's baseline value, or until it is deemed irreversible. Assessments used to follow treatment-related toxicities are directed by symptoms and signs and include physical examination, vital signs (including weight), performance status, and evaluation of adverse events and concomitant medications.

Patients who experience toxicities should be followed as outlined in Table 5-2.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay of > 28 days from the intended day of the next scheduled dose of LCL161 because of inadequate recovery from LCL161 related toxicity, then the patient must be discontinued from the study. However, the patient will continue to be followed for resolution of the toxicity in question, as previously described. All patients will be followed for adverse events and serious adverse events for 30 days following the last dose of study treatment.

Table 5-2 General guidelines for follow-up of study treatment-related toxicity

Toxicity	Follow-up evaluation
Hematology	If CTCAE Grade ≥ 4 neutropenia or thrombocytopenia has been demonstrated, these parameters should be re-evaluated at least twice a week until resolution to CTCAE Grade ≤ 1 or the patient's baseline.
Cardiac	Patients who experience ECG abnormalities indicative of an ischemic cardiac event should be managed according to standard medical practice.
Renal	If serum creatinine ≥ 2 x baseline occurs, this parameter should be repeated at least twice a week until resolution to Grade ≤ 1 or the patient's baseline, and then at least weekly following reinitiation of treatment once creatinine returns to baseline/normal, or to document stabilization at an elevated level.
Neurotoxicity/ Pain	Patients who experience Grade ≥ 2 sensory neuropathy or neuropathic pain or Grade ≥ 1 motor neuropathy should be examined at least once a week until improvement with resolution to Grade ≤ 1 or the patient's new baseline.
Hepatic	If direct bilirubin ≥ 2 x ULN or Grade ≥ 3 AST/ALT has been demonstrated, these parameters should be repeated at least twice a week until resolution to Grade ≤ 1 or the patient's baseline (i.e. Grade ≤ 2 if liver infiltration with tumor present), and then at least weekly until either resolution or stabilization.
Allergy/ Autoimmunity	If a Grade ≥ 3 allergic reaction/hypersensitivity or autoimmunity event occurs and is suspected to be related to LCL161, no further LCL161 should be given and the patient should be discontinued from the study.
Inflammation	Whenever an inflammatory adverse event is suspected, the investigator is encouraged to obtain a biopsy of the affected organ as long as it does not place the patient at a significantly higher medical risk (e.g., skin biopsies for rash,GI biopsy for chronic diarrhea or bronchoscopic biopsy for suspected pneumonitis are appropriate).
Pulmonary	Potential study treatment-related pulmonary adverse events (i.e., Grade ≥ 2) should be evaluated at a minimum by re-evaluation of the chest CT and oxygen saturation measurements, as is standard of care. The standard of care oxygen saturation measurements should be repeated at least twice a week until resolution to Grade ≤ 1 or the patient's baseline. Bronchoscopy for those patients with suspected pneumonia or pneumonitis should be considered to evaluate infectious causes and potentially for biopsy of lung tissue. Pulmonary function testing may be helpful to evaluate the severity of lung disease. A chest radiograph may be used for immediate evaluation; however, it will not replace the need for a follow-up chest CT scan. PFTs may also be obtained at the discretion of the investigator to investigate pulmonary toxicity.
Non-laboratory	Patients who experience non-laboratory DLTs or any additional toxicity that the investigator deems significant will be evaluated at least once a week following demonstration of the toxicity, until resolution or stabilization of the toxicity.

5.2 Dose modifications

5.2.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. All dose modifications should be based on the worst preceding toxicity (CTCAE version 4.03).

If a patient experiences a DLT, study treatment should be interrupted and the toxicity should be followed.

5.2.2 Treatment interruption and treatment discontinuation

5.2.2.1 Dose reductions for DLTs possibly associated with LCL161

Table 5-3 Dose modifications for toxicities suspected related to LCL161

Toxicity	Grade	Actions
Non-hematological	1 or 2	- Continue LCL161 therapy at full dose, with optimal supportive care. - For prolonged (> 1 week) toxicity that interferes significantly with quality of life, two dose level reductions of LCL161 are allowed *-See Table 5-4 for dose level reductions*
	3 or 4	- Delay LCL161 until recovery to grade ≤ 1 with optimal supportive care. Reduce LCL161 dose one dose level. - If symptoms recur, reduce one dose level *-See Table 5-4 for dose level reductions*
Hematological (not observed with LCL161 as a single agent)	1 or 2	- Continue LCL161 therapy at full dose, with optimal supportive care
	3 or 4	- Delay study treatment until neutrophils ≥1.5 x10^9/L (1,500/mm^3), platelets ≥100 x10^9/L (100,000/mm^3) and Hgb ≥ 9.0 g/dL - Reduce LCL161 dose one dose level - If toxicity recurs, reduce LCL161 dose one dose level *-See Table 5-4 for dose level reductions*

Table 5-4 Dose level reduction (weekly dose)

Dose Level	LCL161 Dose
0	**1500 mg**
-1	**1200 mg**
-2	**900 mg**
-3	**600 mg**
-4	**300 mg**

5.2.2.2 Discontinuation of therapy due to study treatment-related toxicity

Study treatment should not be resumed in the case of the following study treatment-related events.

- ≥ Grade 3 cardiac event
- ≥ Grade 3 allergic/hyper-sensitivity, cytokine release syndrome or autoimmune reaction or other non-hematologic events of Grade 4 severity
- > 28-day dose delay due to study treatment-related toxicity.

Patients who discontinue from the study for a study treatment-related adverse event or an abnormal laboratory value must be followed as described in Table 5-2. All interruptions and changes to study drug administration or dose must be recorded appropriately.

5.3 Concomitant medications

The investigator should instruct the patient to notify the study site about any new medications including herbals and supplements he/she takes after the start of the study drug. All concomitant medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after patient consent and through end of study participation for patients enrolled on protocol will be captured.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient is allowed, including drugs given prophylactically, with the following exceptions:

- Other investigational therapies must not be used while the patient is on study.
- Anticancer therapy (e.g., chemotherapy, biologic, immunologic or radiation therapy, and surgery) other than the study treatment (LCL161) must not be given while the patient is on the study with the exception of Hydroxyurea for baseline proliferative patients. For these patients, Hydroxyurea will be allowed at the discretion of the attending physician or PI at a maximum dose of 5 Grams per day.
- Routine use of granulocyte colony stimulating factor (G-CSF) or granulocyte-macrophage colony stimulating factor (GM-CSF) must be used in accordance with the American Society of Clinical Oncology's (ASCO)
- Patients receiving recombinant erythropoietin or darbepoetin alfa prior to starting study drug may continue their pre-treatment doses throughout the study.
- Subjects should not receive high dose, ongoing corticosteroids therapy or any other immunosuppressive treatment while enrolled in this study except as instructed per study protocol and at the discretion of the PI.
- Any immune stimulating agents (e.g., cytokines, vaccines), must not be used while the patient is on the study except inactivated (killed) or component vaccines (e.g. influenza vaccine).
- Acute reactions (e.g., hypersensitivity reactions) should be managed according to standard medical practice, as determined by the investigator.
- Results from the clinical DDI study with midazolam indicate that LCL161 is a potent time-dependent inhibitor of the metabolizing enzyme CYP3A4/5. Therefore, use of medications that have a narrow therapeutic index and that are primarily metabolized by CYP3A4/5 will be discouraged and may only be used with PI approval. In addition, the use of medications that carry a risk for QT prolongation and that are substrates for CYP3A4/5 will be discouraged and may only be used with PI approval. LCL161 is primarily metabolized by cytosolic NADPH-dependent carbonyl reductase(s) (~60%), with a minor contribution of oxidative metabolism (~40%) (mainly CYP2C8, followed by CYP3A). Therefore, use of medications that are strong inhibitors of CYP2C8 will be

discouraged in this study and will require PI approval to use. Caution is recommended when combining LCL161 with any other CYP2C8 or CYP3A4/5-interacting medication.

Patients taking chronic medication should be maintained on the same dose and dose schedule throughout the study period, as medically feasible. Certain medications metabolized primarily by CYP3A4/5 that may pose a safety risk on the day of LCL161 dosing can be held and resumed the following day, at the investigator's discretion.

5.3.1 Packaging and labeling

LCL161 will be supplied as tablets for oral use of 300 mg dosage strength. LCL161 will be dosed on a flat scale and not adjusted to body weight or body surface area.

Supply, receipt and storage

Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, LCL161 should be stored according to the instructions specified on the drug labels. Study medication will be dispensed by an authorized person at the investigator's site. For at home dosing after the initial dose Patients will be provided with adequate supply of LCL161 for self-administration at home until at least their next scheduled study visit.

The film-coated LCL161 tablets are stored in a standard high density plastic bottle with child resistant closure. LCL161 should be stored according to the following conditions: "Do not store above 25°C, protect from moisture, protect from light."

5.3.2 Drug compliance and accountability

5.3.2.1 Drug accountability

Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and, as appropriate during the course of the study, the Investigational Pharmacy will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Novartis.

5.3.3 Disposal and destruction

The drug supply will be destroyed at a Novartis facility, or Novartis will provide guidelines for destruction, if investigational site is approved to destroy drug per prior agreement with Novartis.

6 Visit schedule and assessments

6.1 Study flow and visit schedule

The table below lists all of the assessments and indicates with an "X" the visits when they are performed.

Table 6-1 Visit evaluation schedule

Category	Screening	Cycle 1	Cycles 2-4	Cycle 7	Cycles 10+ (Every 6 cycles starting with cycle 10)	End of Treatment (EOT)	Study Evaluation Completion
Day of Cycle	**-28 to -1**	**1**	**1**	**Day 1 (+/- 5 days)**	**Day 1 (+/- 5 days)**	**Within 7 days of last dose**	**30 days after last dose**
Informed consent	X						
Demography	X						
Inclusion/exclusion criteria	X						
Relevant medical history/ Current Medical Conditions	X						
Concomitant medications[1]	X	Continuous					
Adverse events	X	Continuous (**up to 30 days post study discontinuation)**					X
LCL161 dosing		Once weekly dosing[8]					
Vitals	X	X	X	X	X	X	
Physical Exam[2, 9]	X	X	X	X	X	X	
Serum Pregnancy Test for WCBP[3]	X						
Biochemistry[4]	X		X	X	X	X	
Hematology	X		X	X	X	X	
Urinalysis	X	As needed			As needed		
ECOG performance[7] status	X		X	X	X	X	
EKG	X						
Bone marrow aspiration/biopsy[5]	X		Cycle 4*	X*	X*		
MPN-SAFTSS and MDASI[6, 7]	X		X	X	X	X	
Correlative Studies (Optional)	X**		X**			X**	

* Bone marrow biopsy sample will be collected at Screening, Day 1 of Cycle 4, and then every 3-6 cycles thereafter at the discretion of the treating physician.

** Correlative Studies at Screening, Day 1 of Cycles 2 and 3 and End-of-Treatment Visits

[1] Within 14 days of study day 1

[2] History and physical exam including body weight, spleen and liver measurements. This also includes a transfusion history for 3 months prior to day 1

[3] Pregnancy test (for Females of Child Bearing Potential - FCBP only; within 3 days of day 1)

[4] CBC and differential, electrolytes (Na, K, Cl, HCO3), creatinine, uric acid, BUN, glucose, direct and total bilirubin, uric acid, SGOT and SGPT (within 14 days of study day 1) at screening and per visit evaluation schedule

[5] Bone marrow biopsy and/ or aspirate (within 3 month of study day 1) with cytogenetics (if not done before) and JAK2V617F status and allele burden (if not done before)

[6] Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF TSS) and M. D. Anderson Symptom Inventory (MDASI) questionnaire (within 3 days of study day 1)

[7] ECOG performance status and MPN-SAFTSS and MDSAI questionnaires will be performed/administered if the patient is seen at MDACC but not if seen by their local physician in cycles 4 and beyond

[8] Weekly doses will be administered every 7 days (+/- 3days)

[9] Cycle 1 Day 1 physical exam may be waived if screening exam is done within 3 days prior to Cycle 1 Day 1.

6.2 Assessment types

6.2.1 Efficacy

Descriptive statistics will be utilized to assess time to response and response duration.

Duration of response: duration of response is defined as the date at which the subject's objective status is first noted to be a CR or PR to the date progression is documented (if one has occurred) or to the date of last follow-up (for those subjects who have not progressed).

Time to response: The time to response is defined as the time from study registration to the first date at which the subject's objective status was classified as a response (CR or PR). In subjects who do not achieve a response, time to response will be censored at the subject's last evaluation date. The distribution for each of these event-time variables (duration of response and time to response) will be estimated by Kaplan-Meier curves.

6.2.2 Safety

Safety assessments will consist of the following: monitoring and recording of all adverse events and serious adverse events; the regular monitoring of hematology, blood chemistry, urinalysis; regular measurement of vital signs, physical examination, including weight; and performance status.

These assessments should be performed periodically throughout the study, except for adverse events that will be evaluated continuously.

Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drug and had this confirmed, will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible. We will follow standard reporting guidelines for adverse events.

6.2.3 Biomarkers

Samples will be collected during the course of the study to assess the mechanisms of action of LCL161 in patients with MF. Correlative studies will not be mandatory for patient accrual. These studies will include the analysis of cIAP1, XIAP, and PARP protein levels which will be determined by western blot (actin as loading control) at the following timepoints: baseline, beginning of each cycle for the 1st 3 cycles, and the end of study. All samples will be collected at the time or regularly performed blood draws or bone marrow biopsies so no additional procedures will be required. The samples will be batched and stored for analysis at a later date in the lab of Dr. Bing Carter, MD. In case a collection of blood is missed for correlative studies, this will not be reported as a violation of the study.

7 Adverse Events

7.1 Adverse Events

7.1.1 Definitions and reporting

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

- if it is unclear what study treatment includes, list all drug(s), other therapies, changes to existing therapy, diagnostic procedure, etc. that are specified by the protocol

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

All "suspected adverse reactions" (as defined in 21 CFR 312.32(a)) will be captured in the case report forms. For abnormal chemical values grade 3 or 4, the apogee will be reported per course in the CRF. To ensure patient safety each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence.

- The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial
- Protocol Adverse events and specific data will be entered into CORe/PDMS. CORe/PDMS will be used as the electronic case report form for this protocol.

7.2 Serious Adverse Event Reporting (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge
  of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

The following SAEs are not subject to expedited reporting, but would still be included in the annual report via the SAE log.

a. Infection or cytopenias leading to hospitalization or prolongation of hospitalization Disease progression leading to death, life-threating AE, hospitalization or prolongation of hospitalization, or disability.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

7.2.1 Investigator Communications with Novartis

The Investigator will assess the relationship to study treatment and send the initial SAE form and Novartis SAE coversheet by fax or email within 24 hours to the local Novartis Drug Safety & Epidemiology (DS&E) Department:

FAX: 1.888.299.4565
EMAIL: clinicalsafetyop.phuseh@novartis.com
copy Mark Szarszewski: mark.szarszewski@novartis.com

The investigator must then ensure that the SAE form and coversheet are accurately and fully completed with follow-up information and fax those to Novartis DS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. Follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The SAE form, Novartis SAE coversheet, and fax confirmation sheet must be retained in the regulatory binder. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

7.3 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a MD Anderson SAE and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology (DS&E) department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8 Statistical methods and data analysis

8.1 Sample size calculation

A maximum of 50 patients will be enrolled in the study. All patients will be registered through the Clinical Oncology Research System (CORe) at MDACC, and the estimated accrual rate is approximately 2 patients per month.

Based on the solid tumor trial experience, at dosage level of 1800 mg for LCL161, one patient among 24 developing a grade 3 cytokine release syndrome which is non-hematologic. With the consideration of the safety issue, patients will be given the LCL161 at a lower dose of 1500 mg. The length of each treatment cycle is 28 days. If there are at least 2 out of 6 experiencing DLT or at least 2 out of 3 experiencing DLT at dosage of 1500mg during the first cycle, the trial will be stopped for further investigation.

The primary efficacy endpoint is objective response (OR), defined as CR (complete remission)+PR (partial remission)+CI (clinical improvement) for MF patients after 3 cycles of treatment. The primary objective of this study is to assess efficacy in terms of the objective response rate after 3 cycles of treatment. The two-stage design will be implemented. We assume a target ORR of 35% and a response rate of 18% or lower will be considered not desirable. With a type I error rate of 4% and 80% power, we will enroll 16 patients in the first stage. If 3 or fewer patients achieve OR, the trial will be stopped. If 4 or more out of the first 16 patients have OR, accrual will continue until a total of 50 patients have been enrolled. After the first 16 patients have enrolled, the study will not enroll new patient until enough responses (at least 4 responses out of 16 patients) are observed to warrant the continuation of the study. At the end of the study, if 14 or more out of these 50 patients achieve OR, the treatment of LCL161 will be considered efficacious and is worth further investigation. Under this two-stage design, the probability of early termination is 68% if the true ORR is 18% and the expected sample size is 26.96 patients. NCSS-PASS 2005 software was used to create the design details.

The method of Thall, Simon and Estey [1995] will be used for toxicity monitoring for this study.

Toxicity will be monitored among the 50 patients. Denote the probability of toxicity by p(T), where toxicity is defined as Grade 3-4 clinically relevant non-hematologic toxicity or a serious adverse event that is at least possibly drug related (Common Terminology Criteria for Adverse Events CTCAE version 4.03) and occurs anytime during the treatment. We assume as a priori, p(T) ~ beta (0.6, 1.4). We will stop treating patients if Pr(p(T)> 0.30 | data) >0.9. That is, we will stop the trial for new patient enrollment if at any time during the study, we determine that there is more than 90% chance that the toxicity rate is more than 30%. This toxicity stopping rule will be applied by cohort size of 5, starting from the 5th patient. Stopping boundaries corresponding to this stopping rule are listed in table 8.3a. The operating characteristics are summarized in Table 8.3b. Multc Lean Desktop (version 2.1) was used to generate the toxicity stopping boundaries and the OC table.

Table 8.3a Boundary table for toxicity monitoring

# of patients (in cohort of 5, starting from the 5th patient)	Stop the trial if there are this many patients with toxicities:
5	4-5
10	6-10
15	8-15
20	9-20
25	11-25
30	13-30
35	15-35
40	16-40
45	18-45

Table 8.3b. Operating characteristics for toxicity monitoring

True toxicity rate	Prob(stop the trial early)	Average sample size
0.2	0.02	49.21
0.25	0.08	47.43
0.3	0.22	43.59
0.35	0.44	37.48
0.4	0.69	30.12

Analysis Plan

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The objective response rate (ORR) will be estimated along with the Bayesian 95% credible interval.

Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drugs and had this confirmed, will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency. The proportion of patients with AEs will be estimated, along with the Bayesian 95% credible interval.

Duration of response: duration of response is defined as the date, at which the subject's objective status is first noted, to the date progression (no longer meeting criteria for any type of response). Patients who continue to respond as of the data cut-off date will be censored as of the date of their last assessment documenting continued response.

Time to response: The time to response is defined as the time from study registration to the first date at which the subject's objective status was classified as a response. In subjects who do not achieve a response, time to response will be censored at the subject's last evaluation date. The distribution for each of these event-time variables (duration of response and time to response) will be estimated by Kaplan-Meier curves.

9 Administrative procedures

9.1 Discontinuation of study support

Novartis and the IND Office reserves the right to discontinue support for any study under the conditions specified in the clinical trial agreement.

9.2 Amendments to the protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Novartis, the investigator, and the IND office before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the

scientific quality of the study, require additional approval by the IRB/IEC/REB. A copy of the written approval of the IRB/IEC/REB, must be sent to Novartis.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes.

9.2.1 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigator/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

9.2.2 Disclosure and confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

10 References (available upon request)

Ashkenazi A, Dixit VM (1998) Death receptors: signaling and modulation. Science; 281

Chai J, Du C, Wu JW, et al (2000) Structural and biochemical basis of apoptotic activation by Smac/DIABLO Nature; 406 (6798):855-62.

Du C, Fang M, Li Y, et al (2000) Smac, a mitochondrial protein that promotes cytochrome cdependent caspase activation by eliminating IAP inhibition. Cell; 102(1):33-42.

Fleischman AG, Aichberger KJ, Luty SB, et al (2011) TNF-alpha facilitates clonal expansion of JAK2V617F positive cells in myeloproliferative neoplasms. Blood; 118(24):6392-8.

Green DR, Reed JC (1998) Mitochondria and apoptosis. Science; 281(5381):1309-12.
Gyrd-Hansen M, and Meier P (2010) IAPs: from caspase inhibitors to modulators of NF-kB, inflammation and cancer. Nature reviews/cancer; 10:561-74.

Hofmann HS, Simm A, Hammer A (2002) Expression of inhibitors of apoptosis (IAP) proteins in non-small cell human lung cancer. J Cancer Res Clin Oncol; 128(10): 554-60.

Krajewska M, Krajewski S, Banares S, et al (2003) Elevated expression of inhibitor of apoptosis proteins in prostate cancer. Clin Cancer Res; 9(13):4914-25.

Li L, Thomas RM, Suzuki H, et al (2004) A small molecule Smac mimic potentiates TRAIL and TNFalpha-mediated cell death. Science; 305(5689):1471-4

Shiraki K, Sugimoto K, Yamanaka Y, et al (2003) Overexpression of X-linked inhibitor of apoptosis in human hepatocellular carcinoma. Int J Mol Med; 12(5):705-8.

Tamm I, Richter S, Oltersdorf D, et al (2004) High expression levels of x-linked inhibitor of apoptosis protein and survivin correlate with poor overall survival in childhood de novo acute myeloid leukemia. Clin Cancer Res; 10(11):3737-44.

Tamm I, Kornblau SM, Segall H, et al (2000) Expression and prognostic significance of IAPfamily genes in human cancers and myeloid leukemias. Clin.Cancer Res; 6(5):1796-803.

Van Schaik RH (2008) CYP450 pharmacogenetics for personalizing cancer therapy. Drug Resist Update; 11(3): 77-98

Varfolomeev E, Blankenship JW, Wayson SM, et al (2007) IAP Antagonists Induce Autoubiquitination of c-IAPs, NFKB Activation and TNFa-Dependent Apoptosis. Cell; 131(4): 669-681.

Verhagen AM, Ekert PG, Pakusch M, et al (2000) Identification of DIABLO, a mammalian protein that promotes apoptosis by binding to and antagonizing IAP proteins. Cell; 102(1):43-53.

Vince JE, Wong W, Khan N, et al (2007) IAP antagonists target cIAP1 to induce TNFalphadependent apoptosis. Cell; 131(4):682-693.

Wu H, Tschopp J and Lin SC (2007) Smac mimetics and TNFalpha: a dangerous liaison? Cell; 131(4): 655-658.

Food and Drug Administration (FDA) (2006). Guidance for Industry, Drug Interaction Studies - Study Design, Data Analysis and Implications for Dosing and Labeling, Center for Drug Evaluation and Research (CDER), Draft Guidance (Internet) Available from:
US Department of Health and Human Services (2007) Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. FDA

Simon, R (1989) Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials, 10: 1-10 , 1989

Thall, PF, Simon, R, Estey, EH (1995) Bayesian sequential monitoring designs for single-arm clinical trials with multiple outcomes. Statistics in Medicine 14:357-379