MC1483

Mayo Clinic Cancer Center

A Phase II Study of Combination Midostaurin and Decitabine (MIDDAC) in Elderly Patients Newly Diagnosed with Acute Myeloid Leukemia and FLT3 Mutation

Study Chairs: Aref Al-Kali, MD
Mayo Clinic
200 First Street, SW
Rochester, MN 55905
507/284-2511
507/284-5280 (FAX)

Study Co-chair: [redacted]

Statistician: [redacted]

Drug Availability
Commercial Agents: decitabine
Drug Company Supplied: midostaurin

√Study contributor(s) not responsible for patient care.

Document History	**(Effective Date)**
MCCC Addendum 1	January 13, 2016
MCCC Addendum 2	September 1, 2016
MCCC Addendum 3	July 20, 2017
MCCC Addendum 4	December 12, 2017

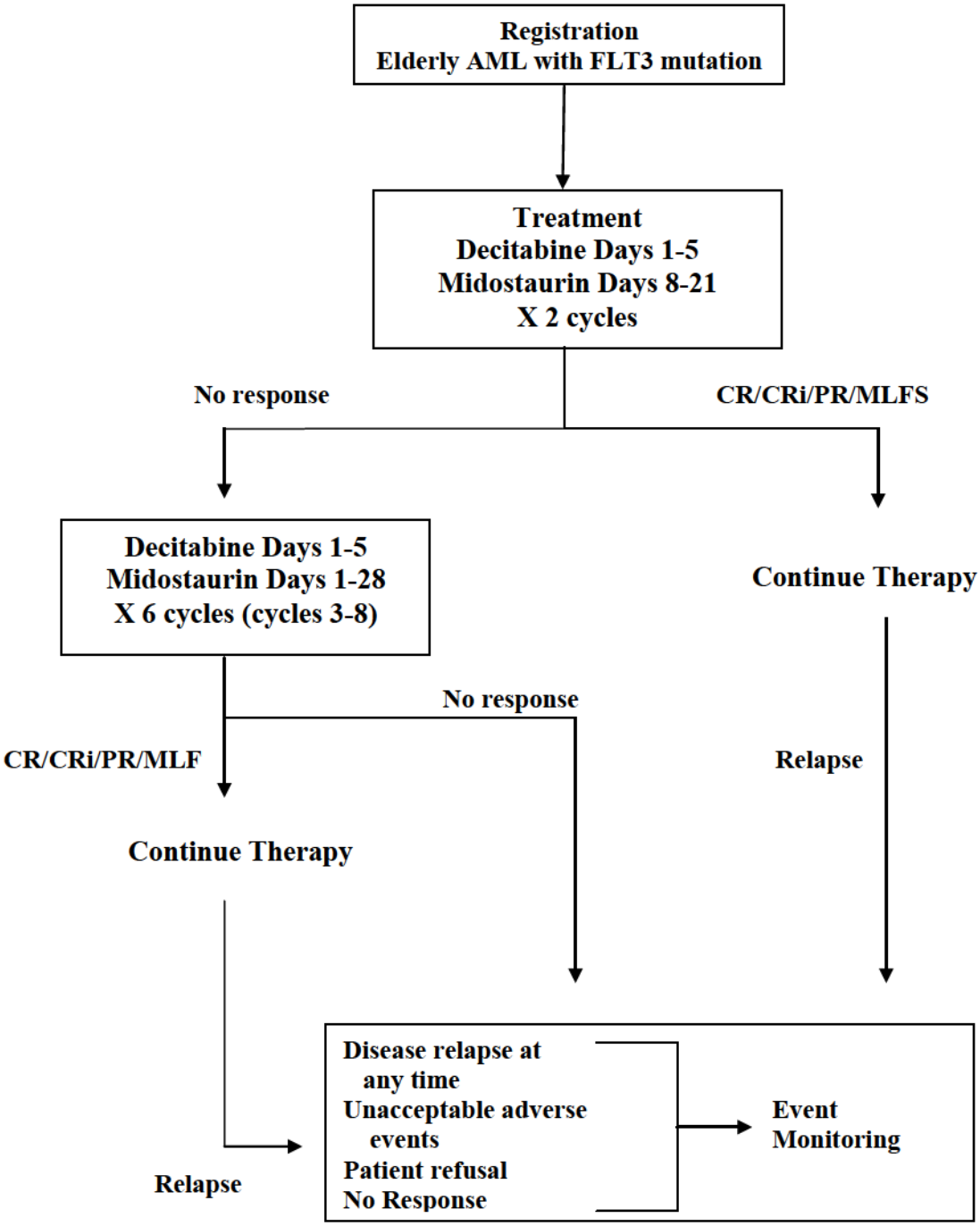
Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted] Quality Assurance Specialist Phone: [redacted] E-mail: [redacted]
Drug administration, infusion pumps, nursing guidelines	[redacted] Phone: [redacted] E-mail: [redacted]
Forms completion and submission	[redacted] Phone: [redacted] Email: [redacted]
Protocol document, consent form, regulatory issues	[redacted] Research Protocol Specialist Phone: [redacted] Email: [redacted]
Adverse Events (AdEERS, MedWatch, Non-AER, AML/MDS)	[redacted] Phone: [redacted] E-mail: [redacted]

*No waivers of eligibility per NCI

Index

Schema



Cycle length 28 days-maximum 18 cycles (see Section 7.12). The next cycle of treatment may be delayed up to 28 days based on investigator opinion. If the next cycle is delayed beyond 28 days, the patient will go to event monitoring per Section 18.0.

Generic name: midostaurin Brand name: n/a Mayo abbreviation: MIDOSTAURIN Availability: Novartis	Generic name: decitabine Brand name: Dacogen Mayo abbreviation: DECIT Availability: Commercial

List of Abbreviations

AE	adverse event
ALT	alanine aminotransferase
AML	Acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
bid	bis in diem/twice a day
CHR	complete hematologic response
CML	chronic myelogenous leukemia
CR	complete response
CRF	case report/record form
CS&E	Clinical Safety and Epidemiology
CT	computerized tomography
CTC	common terminology criteria
CyR	cytogenetic response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FLT3	Fms-like tyrosine kinase-3
GIST	gastrointestinal stromal tumor
HR	hematologic response
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITD	Internal tandem duplicates
ITT	intention-to-treat
IULN	Institutional Upper Limit of Normal
iv	intravenous(ly)
LVEF	left ventricular ejection fraction
MCyR	major cytogenetic response
MTD	maximum tolerated dose
NCI	National Cancer Institute
NEL	no evidence of leukemia
NIH	National Institutes for Health
PD	progression of disease
PFS	progression free survival
PKC412	Midostaurin
po	per os/by mouth/orally
PR	partial response
qd	quaque die/every day
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
TKD	Tyrosine kinase domain
ULN	upper limit of normal
WBC	White Blood Cell Count

1.0 Background

1.1 Overview of acute myeloid leukemia, epidemiology and current treatment

Acute myeloid leukemia (AML) is a malignant disorder of immature hematopoietic cells. It is characterized by differentiation arrest and malignant proliferation of clonal myeloid precursors of the bone marrow. AML represents about 30% of the forms of adult leukemia and the incidence is estimated at 13,000 new cases per year in the U.S. and incidence increases with age. The American Cancer Society also estimates the number of deaths due to AML as 9,000 per year. (American Cancer Society 2011)

The diagnostic workup of acute leukemia is multifaceted and may include bone marrow biopsy, flow cytometry, cytogenetics, and gene mutation analysis. The 2008 WHO classification categorizes myeloid leukemia into numerous subtypes and prognostic groups. The presence of abnormal cytogenetics, or the presence of leukemia-associated gene mutations (FLT3, NPM1, CEPBA) are important prognostic indicators. (Estey 2010) Treatment approaches in AML vary for patients with APL (M3) but have remained relatively unchanged for the past three decades for all other types of AML.

Combination chemotherapy regimens commonly used in treatment of non-APL AML have typically included induction with an anthracycline and nucleoside analog. Complete remission (CR) rates of 65-90% in younger AML patients can be observed with daunorubicin or idarubicin given in conjunction with cytarabine for one to two cycles. (Ravandi 2007) Recently, higher doses of daunorubicin have shown better results in younger AML patients although this benefit did not extend to the FLT3 ITD patients (Fernandez 2009). Consolidation therapy typically involves high dose cytarabine and duration is debated although typically includes three to four cycles of post-remission therapy. (Estey 2010) Despite the high CR rate, the majority of adults with AML will relapse within 3 years with only 40-45% of younger patients achieving cure. (Burnett 2011) There are subsets of AML patients with very poor outcomes, including intermediate or poor risk by cytogenetics or molecular analysis. In such cases, approaches including stem cell transplantation (HSCT) are recommended in CR1. (NCCN Guidelines v1.2012, Estey 2010)

FMS-like tyrosine kinase 3 mutations

The FMS-like tyrosine kinase 3 (FLT3) belongs to the group of class III receptor tyrosine kinases. It belongs to a family of important signaling receptors that include c-KIT, c-FMS, and PDGFR. FLT3 is a growth factor receptor involved in hematopoietic cell growth and differentiation. FLT3 receptor and its ligand (FL) also play an important role in survival and self-renewal of early hematopoietic progenitors, monocytic precursors and in lymphoid development. Activation of FLT3 results in receptor auto-phosphorylation leading to downstream signaling of the RAS/MAPK, JAK/STAT5, and PI3K/AKT pathways. In normal bone marrow (BM), FLT3 is expressed on progenitor cells and regulates stem cell proliferation. As hematopoietic progenitor cells differentiate and mature, FLT3 expression is normally lost.

In AML, signaling of FLT3 pathway is often activated and leads to malignant blast cell proliferation, in part due to over expression of FLT3 receptor in leukemia cells. However, a major research advance was the identification of mutations occurring in the FLT3 gene in AML patients. It is the most common somatic mutation identified in AML, with an incidence of about 25% (Kindler 2010, Kottaridis 2001). Two major types of FLT3 gene mutation have been identified: 1) internal tandem duplication (ITD) and 2) tyrosine kinase domain (TKD) point mutations (PM) and ITDs make up a majority of FLT3 mutations in newly diagnosed patients (Thiede 2002). These duplications are the result of 3 to > 400 base pairs inserted into the receptor in-frame (Schnittger 2002). The ITDs promote ligand-independent FLT3 receptor dimerization and signal activation, culminating in cellular proliferation (Kiyoi 1998, Hayakawa 2000).

The presence of FLT3-ITDs has been found in certain studies to be the strongest predictor of patient outcome (Kottaridis 2001, Kiyoi 1999). AML patients harboring FLT3 ITD mutations are characterized by certain pretreatment features like higher levels of white blood cell counts and blood and bone marrow blasts (Frohling 2002, Thiede 2002). FLT3 ITD has been reported consistently as an unfavorable prognostic marker for relapse-free (RFS) and overall survival (OS) (Kottaridis 2001, Frohling 2002, Thiede 2002, Gale 2008). In a study of 854 AML patients, an ITD was present in 27% of the patients. Although presence of FLT3 mutation did not impact CR rate, long term clinical outcomes varied based on the presence of FLT3 ITD. The relapse rate at 5 years was 64% in patients with the mutation versus 44% in those without. Disease free survival at 5 years was 30% compared to 46% in patients without a mutation and overall survival of 32% compared to 44% of patients without the mutation. (Kottaridis 2001)

Furthermore, additional factors of the FLT3 ITD mutation may impact outcome, including size of the base pair insertion, higher allelic ratio (mutant: wild-type FLT3) and insertion site (Stirewalt 2006, Thiede 2002, Kayser 2009) As details of FLT3 ITD mutations continue to be evaluated, it remains clear that AML with a FLT3 ITD mutation results in higher relapse, shorter DFS and shorter OS which has led to an increased focus on HSCT in CR1 in this group.

1.2 Introduction to investigational treatment(s) and other study treatment(s)

Overview of midostaurin

Midostaurin is an inhibitor of several protein kinase C (PKC) isoforms, of the tyrosine kinase of the vascular endothelial growth factor receptor (VEGFR) and most importantly of the class III tyrosine protein kinases FLT3 (fms-like tyrosine kinase-3) and KIT which are involved in hematopoiesis and play a key role in certain hematopoietic disorders. Midostaurin binds to the catalytic domain of these kinases and inhibits the signaling of the respective growth factors in cells and results in growth arrest. The anti-proliferative effects of midostaurin were easily detectable in FLT3-ITD, FLT3-TKD and FLT3 WT cells (Weisberg 2002, Barry 2007). Midostaurin has also been found to revert the P-glycoprotein (Pgp) mediated MDR (multidrug resistance) phenotype by inhibiting the function of Pgp (Utz 1998).

Midostaurin is currently in Phase II/Phase III clinical development including:

- Two phase II single arm single agent studies in patients with aggressive systemic mastocytosis / Mast Cell Leukemia

- One phase III randomized, double-blind study (CALGB 10603; RATIFY) in patients with FLT3-mutated AML.

The following is a brief summary of the main characteristics of midostaurin. More complete information can be obtained from the current version of Investigators' Brochure.

Clinical experience

Pharmacokinetic and pharmacodynamic data

The clinical pharmacology of midostaurin has been extensively studied in healthy volunteers as well as patients with AML and diabetes mellitus (Yin 2008; Stone 2012). Midostaurin is rapidly absorbed following oral administration with peak plasma concentrations observed 1-3 hours post-dose. Upon daily oral dosing, midostaurin concentrations accumulated in a time linear manner in the first 3-8 days. Thereafter, the PK becomes non-linear with an apparent large increase in CL/F. This relatively high apparent oral clearance necessitates a high dosing rate (e.g. bid administration) to maintain target drug levels in the long term. Midostaurin concentrations reach steady-state after 28 days of daily dosing. (Yin 2008) In vitro studies have shown that midostaurin, CGP62221, and CGP52421 inhibit mutant FLT3 at low nanomolar concentrations, with IC50s of 10-36 nM, 26 nM and 584nM, respectively. (Manley 2003; Stone 2012)

Midostaurin is predominantly metabolized by CYP3A4 iso-enzymes to form two major, pharmacologically active metabolites which may contribute to *in vivo* activity: CGP62221 (half-life ~ 30 hours, comparable to midostaurin's half-life of ~25 hours) and CGP52421 (half-life of ~28 days). Phase I studies in healthy volunteers evaluated the effects of a strong CYP3A4 inhibitor (ketoconazole) and a strong CYP3A4 inducer (rifampin) on concentrations of midostaurin and its metabolites and the effect of midostaurin on midazolam (a sensitive CYP3A4 substrate). Concomitant administration with strong CYP3A4 inhibitors or inducers significantly alters midostaurin concentrations. Midostaurin does not cause a drug-drug interaction with CYP3A4 substrates.

For additional pharmacokinetic information, please refer to the Investigators Brochure.

Overview of efficacy with midostaurin

Midostaurin has demonstrated activity in patients with FLT3-mutated AML/myelodysplastic syndrome (MDS) in studies [CPKC412A2104] and [CPKC412A2104E1]. In the [CPKC412A2104E1] the rate of BR (blast reduction) for the efficacy population (n=92) was 71% in FLT3-mutant patients and 42% in FLT3-WT patients. One partial response (PR) occurred in a FLT3-mutant patient on the 100 mg b.i.d. dose regimen. Both doses levels evaluated in this trial (50 mg b.i.d., and 100 mg b.i.d.) were well tolerated; the toxicity profiles and response rates were similar for the two doses of midostaurin. The results suggest that midostaurin has hematologic activity in both FLT3-mutant and wild-type patients. The degree of clinical activity observed supports further studies that combine midostaurin and other agents such as chemotherapy especially in FLT3-mutant AML (Fischer et al 2010). Preliminary data from the phase Ib study of [CPKC412A2106] of midostaurin in combination with standard

daunorubicin and Ara-C therapy in patients with newly diagnosed AML patients indicate that midostaurin at 50 mg p.o. b.i.d. can be given without major side effects in this patient population (Stone et al 2009, Stone et al 2012). Efficacy data for the 50 mg b.i.d. population was presented at the American Society of Hematology (ASH) in 2009. The investigator assessment of complete response (CR) occurred in 32/40 (80%) of all patients (20/27 (74%) of FLT3–WT patients, 12/13 (92%) of FLT3– mutant patients). One and 2 year overall survival (OS) for the patients with FLT3–mutant AML was 85% and 62%, respectively, and was comparable to that of the FLT3–WT subgroup (81% and 59%, respectively). This data was based on small numbers and not stratified for type of FLT3 mutation (tyrosine kinase domain (TKD), ITD, ITD length, location, or allelic ratio) (Stone et al 2009; Stone et al 2012)

This study supported the ongoing double blind, placebo controlled, phase III study, CPKC412A2301 (CALGB 10603, Ratify), in newly diagnosed FLT3 mutated AML. Enrollment in that trial is complete (N=717) and awaiting the Overall Survival (OS) events required for final analysis.

In addition to the AML programs described above, an ongoing single arm, phase II study, CPKC412D2201 (2201) in aggressive systemic mastocytosis / mast cell leukemia has completed enrollment with stage I (N=40) and extension (N=40) to determine the efficacy and safety of 100 mg twice daily oral midostaurin as a single agent. The Overall Response Rate, per Valent criteria, for stage I is 60% (24/40 eligible patients) including a major response rate of 52.5% (21/40 eligible patients). (Gotlib 2012)

Overview of safety with midostaurin

Overall, approximately 1687 subjects have received midostaurin including ~650 patients with AML / MDS. In AML patients, doses of up to 600 mg per day have been given, but the 50 mg twice daily dose is recommended based upon reaching the IC50 and showing acceptable tolerability. Safety data in AML are based upon three studies: monotherapy in FLT3 mutated patients (2104 Core; N=20), monotherapy in relapsed AML or ineligible for chemotherapy (2104E1; N=95) and front-line combination therapy with daunorubicin and cytarabine (2106; N=69). (Stone 2005, Fischer 2010, Stone 2012). Data from the maintenance phase of the Phase III (2301, CALGB 10603 Ratify) study would also be very informative but the ongoing trial remains blinded at this time. Single agent safety data from 2104E1 will be discussed.

In study 2104E1, patients were randomized to receive midostaurin at doses of 50 mg b.i.d. or 100 mg b.i.d. Of the patients enrolled, 73% were relapsed/refractory and 61% were greater than 60 years of age. Six patients had previously undergone HSCT. Midostaurin was generally well tolerated at both dose levels. All 95 patients experienced at least one AE regardless of relationship to study drug. The most frequent events were grades 1 or 2 nausea (61%; Grade 3 was 1%), vomiting (49%; Grade 3 was 1%), diarrhea (44%; Grade 3 or 4 was 5%), fatigue (38%; Grade 3 was 3%), pyrexia (35%; Grade 3 was 7%) and dyspnea (29%; Grade 3 or 4 9%). The most commonly reported grade 3 / 4 AEs were febrile neutropenia (21%), thrombocytopenia (19%), neutropenia (12%), anemia (13%) and pneumonia (12%). [Inv Brochure ed 16, Table 6-20] The decreases observed in the hematology parameters were as expected for this patient population. Only one patient discontinued treatment due to a hematologic

abnormality (grade 3 febrile neutropenia). The majority of new or worsened biochemistry abnormalities were of CTC grade 1-2. There were grade 3 or 4 abnormalities in AST/ALT in 13% patients (2 were Grade 4, both receiving 100 mg b.i.d.), amylase 7% and albumin 5%. The full table of newly occurring or worsening hematology and chemistry abnormalities is shown in the Investigators Brochure.

SAEs were reported for 71 (75%) patients and most commonly included: febrile neutropenia (20 patients), pneumonia (17 patients), pyrexia (13 patients), dyspnea (8 patients), thrombocytopenia (7 patients) and anemia (6 patients). The incidence of SAEs was similar for both dose groups. SAEs were mostly considered to be due to disease progression. Eighteen (19%) patients had SAEs that were considered related to study drug, with grade 3/4 anemia and thrombocytopenia being the most frequently reported.

A pooled safety analysis was performed using data available from 16 solid tumor or AML/MDS studies. Trials included combinations with 5-FU, paclitaxel, gemcitabine, carboplatin, cisplatin, daunorubicin, and cytarabine. The pooled analysis included 627 subjects and the most common drug related toxicities (> 20%) in these phase I/II trials were nausea, vomiting and diarrhea, fatigue, fever, headache, constipation, anemia and decreased appetite.. AEs occurring less frequently (10-19%) included peripheral edema, thrombocytopenia, cough, abdominal pain, dyspnea, hypokalemia, febrile neutropenia, insomnia, neutropenia, dizziness, asthenia, back pain, chills, rash and hypotension (Investigators Brochure, ed 17) In the pooled analysis, frequencies of cardiac events were consistent with the investigated populations.

A Phase I trial evaluated the effect of midostaurin on the QTc interval in healthy volunteers in a thorough QTc study. The mean maximum change from baseline (QTcF) for midostaurin compared with placebo demonstrated a lack of QTcF prolongation effects. (DelCorral 2012) This trial evaluated midostaurin and the short acting metabolite but could not investigate effects of the long-acting metabolite at steady state. The long acting metabolite information cannot be attained from a healthy volunteer study thus will be provided from the CALGB 10603 (Ratify) dataset.

Overall, AEs suspected to be related to midostaurin treatment were mostly Grade 1 and 2 gastrointestinal events requiring little or no intervention. These were considered related to midostaurin, as the frequency increased at higher dose levels. At the 100 mg twice daily dose in AML patients with chemotherapy, patients discontinued treatment more frequently due to nausea and vomiting despite addition of antiemetic therapy which contributed to selection of a 50 mg twice daily dose which was found to be well tolerated. In addition to prophylactic anti-emetics, administering the doses with meals can reduce gastrointestinal AEs. These AEs are most common in the early cycles of administration. In the ongoing ASM/MCL studies, patients are tolerating the 100 mg twice daily dose for up to 4 years; however, prophylactic anti-emetics are given to all patients.

Overview of decitabine

Decitabine, one of the hypomethylating agents, is FDA approved for the management of myelodysplastic syndrome. In Europe decitabine is also approved for AML in elderly patients 65 or older. It has been also found to beffectiv ein patients with AML. For elderly AML patients unfit for chemotherapy, hypomethylating agents are the cornerstone for treatment due to its low toxicity and safe profile. In a phase III study (Kantarjian 2012), decitabine given 20 mg/m2 as 1-hour intravenous infusion daily for five days every four weeks improved response rates compared with standard therapies without major differences in safety. CR was achieved in 18% with decitabine versus 8% in the other arm.

1.3 Study rationale/ purpose

AML has been a challenging cancer for hematologists and adult patients. Combination chemotherapy using cytarabine and anthracycline (known as 7+3) induction success and relapse rates have been challenged by many concepts but yet remains the standard therapy. These strategies included using higher doses of anthracycline or cytarabine, addition of novel agents (like proteosome inhibitors or monoclonal antibodies (like gemtuzumab ozogamicin), or even using agents directed against drug-resistance targets. Fernandez H et colleagues randomized 657 patients diagnosed with AML between the ages of 17-60 to receive 7+3 but at different doses for daunorubicin (90 mg/m2 vs 45 mg/m2). Patients who received high dose daunorubicin had higher complete remission rates (70% vs 57%, p<0.001) and better median overall survival (23.7 months vs 15.7 months, p=0.003){Fernandez, 2009}. In a similar study reported by Lowenberg et al, 813 patients were randomized to the same treatment but in patients equal or older than 60 years. The complete remission rate favored the higher dose daunorubicin (64% vs 54%, p=0.002), however the overall survival did not differ significantly {Lowenberg, 2009}. Dose intensification of cytarabine was studied compared to standard dose (2gm/m2 IV q12 hours x 12 doses vs. 200 mg/m2/day continuos IV daily x 7 days) in addition to daunorubicin 45 mg/m2 daily x 3 days in AML patients less than 65 years old. A total of 665 patients were treated where CR rates 55% vs 58% (high vs standard dose cytarabine) for patients aged less than 50 and there was no significant difference in 4-year overall survival (32% vs 22%, p=0.41){Weick, 1996}. The British hematologists tested the role of adding gemtuzumab ozogamicin 3mg/m2 on day 1 of induction and course 3 of consolidation) to induction chemotherapy in their MRC AML 15 trial in 1113 patients diagnosed with AML and age less than 60{Burnett, 2011 #58}. Unfortunately, no overall survival benefit was found to adding this treatment in neither induction nor consolidation. On subsequent analysis, patients with favorable cytogenetics had a favorable effect from adding gemtuzuamb (p=0.001). Finally, in randomized study done by ECOG (3999), the addition of zosuquidar (a modulator of P-glycoprotein), did not improve the outcome of older patients newly diagnosed with AML (499 patients){Cripe, 2010}. Remission rate was 52% vs 49% (p0.158) on placebo, while median overall survival was 7.2 vs 9.4 months on placebo compared to patients who received zosuquidar.

Over the last decade, molecular breakthroughs in understanding the genes role and pathways governing the cell cycles, proliferation, apoptosis and transcription have revolutionized our understanding and treatment of myeloid disease, especially chronic myeloid leukemia, myeloproliferative neoplasms and acute myeloid leukemias. Based on this molecular profiling we are able to identify high risk AML cases for low chance of remission and high risk of relapse. Consequently this affected our treatment recommendation, especially with regards to whether to proceed with allogeneic transplantation or not. For example patients harboring CEBPA mutation (single vs double mutations) had a favorable outcome compared with wild type AML cases {Taskesen, 2011}. In fact double mutation CEBPA was the only prognostic factor for overall survival on multivariate analysis (hazard ratio 0.36, p<0.0001). On the other hand, high EVI1 expression in young patients diagnosed with AML predicts worse outcome by having low CR rates (odd ratio 0.54, p=0.002) and adverse event-free survival (hazard ratio 1.46, p<0.001){Groschel, 2010}. Patients who received allogeneic stem cell transplantation in CR1 had a better 5-year relapse free survival (33% vs 0%) compared to without transplantation. FLT3 is another potential gene, where mutations (internal tandem duplicate or tyrosine kinase domain mutation) predicts worse clinical outcome (especially in patients with normal cytogenetics){Kottaridis, 2001}{Whitman, 2008 }{Stirewalt, 2006}. This became of utmost significance since many FLT3 inhibitors have been tested in trials with encouraging results. This include both as a single agent and in combination with chemotherapy {Fischer, 2010}{Levis, 2011 #69}{Borthakur, 2011}{Al-Kali, 2011 }{Zarrinkar, 2009}.

We plan to study the clinical efficacy of PKC412 in combination with standard decitabine in elderly patients with FLT3 mutated AML as a frontline therapy. We will assess their CR rates, survival outcome (progression-free survival (PFS) and overall survival (OS)) in addition to predictive factors for superior outcome. Decitabine is one of the well-established and widely used regimens for the treatment of elderly AML. In addition, it has been FDA approved for the treatment of patients with myelodysplastic syndrome (MDS).

2.0 Goals

2.1 Primary

2.11 To determine the complete response rate for elderly patients with FLT3 mutated AML using midostaurin and decitabine

2.2 Secondary

2.21 Determine the 1-year OS and PFS rates.

2.22 Determine overall response rates in patients treated with this regimen.

2.23 Determine the complete response duration in patients treated with this regimen.

2.24 Assess the safety and toxicity of this regimen based on NCI CTCAE version 4.0.

2.3 Correlative Research

2.31 Assess the prognostic and predictive factors (FLT3 ITD vs TKD mutation) for patients treated with this regimen.

2.32 Explore genetic targets for this disease.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥ 60 years old.

3.12 Unfit for chemotherapy based on investigator assessment or patient not willing to receive intensive induction as advised by investigator.

3.13 Untreated, histological confirmed acute myeloid leukemia (AML) based on WHO 2008 criteria (See Appendix IV) with either/or both:

- FLT3 ITD mutation
- FLT3 TKD mutation

3.14 ECOG Performance Status (PS) 0, 1, 2 or 3 (Appendix II).

3.15 The following laboratory values obtained ≤ 7 days prior to registration.

- Serum amylase and lipase ≤ 1.5 x ULN
- Total Bilirubin ≤1.5 x ULN [Does not apply to patients with isolated hyperbilirubinemia (e.g., Gilbert's disease), in that case direct bilirubin should be ≤ 2 x ULN]
- Alkaline phosphatase ≤3 x ULN
- SGOT (AST) ≤2.5 x ULN
- SGPT (ALT) ≤2.5 x ULN
- Creatinine ≤2 x ULN

3.16 Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.17 Provide informed written consent.

3.18 Willing to return to consenting Mayo Clinic (Mayo Clinic's campus in Rochester), for follow-up during the Active Monitoring Phase of the study.

3.19 Willing to provide bone marrow aspirate and blood samples for correlative research purposes (see Sections 6.*2 and 14.1).*

3.2 Exclusion Criteria

3.21a 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 3 months after treatment completion.

Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. NOTE: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). NOTE: For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
- 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 or other
  forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

NOTE:

- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- 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 vasomotor symptoms).

OR

3.21b Sexually active males unless they use a condom during intercourse while taking drug and for 5 months after stopping midostaurin medication.

NOTE:

- They 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.

3.22 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.23 Immunocompromised patients (other than that related to the use of corticosteroids) including patients confirmed to be HIV positive or have active viral hepatitis.

3.24 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements. Patients with any other known concurrent severe and/or uncontrolled medical condition (except carcinoma in-situ), which could compromise participation in the study (e.g. uncontrolled infection, uncontrolled diabetes, chronic active pancreatitis) .

3.25 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.26 Other active malignancy ≤1 year prior to registration. EXCEPTIONS: Non-melanotic skin cancer or carcinoma-in-situ of the cervix.

3.27 Previous treatment with specific chemotherapy (cytarabine, idarubicin, daunorubicin) or hypomethylating drug (decitabine or azacitidine) for a hematological disorder. EXCEPTIONS: Prior hydroxyurea allowed. Secondary AML is allowed.

3.28 Impaired cardiac function including any of the following:

- Inability to monitor the QT interval on ECG
- Congenital long QT syndrome or a known family history of long QT syndrome.
- Clinically significant resting brachycardia (<50 beats per minute)
- QTc > 450 msec on baseline ECG. NOTE: If the ECG shows a QTc interval greater than 450 msecs at screening triplicates should be performed, one minute apart to confirm the finding (after replacement of any electrolyte imbalance). If 2/3 or 3/3 of the ECGs confirm the QT prolongation (i.e. QTc interval > 450 msecs) the patient must not be included into the trial.
- Myocardial infarction ≤3 months prior to starting study
- Other clinically significant uncontrolled heart disease (e.g. unstable angina, congestive heart failure or uncontrolled hypertension)
- History of or presence of clinically significant ventricular, atrial tachyarrhythmias or ejection fraction cutoff
- Left ventricle ejection fraction <45%
- History of Congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.29a Patients currently receiving treatment with strong CYP3A4 inhibitors

and treatment that cannot be either discontinued or switched to a different medication prior to starting study drug. Patients receiving any medications or substances that are strong inhibitors of CYP3A4. All Azoles but fluconazole are discouraged to be used in patients requiring treatment with antifungal antibiotics.

Use of the following strong inhibitors is prohibited ≤ 7 days prior to registration.

Strong Inhibitors of CYP3A4/5 > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance
Boceprevir (Victrelis®) Clarithromycin (Biaxin®, Biaxin XL®) Conivaptan (Vaprisol®) Indinavir (Crixivan®) Itraconazole (Sporanox®) Ketoconazole (Nizoral®) Lopinavir/Ritonavir (Kaletra®) Mibefradil Nefazodone (Serzone®) Nelfinavir (Viracept®) Posaconazole (Noxafil®) Ritonavir (Novir®, Kaletra®) Saquinivir (Fortovase®, Invirase®) Telaprevir (Incivek®) Telithromycin (Ketek®) Voriconazole (Vfend®) troleandomycin cobicistat tipranavir

3.29b Receiving any medications or substances that are **inducers** of CYP3A4. Use of the following inducers are prohibited ≤ 7 days prior to registration.

Strong Inducers of CYP3A4/5 > 80% decrease in AUC
Avasimibe Carbamazepine (Carbatrol®, Epitol®, Equetro™, Tegretol®, Tegretol-XR®) Phenytoin (Dilantin®, Phenytek®) Rifampin (Rifadin®) St. John's wort mitotane rifabutin phenobarbital
Moderate Inducers of CYP3A4/5 50-80% decrease in AUC
Bosentan (Tracleer®) Efavirenz (Sustiva®)

Etravirine (Intelence®)
Modafinil (Provigil®)
Nafcillin
Genistein
Ritonavir
Talyiraline
Thioridazine
Tipranavir
Nevirapine (Viramune®)
Phenobarbital (Luminal®)
Rifabutin (Mycobutin®)
Troglitazone

3.29c Patients currently receiving treatment with any medications that have the potential to prolong the QT interval and the treatment cannot be either discontinued or switched to a different medication prior to starting study drug. NOTE: Prohibited medications are listed in Appendix Ia "Drugs With Risk of Torsades de Pointes." Appendix Ib contains drugs that should be used with caution due to possible or conditional risk of Torsades de Pointes.

3.29d Impaired gastrointestinal (GI) function or GI disease that may significantly alter the absorption of study drug (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection or gastric bypass surgery).

3.29e Acute or chronic pancreatic disease.

3.29f Known cytopathologically confirmed CNS infiltration.

3.29g Acute or chronic liver disease or severe renal disease considered unrelated to the cancer.

3.29h History of significant congenital or acquired bleeding disorder unrelated to cancer.

3.29i Major surgery ≤4 weeks prior to registration of the study or who have not recovered from prior surgery regardless of time since surgery.

3.29j Treatment with other investigational agents ≤30 days or 5 half - lives of registration.

3.29k Diagnosis of AML-M3 (or acute promyelocytic leukemia).

4.0 Test Schedule

All routine assessments must be performed within ± 7 days of the day indicated on the Visit Schedule.

	Pre-Treatment	Active Treatment					
Tests and procedures	≤ 7 days prior to registration*	Cycle 1, Day 1	Cycle 1, Day 8	Cycle 1 Day 21	Cycles 2 and above, Day 1	Cycles 2 and above, Day 8[7]	Early Discontinuation or End of Treatment
History and exam, weight, vitals, PS	X	X			X	X	X
Height	X						
Adverse event assessment	X	X			X		X
BM testing[2]	X				X[2]		X
Biomarkers FLT3 Mutation by PCR	X						X
Pregnancy Test	X						
Hematology group(CBC) HgB, , PLT, WBC with diff.[1]	X	X[1]	X	X	X[1]	X	X
Serum Chemistry (magnesium, potassium, phosphorus, total bilirubin, direct bilirubin[5], alkaline phosphatase, AST, ALT, creatinine)	X	X	X	X	X	X	X
Serum Chemistry (Serum Amylase & Lipase)	X	X			X		X
MUGA/Echo	X						
LDH	X						
Urine analysis (proteinuria, hematuria)[R]	X						
ECG (QTcF results preferred)[R 3]	X		X			X[3]	X
Patient Medication Diary (Appendix III[4])			X		X	X	
Research Correlatives[R, 6]	X		X		X[6]		

* Labs done on the same day of consent but prior to consenting do not need to be repeated.

1. CBC will be done weekly for cycle 1-4. After cycle 4, to be performed Day 1 and Day 8.
2. Bone marrow (BM) sampling will be done upon screening, and day 1 of cycle 3, 5, 9 and then as clinically needed. Recent bone marrow within 21 days (even prior to consenting) will be acceptable and FLT3 PCR could be done on peripheral blood if blasts >10%. Outside FLT3

testing at bone marrow biopsy will be allowed and used if done.

3. ECGs will be performed locally at screening, Day 8 (prior to dosing) of each cycle, and when there's any dose change due to QTc prolongation or re-initiation after a dose interruption. When a dose change occurs due to QTc prolongation or upon re-starting midostaurin, an ECG must be obtained at 7 days afterwards. QTcF results are preferred, however all reporting methods will be accepted.
4. The diary must begin the day the patient starts taking midostaurin and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team. Patients will be asked to return all unused medication at each visit.
5. Get direct bilirubin if total bilirubin > upper normal limit.
6. Correlatives for blood and bone marrow. See section 14.
7. If midostaurin is started on day 1, then do these tests on day 1. If midostaurin is started on day 8, then do these tests on day 8.

R Research funded (see Section 19.0). This will be charged to study and not to patient's account.

5.0 Grouping Factors: None

6.0 Registration Procedures

6.1 To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page (http://ccswww.mayo.edu/training) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted] If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.2 Correlative Research
A mandatory correlative research component is part of this study. The patient will be automatically registered onto this component (See Sections 3.19 and 14.0).

6.3 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.4 Prior to accepting the registration, registration application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form

- Existence of a signed authorization for use and disclosure of protected health information

6.5 At the time of registration, the following will be recorded:
- Patient has/has not given permission to store and use his/her sample(s) for future research of AML at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.6 Treatment cannot begin prior to registration and must begin ≤ 7 days after registration.

6.7 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 All required baseline symptoms (see Section 10.5) must be documented and graded.

6.9a Treatment on this protocol must commence at Mayo Clinic Rochester under the supervision of a hematologist.

6.9b Study drug is available on site.

7.0 Protocol Treatment

7.1 Treatment Schedule

7.11 Patients eligible for the study based on screening tests will be enrolled on the study.
- Patients will proceed to next cycle every 28 days (or later) based on investigator opinion when reviewing each case based on hematological and physical findings.
- Patients who tolerate combination therapy well and fail to achieve CR/CRi/PR/morphologic leukemia-free state by end of cycle 2, could get midostaurin on days 1-28 of each subsequent cycle, rather than just days 8-21, as per treating MD decision.
- Patients who achieve a CR/CRi/PR/morphologic leukemia-free state by end of cycle 8 will continue on current regimen.
- Patients who fail to achieve a CR/CRi/PR/ morphologic leukemia-free state in bone marrow blasts by end of cycle 8 will go to event monitoring.
- Patients will get a repeat bone marrow biopsy on day one of cycles 3, 5, 9 and then as clinically indicated (see Test Schedule, section 4.0). Patients who achieve CR/CRi will not need repeat bone marrow assessment unless deemed necessary by investigator.
- Hydroxyurea and/or leukocytapheresis use is allowed to control rising blasts as deemed necessary by treating investigator at any

time.

Cycle length = 28 days (+/- 7 days)

Agent	Dose	Route	Day	Comments
Decitabine[1]	20 mg/m^2	IV	1-5	Could be given days 2-5 by local MD (outside Mayo Clinic).
Midostaurin[2]	50 mg twice/day	Oral	8-21	Midostaurin could be given continuously (day 1-28) starting cycle 3 based on MD decision (see 7.11).

1. May be held as per treating physician judgment.
2. If decitabine is held, then midostaurin will be held. If decitabine is administered, midostaurin cannot be held, but can be omitted.

7.12 Maximum cycles of midostaurin are 18, after which a discussion with Novartis will be done on a per patient basis whether to keep patient on continued therapy with the combination of decitabine and midostaurin on study (continue active monitoring per section 4.0).

7.13 If midostaurin is discontinued, single agent Decitabine may be given beyond cycle 18 off protocol until relapse or disease progression off protocol. The patient will go to event monitoring per section 18.0

Note: If single agent Decitabine is being given off protocol, the end of active treatment form should be filled out at the end of cycle 18. Reason treatment ended should be reported as treatment completed per protocol criteria.

7.14 **Stem Cell Transplantation (SCT):** Allogeneic stem cell transplantation for intermediate and high risk patients (based on treating MD assessment) will be allowed at any time if a suitable donor is found and patient performance status allows. Decitabine and Midostaurin will be discontinued and the patient will go to event monitoring per section 18.0

7.15 If either drug is discontinued during treatment, the patient will go to event monitoring per section 18.0

8.0 Dosage Modification Based on Adverse Events

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

Note: If either drug is discontinued during treatment, the patient will go to event monitoring per section 18.0

8.1 Dose Levels (Based on Adverse Events in Tables below)

Dose Level	Dose	Drug Name
0	50 mg orally bid	midostaurin

8.2 Midostaurin dose adjustments for AE at least possibly related to treatment

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION
AT TIME OF NEXT DOSE (All treatment days of each cycle)			
Blood and lymphatic system disorders	Grade 4 Febrile Neutropenia	Midostaurin[1]	1st event: First event days 2-28, omit midostaurin dose until recovery then restart at 50mg b.i.d 2nd event : Omit midostaurin until recovery then restart at 25mg b.i.d for 2 weeks and then re-escalate to 50mg b.i.d as tolerated. 3rd event: Third event, patient should be discontinued if neutropenia is attributable to midostaurin
Investigations	Grade 3 or 4 increased Bilirubin, AST, or ALT		If alternate causes of liver dysfunction have been managed, but liver dysfunction persists, Omit midostaurin until recovery to Grade 2 then restart. If this is felt to be related to study drug and the re-challenge results in a subsequent Grade 3 or 4 elevation, then patient should be discontinued from treatment.
Gastrointestinal Disorders	Grade 2 Nausea or Vomiting	Midostaurin[1]	If this develops despite use of standard anti-emetic therapy and persists for at least 3 days, Omit midostaurin for 3 days (6 doses) and resume midostaurin as tolerated.
	Grade 3 or 4 Nausea or Vomiting		If this develops and persists despite use of standard anti-emetic therapy, omit midostaurin until recovery to Grade 2 (or at least 3 days) then restart. If this is felt to be related to study drug and the re- challange results in a subsequent Grade 3 or 4 toxicity then the patient should be discontinued from treatment.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION
Gastrointestinal Disorders	Grade 3 or 4 Diarrhea		If this develops and persists despite use of standard anti-diarrheal therapy(see section 9.4), omit midostaurin until recovery to Grade 2 (or at least 3 days) then restart.
Respiratory, thoracic and mediastinal disorders	Grade 3 or 4 Pneumonitis		Omit midostaurin until recovery to ≤ Grade 1 and then resume dosing.
Investigations	Currently the effect of midostaurin on QTc interval prolongation is not fully characterized. Therefore, all patients experiencing a post baseline prolonged QTc interval must have potassium and magnesium checked and any electrolytes imbalances corrected. Additionally, the investigator should consider the risk benefit of any concomitant medications that may prolong the QTc interval. For the purpose of this trial, the correction formula according to Fredericia, i.e. QTc**F** is being referred to - wherever QTc is mentioned.		
	Electrocardiogram QT corrected interval prolonged- ECG > 450msec	Midostaurin[1]	If the ECG shows a QTc interval greater than 450 msecs during the trial, triplicates should be performed, one minute apart to confirm the finding (after replacement of any electrolyte imbalance).
	ECG QTc interval > 450 msecs and ≤ 470 msecs		Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Continue midostaurin at the same dose.
	ECG QTc interval > 470 msecs and ≤ 500 msecs,		Check magnesium and potassium levels and correct any abnormalities. If possible, stop any medications that may prolong the QTc interval. Decrease midostaurin to 25 mg twice daily 1 dose level for the remainder of the cycle Resume midostaurin at the initial dose in the next cycle provided that QTc interval improves to ≤ 470 msecs.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION
	ECG QTc interval > 500 msecs	Midostaurin	Check magnesium and potassium levels and correct any abnormalities. Omit midostaurin for the remainder of the cycle, and, if possible, stop any medications that may prolong the QTc interval. If QTc improves to ≤ 470 msecs just prior to the next cycle, resume midostaurin at the initial dose. If QTc interval is not improved in time to start the next cycle do not administer midostaurin during that cycle.
Other Non-hematological	Grade 4 Non-Hematologic		Discontinue midostaurin for non-hematologic grade 4 toxicity (including grade 4 vomiting, diarrhea, and pneumonitis). Midostaurin should be held for other non-hematologic grade 3 toxicity until recovery to ≤ Grade 2. Upon recovery, the patient may restart dosing. If additional toxicity recurs, the midostaurin dose will be reduced to 25mg b.i.d. In the event of additional toxicity requiring dose modification, further dose reductions to midostaurin 25mg Q.D. will be allowed. If the patient tolerates the lower dose of midostaurin (25 mg b.i.d), a dose increase back to 50mg b.i.d may be attempted as tolerated. Fatigue and hair loss are exempted.

[1]If decitabine is held, then midostaurin will be held. If decitabine is administered, midostaurin cannot be held, but can be omitted.

All dose modifications should be based on the worst preceding toxicity. Common Toxicity Criteria for Adverse Events (CTCAE Version 4.0)

If midostaurin is omitted due to QTc prolongation or when there's any dose change, an ECG must be obtained at 7 days afterwards.

8.3 Decitabine dose modification:

- Modification will be done as per standard recommendation and treating physician judgement for patient's best interest and will be mainly based on non-hematological AEs.
- For creatinine AEs, creatinine clearance will be calculated using Cockcroft formula with total body weight and gender adjustment.

9.0 Ancillary Treatment/Supportive Care

9.1 Antiemetics may be used at the discretion of the attending physician.

9.2 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations.

9.3 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.4 **Antifungal antibiotics:** It is highly recommended to avoid concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, voriconazole, posaconazole). The suggested antifungal regimens from a drug metabolism perspective to avoid to use is described below:
Prophylaxis:
Fluconazole (moderate CYP3A4 inhibitor)
Caspofungin

If a patient requires active treatment for a fungal or mold infection and there are no other treatment options it becomes necessary to administer an azole which is a strong CYP3A4 inhibitor. If this is needed, the suggested agents from a drug metabolism and safety perspective include:

Treatment
Voriconazole
Posaconazole
These are both strong CYP3A4 inhibitors and will likely increase midostaurin concentrations, therefore, if there are no other treatment options to treat the infection, a dose reduction by 50% of midostaurin is required to compensate for the drug interactions with these strong CYP3A4 inhibitors. With intra-patient variability with regard to CYP3A4 inhibition and midostaurin pharmacokinetics, the suggested approach is to avoid strong CYP3A4 inhibitors unless there are no treatment alternatives.

9.5 Hydroxyurea: Can be used for control of elevated WBC/blasts at any time of treatment for patient best care and avoid complications of hyperleukocytosis.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.52 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

- **NOTE:** A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol.

NOTE: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).

Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm**

NOTE: The combination of an investigational agent with a commercial agent is considered investigational.

Routine Reporting

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.52.

  NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for CTEP investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.

- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

- Commercial agent expedited reports must be submitted to the FDA via MedWatch.

- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

10.32 Special Situations for Expedited Reporting and submission of Notification Forms

Exceptions to Expedited Reporting and Submission of Notification Forms: EXPECTED Serious Adverse Events [1]

An expedited report or notification form may not be required for specific Serious Adverse Events where the AE is listed in Section 15.0 of the protocol as **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supersede the standard Expedited Adverse Event Reporting and Notification Form Requirements (see footnote 1):

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
General disorders and administration site conditions	Fatigue Febrile neutropenia	≤Grade 3
Metabolism and nutrition disorders	Hypophosphatemia	≤Grade 3
Blood and lymphatic system disorders	Anemia	≤Grade 4
Investigations	Lymphocyte count decreased	≤Grade 4
	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood cell decreased	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

10.321 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormalities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.322 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention

under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

  - Death attributable to a CTCAE term.

  - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

  - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

  - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

  - Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.323 **Secondary Malignancy**

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE need to be reported. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloid Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.324 **Second Malignancy**

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.32 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

Effective Date: May 5, 2011

Additional instructions:

Additional Instructions:

1. An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
2. Submit form to the FDA, MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, by fax at [redacted] or online at http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm.

   Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed

REPORTING TO NOVARTIS

Contact Novartis within 24 hours: 877-778-9739(see appendix V)

Reporting

For patients who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period (or 5 half-lives) whichever is longer) should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form, such as a FDA MedWatch Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department at Fax Number: [redacted].

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed as an appendix to the Site Agreement. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to

that event regardless of when it occurs. The 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 withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Pregnancy reporting

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 Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to midostaurin. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

1. Use paper *Adverse Event Expedited Report – Single Agent* or *Multiple Agents* report available from the CTEP Home Page at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/34-adeersv4_mat.pdf . AdEERs Templates. Submit to Novartis (see fax sheet included in the forms packet) (see Appendix V).

   Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

10.5 Other Required Reporting

10.51 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation

Investigations	Electrocardiogram QT corrected interval prolonged	X	X
	Blood bilirubin increased	X	X
	Alanine aminotransferase increased	X	X
	Aspartate aminotransferase increased	X	X
	Lipase increased	X	X
Skin and subcutaneous tissue disorders	Rash maculo-papular	X	X

10.52 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.51:

10.521 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.522 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.53 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

11.1 Complete hematologic response (CR)
Less than 5% blasts in a non-hypocellular marrow with a granulocyte count $\geq$ 1.0, and a platelets count $\geq$ 100 with complete resolution of any extramedullary disease and absence of peripheral blood blasts. The patient is in sustained CR if they have previously achieved a CR and continue to meet the CR criteria (at least 28 days).

CR incomplete (CRi) is called if patient meets all CR criteria except for residual neutropenia (ANC<1 x10^9/L) or thrombocytopenia (platelets<100 x10^9/L)

11.11 Complete cytogenetic remission (CCyR)
The absence of chromosome abnormalities (if present at diagnosis) on conventional cytogenetic study using G-banding (at least 10 metaphases present).

11.12 Complete molecular remission (CMR)
The achievement of negative PCR for FLT3 mutation (if done and if present at diagnosis).

11.13 MRD: Minimal Residual Disease

Positive PCR for FLT3 mutation or flow cytometry for FLT3 overexpression from peripheral blood or bone marrow.

11.2 Morphologic leukemia-free state (MLFS):
If bone marrow blasts <5%, absence of Auer rods blasts, absence of extramedullary disease without hematological recovery.

11.3 Partial response (PR)
The presence of trilineage hematopoiesis in the bone marrow with recovery of ANC and platelet count to above levels, but with 5-25% bone marrow blasts and ≥50% decrease in bone marrow blast percentage from baseline.

11.4 No response (NR)
Failure to achieve a PR, MLFS, CRi, or CR.

11.5 Relapse:
Disease recurrence after achieving CR. Disease recurrence is defined by blast ≥5% in the bone marrow, or recurrence of peripheral blood blasts or extramedullary involvement.

11.6 Treatment failure:

Resistant disease: Failure to achieve CR/CRi/PR/morphologic leukemia-free state by the end of 8 cycles of induction .

Note: These patients will be recorded as an objective status of NR to document depth of response but will be considered treatment failures at the time of analysis.

Death in aplasia: Death occurring ≥ 7 days following completion of treatment with aplastic/hypoplastic bone marrow (obtained within 7 days of death) with no evidence of persistent leukemia

Death from indeterminate cause: Death occurring during therapy or < 7 days following treatment completion, or ≥ 7 days following completion of treatment with no blast in the blood but no bone marrow examination available

12.0 Descriptive Factors

12.1 FLT3 mutation at baseline: ITD vs. TKD vs. both

12.2 Bone marrow transplant candidate: Yes vs. No.

12.3 NPM1(Mutation): Positive vs. Negative vs. Not Done

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Criteria for Patient Initiation of Event Monitoring:

- Delay > 28 days for the next cycle (due to non-hematological drug toxicity)
- Disease relapse
- Failure to achieve CR or CRi or PR or MLFS by end of cycle 8
- Patient withdraws consent to continue in the trial
- Patient develops an intercurrent illness that precludes further participation
- The Investigator withdraws the patient in the patient's best interests
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator precludes further trial participation
- Patient discontinues either the Decitabine or the Midostaurin in the maximum 18 cycles.

All attempts should be made to complete the End of Study procedures if a patient withdraws from the trial early. The patient will go to the event-monitoring phase per Section 18.0.

13.2 Patients who achieve and sustain a CR/CRi/PR/MLFS by end of cycle 8, will receive a maximum total of 18 cycles of treatment. After 18 cycles, the patient will go to event monitoring, unless they are continuing the combination of midostaurin and decitabine beyond 18 cycles per section 7.12.

13.3 Event monitoring: Patients who are alive will be followed in event monitoring every 6 months until death or up to 2 years from registration.

13.4 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the event-monitoring phase of the study (or off study, if applicable).

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.5 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

13.6 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol

	Mandatory (M) or Optional (O)	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Screening	Cycle 1 Day 8 (pre-midostaurin treatment, 30 mins pre-dosing)	Day 1 Cycles 3, 5, and 9	Temperature Conditions for Storage /Shipping
Correlative studies - See sect. 14.21	M	Blood	BD Vacutainer EDTA 10ml 366643	30-40 ml in total(10 ml tubes)	yes	yes	No	Ship right away away (ice bags +4C) or pick up, room temperature
Correlative studies - See sect. 14.21	M	Bone marrow aspirate[1]	BD Vacutainer EDTA 10ml 366643	20-30 ml in total(4 ml tubes)	yes	no	yes	Ship right away away (ice bags +4C) or pick up, room temperature

1. If bone marrow done previously , this may be omitted.

When possible, samples should be obtained prior to the midostaurin dose. The exact time since the last dose of midostaurin should be documented. For the correlative studies, blood samples should be collected at screening, cycle 1 day 8. For the correlative studies, bone marrow aspirate samples should be collected at screening, and day 1 of cycle 3, 5, 9.

14.2 Collection and Processing

14.21 Genetic Targets Correlative studies: Compare the pre-treatment with post-treatment samples for the alterations of direct and potential-indirect targets for both midostaurin and decitabine:

1) FLT3 gene mutation status will be assessed (at Mayo Clinic Labs) for response stratification and MRD assessment by DNA sequencing;

2) Measurement of FLT3 kinase activities by PCR and Western blot, including FLT3 phosphorylation, total protein expression and downstream effectors (e.g. AKT, ERK, STAT5);

3) Determination of DNMT activity, including DNMT RNA and protein expression (by PCR and Western blot), expression of methylation-silenced tumor suppressor genes (by PCR), global DNA methylation (by LINE-1 or dotblot), gene promoter methylation analysis (by bisulfite sequencing);

4) Detection of microRNAs expression (by qPCR), because previous report show that *miR29b* functions as DNA methylation modulator (Garzon and Liu *et al*, 2009), regulates the activity of c-KIT (Liu *et al*, 2010), a FLT3-like receptor tyrosine kinase and predicts the outcome of decitabine therapy (Blum W *et al*, 2010).

5) Determination of indirect and potential targets, including the genes controlling histone modifications and RNA methylation by qPCR, Western blot, Dotblot and bisulfite sequencing.

6) Investigate the synergistic effect (using the methods above) of decitabine combined with PKC412 on the activities of DNA methylation and kinases, including their gene expression, alteration of downstream effectors and ultimately the synergetic clinical outcomes.

7) Gene and microRNA profiling. In order to further understand the molecular mechanism of drug effects, gene and miR microarrays will be performed in the group of a) responder versus non-responder; b) pre-treatment versus post-treatment. These experiments will identify innovative therapeutic targets.

8) Determination of growth factors, ligands and cytokines in plasma. It is increasingly recognized that leukemia are caused by the cooperation of multiple gene networks, not just a single pathway. Our preliminary data showed that there exists a crosstalk/interplay between methylation and kinases as well as the relevant cytokines, growth factors and lipid binding proteins. To precisely understand the molecular mechanisms underlying the anti-leukemia effects of midostaurin and decitabine, it is necessary to carry out the Western blot or/and ELISA to assess the changes of these gene networks pre- versus post- treatment.

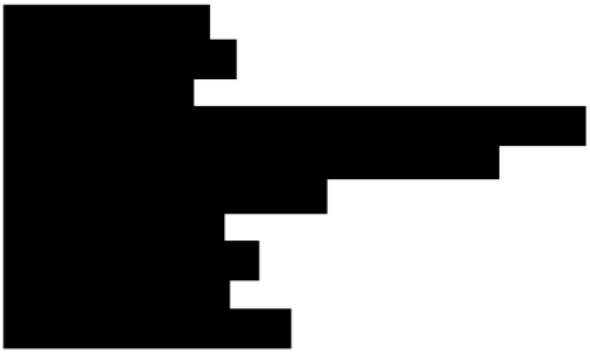
14.3 Shipping and Handling

14.31 Correlative studies will be performed at Hormel Institute, University of Minnesota, by [redacted] Samples can be shipped Monday-

Thursday. Samples that come in on Friday will be refrigerated and shipped on the following Monday. Label the individual samples with the study number MC1483 and the unique study identification number for the patient.

Please ship to the address below.

Contact information is below.



14.32 FLT3 analysis gene sequencing will be performed at the Mayo Clinic in Rochester, MN, per standard testing.

14.33 Handling Specimens

After receipt by the analytical laboratory, samples will be stored at -20 °C or less until analysis.

15.0 Drug Information

15.1 Midostaurin (PKC412, CGP41251)

15.11 **Background:** Midostaurin inhibits several protein kinase C (PKC) isoforms of the tyrosine kinase of the vascular endothelial growth factor receptor (VEGFR) and, most importantly, of the class III tyrosine protein kinases FLT3 (fms-like tyrosine kinase-3) and KIT, which are involved in hematopoiesis as well as playing a key role in certain hematopoietic disorders. Midostaurin binds to the catalytic domain of these kinases and inhibits the mitogenic signaling of the respective growth factors in cells and results in growth arrest.

Importantly, midostaurin has been found to revert the P-glycoprotein (Pgp) mediated MDR (multidrug resistance) phenotype by inhibiting the function of Pgp. Studies which analyzed the sensitivity of Pgp expressing and non-expressing AML blast cells with either FLT3-ITD (internal tandem duplication) mutations or FLT3 wild-type (WT) status towards midostaurin, indicated significant pro-apoptotic activity of midostaurin against both mutated and non-FLT3-mutated blast cells with Pgp expression.

Efficacy of midostaurin has also been shown for myeloproliferative disorders (MPD) induced by ZNF198-FGFR1 or by FIP1L1-PDGFRα.

15.12 **Formulation:** Midostaurin is available as 25 mg soft gelatin capsules, a 25 mg/mL oral solution for pediatric patients, and a 50 mg/5 mL IV solution for infusion (limited to use in the absolute BAV study CPKC412A2120)

The capsule filling solution contains the following excipients, in addition to the drug substance: all-rac-α-Tocopherol / vitamin E, corn oil-mono-di-triglycerides, dehydrated alcohol, polyethylene glycol 400, polyoxyl-40-hydrogenated castor oil. The capsule shell contains gelatin (porcine), glycerol, iron oxide red, iron oxide yellow, and titanium dioxide.The capsules are printed and contain traces of the following excipients: carminic acid E120, aluminum chloride hexahydrate / aluminum chloride, sodium hydroxide, hypromellose, propylene glycol, and isopropyl alcohol.

The 25 mg/mL oral solution contains all-rac-α-tocopherol / vitamin E, corn oil-mono-di-triglycerides, dehydrated alcohol, polyethylene glycol 400, polyoxyl 40 hydrogenated castor oil.

The IV solution for infusion contains propylene glycol 300, polysorbate 80, and dehydrated alcohol.

15.13 **Preparation and storage:** The soft gelatin capsules are packaged in blister packs which are to be stored below 25°C. The oral solution is provided in a 50 mL amber glass bottle and should be stored at 2-8°C before first use. The IV solution for infusion should be stored at 2-8°C, protected from light.
NOTE - The medicine must be disposed properly. After use, remaining capsules, closed oral solution bottles, and the corresponding dispensing system should be returned to the clinical site. Spills should be removed immediately by the use of paper tissue and disposed in a trash bin. The product should not be disposed in a sink or toilet. Contact of the product with the skin should be avoided.

15.14 **Administration:** Midostaurin should be administered orally, twice daily at the same time every day and together with food.

Capsules should be swallowed whole with a glass of water, and must not be chewed or crushed. Remove from the blister pack just prior to administration.

Midostaurin 25 mg/mL oral solution should be allowed to equilibrate to room temperature for approximately 1 hour until the solution is clear. Dose is withdrawn using a 1 mL or 4 mL oral syringe and diluted in water prior to administration. Dose must be taken immediately after dilution.

15.15 **Pharmacokinetic information:**

a) Absorption – rapid oral absorption of midostaurin with Tmax of 1-3 hours. Cmax and AUC of midostaurin increase in an apparent doseproportional manner after administration of single doses up to 50mg and in a less than proportional manner thereafter. Upon daily oral dosing, midostaurin concentrations accumulated in a time-linear manner in the first 3-6 days. Thereafter, the PK becomes time-dependent; the plasma concentrations of midostaurin decreased substantially between Days 6-14, and reached a new plateau after 2-3 weeks of daily dosing. The AUCinf of midostaurin increased by 22% and by 59% with standard meal and high fat meal respectively. The Cmax was decreased by 20% and 27%, respectively. Median Tmax of midostaurin was delayed with administration of a meal compared to the fasted condition by 2.5 to 3h. The recommendation is to administer midostaurin with food.

b) Distribution – Midostaurin was observed to be widely distributed in humans with a high tissue distribution of Vz/F= 99 L. Midostaurin and its metabolites were distributed mainly in plasma rather than red blood cells. [14C] midostaurin was highly bound to human plasma proteins (99.2%), which was also observed in patients. The binding was independent of concentration over the concentration range of 100 – 5000 ng/mL, and was unaffected by high concentrations of α-acid glycoprotein.

c) Metabolism – Midostaurin is predominantly metabolized by CYP3A4 into two major active circulating metabolites, CGP62221 (via O-demethylation) and CGP52421 (via hydroxylation) in humans. The concentration of CGP52421 increased gradually with time and appeared to reach a steady state after 28 days of a multiple dosing regimen. It is possible that auto-induction, protein binding competition and displacement, and/or a combination of both play a role in the pharmacokinetics of midostaurin.

d) Excretion – Elimination of midostaurin from plasma was slow with an apparent terminal half-life of about 17 hours (range 5-31 hours). The apparent terminal half-life of CGP62221 was estimated as 39 hours. The metabolite CGP52421 accumulated in plasma over treatment cycles and its apparent terminal half-life was estimated as >1 month. Fecal excretion is the major pathway for elimination of midostaurin, CGP62221, and CGP52421. Urinary excretion plays a minor role.

15.16 **Potential Drug Interactions:** Some preclinical observations suggest that midostaurin may enhance the effect of irradiation, but the potential clinical significance in terms of risk-benefit of this is currently unknown. The effect is more pronounced in p53+ than in p53- cells.

Co-administration of midostaurin with the potent CYP3A4 inhibitor ketoconazole, resulted in a 10-fold increased exposure of midostaurin. However, data from studies evaluating the co-administration of strong CYP3A4 inhibitors with midostaurin indicate the potential to increase exposure of midostaurin, with little clinical relevance. Nevertheless, co-administration of a strong CYP3A4 inhibitor with midostaurin should be handled with caution. CYP3A4 strong inhibitors include: clarithromycin, telithromycin, troleandomycin, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir, itraconazole, ketoconazole, posaconazole, voriconazole, boceprevir, telaprevir, cobicistat, conivaptan, nefazodone.

Caution should be exercised for patients receiving moderate CYP3A4 inhibitors. A list of these agents is found at:
http://medicine.iupui.edu/clinpharm/ddis/main-table

Co-administration of midostaurin with the potent CYP3A4 inducer, rifampicin, decreased the Cmax and AUC of midostaurin by 73% and 94%, respectively. To avoid sub-therapeutic exposure to midostaurin, moderate or strong CYP450 3A4 inducers should not be co-administered. Strong CYP3A4 inducers include: avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), and St. John's wort. Moderate CYP3A4 inducers include: bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, and tipranavir.

15.17 **Known potential toxicities**: Aggressive Systemic Mastocytosis (ASM), and Acute Myeloid Leukemia (AML)

Very Common (≥10%): leukopenia, lymphopenia, febrile neutropenia (AML), petechiae, sinus tachycardia, anorectal discomfort, constipation, diarrhea, hemorrhoids, stomatitis, nausea, vomiting, fatigue, peripheral edema, pyrexia, hypersensitivity (AML), device related infection, URTI (ASM), UTI, APTT prolonged, increased ALT, increased AST, increased amylase, increased lipase, decreased hemoglobin, decreased neutrophil count, decreased absolute neutrophils, decreased absolute lymphocytes, hyperglycemia, increased glucose, hypokalemia, hyponatremia, increased total bilirubin, hyperuricemia, back pain, arthralgia, headache, dizziness, insomnia, cough, dyspnea, epistaxis, pleural effusion (ASM), laryngeal pain, hyperhidrosis, exfoliative dermatitis, hypertension,

hypotension (AML)
Common (≥ 1- 10%): febrile neutropenia (ASM), pericardial effusion, eyelid edema, vertigo, abdominal discomfort, abdominal distension, dyspepsia, GI hemorrhage, asthenia, chills, edema, catheter related thrombosis, hypersensitivity (ASM), bronchitis, erysipelas, cystitis, herpes zoster, oral herpes, pneumonia, sepsis, sinusitis, URTI (AML), hypercalcemia, increased weight, confusion, fall, bone pain, pain in extremities, neck pain, syncope, tremor, disturbance in attention, ARDS, pleural effusion (AML), oropharyngeal pain, nasopharyngitis, keratitis, dry skin, hematoma, hypotension (ASM)
Uncommon (≥ 0.1 – 1%): anaphylactic shock, neutropenic sepsis

15.18 **Drug procurement:** Midostaurin capsules will be provided free of charge to study subjects by Novartis.

15.19 Nursing Guidelines

15.191 Patients should be instructed to take medication at the same time every day, twice daily with food. Capsules must be swallowed whole with a glass of water and cannot be chewed or crushed. Oral solution is available for pediatric patients–follow separate preparation instruction in section 15.14. Medicine must be properly disposed of. Do not pour down a sink or toilet. Wipe up spills immediately. Avoid skin contact.

15.192 Assess patient's concomitant medications, including OTC and herbal products. Midostaurin has interactions with drugs that are metabolized via CYP3A4 and caution should be exercised for patients who are on these agents. For more details refer to section 15.16 of the protocol.

15.193 Gastrointestinal side effects are common, including nausea, vomiting, and diarrhea. Treat symptomatically and monitor for effectiveness. Patients should be premedicated for the prevention of nausea and vomiting.

15.194 Monitor creatinine and renal function as renal impairment/failure has been seen.

15.195 Instruct patients to report any signs/symptoms of CHF/LVEF dysfunction, including chest pain, SOB, and edema.

15.196 Monitor CBC w/diff as cytopenias can be seen. Instruct patients to report any signs/symptoms of infection and/or any unusual bruising/bleeding to the study team.

15.197 Monitor glucose levels per protocol as hyperglycemia has been seen. Diabetics may need additional monitoring.

15.198 Back pain and arthralgia's have been seen. Treat symptomatically and monitor for effectiveness.

15.2 DECIT (2–deoxy–5–azacytidine), Decitabine, Dacogen®

15.21 Background: Decitabine is directly incorporated into DNA and causes inhibition of DNA methyltransferase, leading to hypomethylation of DNA and cellular differentiation or apoptosis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation.

15.22 Formulation: Decitabine for injection is a white to almost white sterile lyophilized powder supplied in a clear colorless glass vial. Each 20 mL, single dose, glass vial contains 50 mg decitabine, 68 mg monobasic potassium phosphate (potassium dihydrogen phosphate) and 11.6 mg sodium hydroxide.

15.23 Preparation and Storage: Decitabine should be aseptically reconstituted with 10 mL of Sterile Water for Injection (WFI); upon reconstitution, each mL contains approximately 5 mg of decitabine at pH 6.7-7.3. Immediately after reconstitution, the solution should be further diluted per recommended procedure with infusion fluids, such as 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a final drug concentration of 0.1 - 1.0 mg/mL. Unless used within 15 minutes upon reconstitution, the diluted solution must be prepared using cold infusion fluids and stored at 2-8°C for a maximum of 4 hours prior to administration. Each 20-mL vial contains 50 mg decitabine.

15.24 Administration: Decitabine is administered intravenously over 1 hour.

15.25 Pharmacokinetic information
Distribution: Approximately 63 to 89 L/m2
Metabolism: Possibly via deamination by cytidine deaminase
Half-life elimination: Approximately 30 to 35 minutes

15.26 Known potential drug interactions: No known cytochrome P450 drug-drug interactions. Concomitant use with known myelosuppressive agents may enhance the adverse/toxic effects.

15.27 Known potential toxicities:
Common known potential toxicities, > 10%:
Cardiovascular: Peripheral edema, pallor, edema, cardiac murmur, hypotension
Central nervous system: Fever, fatigue, headache, insomnia, dizziness, chills, pain, confusion, lethargy, anxiety, hypoesthesia
Dermatologic: Petechiae, bruising, rash, erythema, cellulitis, lesions, pruritis
Endocrine & metabolic: Hyperglycemia, hypoalbuminemia, hypomagnesemia, hypokalemia, hyperkalemia, hyponatremia
Gastrointestinal: Nausea, constipation, diarrhea, vomiting, anorexia, abdominal pain, stomatitis, dyspepsia
Hematologic: Neutropenia, thrombocytopenia, anemia, febrile neutropenia, leukopenia, lymphadenopathy
Hepatic: Hyperbilirubinemia, alkaline phosphatase increased
Neuromuscular & skeletal: Rigors, arthralgias, limb pain, back pain, weakness
Respiratory: Cough, dyspnea, pneumonia, pharyngitis, lung crackles, heart failure

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Tachycardia, chest pain/discomfort, facial edema, hypertension, heart failure
Central nervous system: depression, malaise
Dermatologic: Alopecia, dry skin, urticarial
Endocrine & metabolic: Hyperuricemia, LDH increased, bicarbonate increased or decreased, dehydration, hypochloremia, hypoproteinemia
Gastrointestinal: Mucosal inflammation, weight loss, gingival bleeding, hemorrhoids, loose stools, tongue ulceration, dysphagia, oral candidiasis, toothache, abdominal distension, gastroesophageal reflux (GERD), glossodynia, lip ulceration, oral pain, tooth abscess
Genitourinary, urinary tract infection, dysuria, polyuria
Hematologic: Bacteremia, hematoma, pancytopenia, thrombocythemia
Hepatic: Ascities, AST increased, hypobilirubinemia
Neuromuscular & skeletal: Myalgias, falling, chest wall pain, muscle spasms, bone pain, musculoskeletal discomfort
Ocular: Blurred vision
Otic: Ear pain
Respiratory: Abnormal breath sounds, hypoxia, upper respiratory tract infections, pharyngolaryngeal pain, rales, pulmonary edema, sinusitis, pleural effusion, postnasal drip, sinus congestions
Miscellaneous: Candidal infections, staphylococcal infection, transfusion reaction, night sweats

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Anaphylactic reaction, atrial fibrillation, bronchopulmonary aspergillosis, cardiomyopathy, cardiorespiratory arrest/failure, catheter site hemorrhage, cholecystitis, fungal infection, gastrointestinal hemorrhage, gingival pain, hemoptysis, hypersensitivity, intracranial hemorrhage, mental status change, MI, mycobacterium avium complex infection, peridiverticular abscess, pseudomonal lung infection, pulmonary embolism, pulmonary infiltrates, pulmonary mass, renal failure, respiratory arrest, sepsis, splenomegaly, supraventricular tachycardia, Sweet's syndrome (acute febrile neutrophilic dermatosis), urethral hemorrhage

15.28 Drug procurement: Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.15.2 DECIT (2–deoxy–5–azacytidine), Decitabine, Dacogen®

15.29 <u>Nursing Guidelines:</u>

1) Monitor CBC. Myelosuppression is a dose limiting factor. Instruct patient to report any signs or symptoms of infection, unusual bruising or bleeding to the health care team.

2) Nausea and vomiting is common. Premedicate with antiemetics and assess for their effectiveness.

3) Certain infections were seen more commonly in patients treated with decitabine; including pneumonia, fungal, candidal, infections and cellulitis. Instruct patient to report any signs or

symptoms of infections immediately.

4) Patients may experience fatigue. Instruct in an energy conserving lifestyle.

5) Monitor liver function tests. Report any abnormalities to the treating MD.

6) Please note that not all nursing guidelines may be known at this time. Monitor patient carefully and report all adverse events to the MD and as required by your institution for adverse event monitoring.

16.0 Statistical Considerations and Methodology

16.1 Overview: This is a phase II study of a combination of midostaurin and decitabine in elderly patients with newly diagnosed AML and FLT3 mutation. This study will use a one-stage binomial design to assess the efficacy of this combination.

16.11 Endpoint: The primary endpoint in this trial is the proportion of complete responses during therapy. A success is defined as a CR or CRi as the objective status during therapy. Throughout Section 16.0, complete response will be considered synonymous with "success", unless specified otherwise. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

16.2 Statistical Design:

16.21 Decision Rule:
In previous studies of elderly AML patients treated with single agent decitabine as frontline therapy, complete response rates of 15%-24% were seen ({Cashen, 2010 #813}{Lubbert, 2007 #812}). An improvement in complete response rate with the addition of midostaurin to decitabine would be of interest.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 10%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 30%. A one-stage binomial design uses 24 evaluable patients to test the null hypothesis that the true complete response rate is at most 10%.

16.211 Final Decision Rule: Enter 24 evaluable patients into the study. If 4 or fewer successes are observed in the first 24 evaluable patients, we will consider this regimen ineffective in this patient population. If 5 or more successes are observed in the first 24 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

16.212 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.34.

16.22 Sample Size: This study is expected to require 24 evaluable patients. We anticipate accruing 2 additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the study is expected to accrue a maximum of 26 patients overall.

16.23 Accrual Rate and Study Duration: The anticipated accrual rate is 1 evaluable patient per month. Therefore, the accrual period is expected to be approximately 2 years. The primary endpoint will be evaluated approximately 2.75 years after the trial opens, or after the last patient accrued has been observed for at least 6 months. The total study duration is expected to be approximately 3 years.

16.24 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .09, i.e. there is a 9% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.10	0.15	0.20	0.25	0.30
Then the probability of declaring that the regimen warrants further study is…	0.09	0.29	0.54	0.75	0.89

16.25 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study

16.3 Analysis Plan

16.31 Primary Outcome Analyses:

16.311 Definition: The primary endpoint of this trial is the proportion of complete responses to therapy. A success is defined as a CR or CRi as the objective status. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for complete response.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Exact binomial confidence intervals for the true success proportion will be calculated.

16.32 Secondary Outcome Analyses:

16.321 Overall survival time is defined as the time from registration to death due to any cause. The distribution of overall survival will be estimated using the method of Kaplan-Meier{Kaplan E, 1958 #831}. In addition, the overall survival rate at 1 year after registration will be reported.

16.322 Progression-free survival time is defined for all evaluable patients as the time from registration to the time of relapse or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier. In addition, the progression-free survival rate at 1 year after registration will be reported.

16.323 The overall response rate will be estimated by the total number of complete or partial responses (CR, CRi, MLFS, or PR) divided by the total number of evaluable patients. All evaluable patients will be used for this analysis. Exact binomial 95% confidence intervals for the true overall response rate will be calculated.

16.324 Duration of complete response is defined for all evaluable patients who have achieved a CR or CRi as the date at which the patient's objective status is first noted to be a CR or CRi to the earliest date relapse is documented. The distribution of duration of complete response will be estimated using the method of Kaplan-Meier. If there are a sufficient number of CR/CRi, a landmark analyses may be performed to compare duration of CR/CRi in patients who first achieved a CR/CRi at 2 months vs those who first achieved a CR/CRi at 8 months.

16.325 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.33 Correlative Analyses

16.331 Prognostic and predictive factors including age and FLT3 mutation by ITD vs. TKD vs. both will be assessed. These factors will be summarized and used to help characterize the types of patients accrued to this trial. In addition, we will explore differences in the distributions of these risk factors by clinical outcome (CR/CRi vs. not, OS and DFS). Nonparametric quantitative comparisons by group will be made as appropriate (Fisher's exact or Wilcoxon rank sum). Kaplan-Meier methods

and log rank statistics will be used to compare between groups for time to- event measures. Given the limited number of patients, the difference in risk factor distribution by outcome will be largely exploratory.

16.332 MRD will be assessed by PCR for FLT3 mutation (if FLT3 is repeated) or flow cytometry . MRD status will be correlated with response using Fisher's exact test. In addition, the relationship between MRD status (positive vs. negative) and disease-free survival will be evaluated using landmark analyses.

16.34 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final endpoint estimates and confidence intervals.

16.4 Data & Safety Monitoring:

16.41 The principle investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.42 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- if 4 or more patients in the first 12 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment excluding infections and hypophosphatamia, hypocalcemia, hypo- or hyperkalemia, hyperuricemia as these abnormal lab results tend to resolve quickly (≤7 days) without affecting or jeopardizing patient safety.

- if after the first 12 patients have been treated, 30% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment excluding infections and hypophosphatamia, hypocalcemia, hypo- or hyperkalemia,

hyperuricemia as these abnormal lab results tend to resolve quickly (≤7 days) without affecting or jeopardizing patient safety.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClinicialTrials.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 2.5 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 6 months.

16.6 Inclusion of Women and Minorities

16.61 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 30% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	0	1	0	1
Not Hispanic or Latino	8	17	0	25
Ethnic Category: Total of all subjects*	8	18	0	26
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	0	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0	0
White	8	17	0	25
Racial Category: Total of all subjects*	8	18	0	26

Ethnic Categories:	Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino." Not Hispanic or Latino
Racial Categories:	American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment. Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.) Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American." Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands. White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens: None.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

Case Report Form (CRF)	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
Adverse Event - Baseline	
Research Blood Submission	
Research Bone Marrow Submission	
Measurement Bone Marrow and Biopsy - Baseline	
Bone Marrow Biopsy and Aspirate Report including the FLT3 mutation by PCR and cytogenetics.	
End of Active Treatment/Cancel Notification	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Evaluation/Treatment	X	X
Nadir/Adverse Event	X	X
Measurement and Disease Response	X	X
Bone Marrow Biopsy and Aspirate Report including the FLT3 mutation by PCR and cytogenetics	X[1]	X
Research Blood Submission	X[1]	
Research Bone Marrow Submission	X[1]	
End of Active Treatment/Cancel Notification		X
ADR/AER	At each occurrence (see Section 10.0)	

1. Only when required by the Test Schedule (see Section 4.0 and 14.0)).

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 6 months until PD[2]	At PD[2]	After PD q. 6 mos.	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 2 years after registration, no further follow-up is required.
2. Submit copy of documentation of response or progression to the MCCC Operations Office, Attention: QAS for MC1483.

19.0 Budget

19.1 Costs charged to patient: routine clinical care.

19.2 Tests to be research funded: Study drug, urinalysis, ECG, blood and aspirate correlatives.

19.3 Other budget concerns: Protocol administration, data management and statistical analysis efforts will be by funded by Novartis.

20.0 References

1. American Cancer Society (2011) Cancer Facts & Figures. Atlanta, GA.

2. Barry EV, Clark JJ, Cools J, et al (2007) Uniform sensitivity of FLT3 activation loop mutants to the tyrosine kinase inhibitor midostaurin. Blood. 110(13):4476- 4479.

3. Burnett A (2011) Acute Myeloid Leukemia in Postgraduate Hematology. Sixth Edition. Wiley-blackwell publishing. Edited by A Victor Hoffbrand. West Sussex UK.

4. Burnett A, Wetzler M, Lowenberg B (2011) Therapeutic Advances in Acute Myeloid Leukemia. J Clin Oncol. 29:487-494.

5. Cashen, A. F., G. J. Schiller, et al. (2010). "Multicenter, Phase II Study of Decitabine for the First-Line Treatment of Older Patients With Acute Myeloid Leukemia." Journal of Clinical Oncology **28**(4): 556-561.

6. Del Corral A, Dutriex C, Huntsman-Labed A, et al (2012) Midostaurin does not prolong cardiac repolarization defined in a thorough electrocardiogram trial in healthy volunteers Cancer Chemotherapy and Pharmacology; 69(5): 1255-1263.

7.Estey E (2010) Understanding and Managing Ultra High-Risk Hematological Malignancies: High Cytogenetic or Molecular Genetic Risk Acute Myeloid Leukemia. Hematology 2010:474-480.

8.Fernandez HF, Sun Z, Yao X, et al (2009) Anthracycline Dose INtenstification in Acute Myeloid Leukemia. New England Journal of Medicine; 361:1249-1259.

9.Fischer T, Stone R, DeAngelo D, et al (2010) Phase IIB trial of oral midostaurin (PKC412), the FMS-like tyrosine kinase 3 receptor (FLT3), and multi-targeted kinase inhibitor, in patients with acute myeloid leukemia and high risk myelodysplastic syndrome with either wild type or mutated FLT3. J Clin Oncol; 28(28): 4339-4345.

10. Flockhart DA (2009) Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007) Version 5.0 released on Jan 12, 2009. http://medicine.iupui.edu/flockhart/table.htm.

11. Gale RE, Green C, Allen C, et al (2008) The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. Blood;111:2776-2784.

12. Gotlib J, Kluin-Nelemans H, George T, et al (2012) KIT Inhibitor Midostaurin in Patients with Advanced Systemic Mastocytosis: Results of a Planned Interim Analysis of the Global CPKC412D2201 Trial. Blood. 2010;116:[abstract 316].

13. Hayakawa F, Towatari M, Kiyoi H, et al (2000) Tandem-duplicated Flt3 constitutively activates STAT5 and MAP kinase and introduces autonomous cell growth in IL-3-dependent cell lines. Oncogene;19(5):624-631.

14. Kantarjian H, Thomas X, Dmoszynska A, et al (2012) Multicenter, Randomized, Open-Label, Phase III Trial of Decitabine Versus Patient Choice, With Physician Advice, of Either Supportive Care or Low-Dose Cytarabine for the Treatment of Older Patients With Newly Diagnosed Acute Myeloid Leukemia. J Clin Oncol; 30 (21): 2670-2677

15. Kaplan E, M. P. (1958). "Nonparametric estimation for incomplete observations." J

Am Stat Assoc(53): 457-481.

16. Kayser S, Schlenk RF, Londono MC, et al (2009) Insertion of FLT3 internal tandem duplication in the tyrosine kinase domain-1 is associated with resistance to chemotherapy and inferior outcome. Blood;114(12):2386-2392.

17. Kindler T, Lipka D, Fisher T (2010) FLT3 as a therapeutic target in AML: still challenging after all these years. Blood;116:5089-5102.

18. Kiyoi H, Naoe T, Nakano Y, et al (1999) Prognostic implication of FLT3 and N-RAS gene mutations in acute myeloid leukemia. Blood;93(9):3074-3080.

19. Kiyoi H, Towatari M, Yokota S, et al (1998) Internal tandem duplication of the FLT3 gene is a novel modality of elongation mutation which causes constitutive activation of the product. Leukemia;12(9):1333-1337.

20. Kottaridis PD, Gale RE, Frew ME, et al (2001) The presence of a FLT3 internal tandem duplication in patients with acute myeloid leukemia (AML) adds important prognostic information to cytogenetic risk group and response to the first cycle of chemotherapy: analysis of 854 patients from the United Kingdom Medical Research Council AML 10 and 12 trials. Blood;98:1752-1710.

21. Levis M (2011) FLT3/ITD AML and the law of unintended consequences. Blood 117:697-6990.

22. Levis M, Brown P, Smith B, et al (2006) Plasma inhibitory activity (PIA): a pharmacodynamic assay reveals insights into the basis for cytoxic response to FLT3 inhibitors. Blood 108:3477.

23. Lubbert, M., B. Ruter, et al. (2007). "Continued Low-Dose Decitabine (DAC) Is an Active First-Line Treatment in All Cytogenetic Subgroups of Older AML Patients: Results of the FR00331 Multicenter Phase II Study." ASH Annual Meeting Abstracts **110**(11): 300-.

24. Manley PW, Boulton C, Caravatti G, et al (2003) Preclinical profile of PKC412 (midostaurin) as an FLT3 inhibitor for the therapy of AML. Presented at the American Association for Cancer Research Annual Meeting, Washington, DC, July 11-14, 2003 (poster 1004).

25. Meshinchi S, Alonzo TA, Stirewalt DL, et al (2006) Clinical implications of FLT3 mutations in pediatric AML. Blood;108(12):3654-3661.

26. NCCN Guidelines v1. (2012) National Comprehensive Care Network. NCCN Clinical Practice Guidelines in Oncology – Acute Myeloid Leukemia. Version 2.2012.

27. Ravandi F, Burnett A, Agura E, et al (2007) Progress in the Treatment of Acute Myeloid Leukemia. Cancer;110:1900–10.

28. Sato T, Yang X, Knapper S, et al (2011) FLT3 ligand impedes the efficacy of FLT3 inhibitors in vitro and in vivo. Blood;117(12):3286-3293.

29. Schnittger S, Schoch C, Dugas M, et al (2002) Analysis of FLT3 length mutations in 1003 patients with acute myeloid leukemia: correlation to cytogenetics, FAB subtype, and prognosis in the AMLCG study and usefulness as a marker for the detection of minimal residual disease. Blood;100(1):59-66.

30. Stone RM, DeAngelo DJ, Klimek V, et al (2005) Patients with acute myeloid leukemia and an activating mutation in FLT3 respond to a small-molecule FLT3 tyrosine kinase inhibitor, PKC412. Blood; 2005;105:54-60.

31. Stone RM, Fischer T, Paquette R, et al (2009) A phase 1b study of midostaurin (PKC412) in combination with daunorubicin and cytarabine induction and high-dose cytarabine consolidation in patients under age 61 with newly diagnosed de novo acute myeloid leukemia: overall survival of patients whose blasts have FLT3 mutations is similar to those with wildtype FLT3. ASH 2009 Abstract #634, Blood, Vol 114.

32. Stone RM, Fischer T, Paquette R, et al (2012) Phase IB study of FLT3 kinase inhibitor midostaurin with chemotherapy in younger newly diagnosed adult patients with acute myeloid leukemia. Leukemia 26, 2061-2068.

33. Thiede C, Steudel C, Mohr B, et al (2002) Analysis of FLT3-activating mutations in 979 patients with acute myelogenous leukemia: association with FAB subtypes and identification of subgroups with poor prognosis. Blood;99(12):4326-4335.

34. Utz I, Spitaler M, Rybczynska M, et al (1998) Reversal of multidrug resistance by staurosporine derivativesCGP41251 and CGP42700. Int. J. Cancer.; 77: 64-9.

35. Weisberg E, Boulton C, Kelly LM, et al (2002) Inhibition of mutant FLT3 receptors in leukemia cells by the small molecule tyrosine kinase inhibitor PKC412. Cancer Cell; 1: 433-443.

36. Yin O, Wang Y, Lanza C, et al (2008) Pharmacokinetics (PK) and pharmacodynamics (PD) of midostaurin (PKC412) in patients with acute myeloid leukemia (AML). J Clin Oncol 26:388s, (abstr 7064).

Appendix Ia: Drugs with Risk of Torsades de Pointes

This list contains medications that are generally accepted (and documented in published data) as having an increased risk of QT prolongation and/or torsades de pointes. Concomitant administration of midostaurin and a medication on this list is **prohibited**.

Generic Name	Brand Name	Comments
Amiodarone	Cordarone®, Pacerone®	Low risk torsades de pointes
Arsenic trioxide	Trisenox®	Torsades de pointes
Bepridil	Vasocor®	
Chloroquine	Aralen®	
Chlorpromazine	Thorazine®	
Cisapride	Propulsid®	Restricted availability in U.S.
Clarithromycin	Biaxin®	
Disopyramide	Norpace®	Torsades de pointes
Dofetilide	Tikosyn®	Torsades de pointes
Dolasetron	Anzemet®	
Droperidol	Inapsine®	Torsades de pointes
Erythromycin	Erythrocin®, E.E.S. ®	IV > PO
Halofantrine	Halfan®	
Haloperidol	Haldol®	IV > PO, high doses increase QT prolongation and torsades de pointes
Ibutilide	Corvert®	Torsades de pointes, female > male, non-Caucasian > Caucasian
Levomethadyl	Orlaam®	
Mesoridazine	Serentil®	
Methadone	Dolophine®, Methadose®	
Pentamidine	Pentam®, Nebupent®	
Pimozide	Orap®	
Procainamide	Pronestyl®, Procan®, Procanbid®	N-acetylprocainamide causes torsade de pointes, not parent compound
Quinidine	Cardioquin®, Quinaglute®	Torsades de pointes
Sotalol	Betapace®	Torsade de pointes female > male
Sparfloxacin	Zagam®	
Thioridazine	Mellaril®	

Note: the above list is not all-inclusive.

References:

Al-Khatib SM, Allen LaPointe NM, Kramer JM, Califf RM. What Clinicians Should Know About the QT Interval. *Journal of the American Medical Association* 2003;289:2120-2127.

Crouch MA, Limon L, Cassano AT. Clinical Relevance and Management of Drug-Related QT Interval Prolongation. *Pharmacotherapy* 2003;23:887-908.

Kies SJ, Pabelick CM et al. Anesthesia for Patients with Congenital Long QT Syndrome. *Anesthesiology* 2005;102:204-210

Li EC, Esterly JS, Pohl S, Scott SC, McBride BF. Drug-Induced QT-Interval Prolongation: Considerations for Clinicans. *Pharmacotherapy* 2010;30:684-701.

Roden DM. Drug-Induced Prolongation of the QT Interval. *The New England Journal of Medicine* 2004;350:1013-1022.

http://www.azcert.org/medical-pros/druginteractions.cfm Accessed 5/13/11

Appendix Ib: Drugs with Possible or Conditional Risk of Torsades de Pointes

This list contains medications that, in some reports, have been associated or weakly associated with causing torsades de pointes and/or QT prolongation. There is insufficient data that these medications alone may cause torsades de pointes and/or QT prolongation, however when midostaurin is given concomitantly with a medication on this list (or other risk factors are present such as bradycardia, electrolyte disturbances, congenital long QT syndrome, or concomitant drugs that inhibit metabolism), there may be possible or conditional risk of torsades de pointes and/or QT prolongation. Extreme caution and careful monitoring should be instituted with concomitant administration of midostaurin and a medication on this list.

Generic Name	Brand Name	Comments
Alfuzosin	Uroxatral®	
Amantadine	Symmetrel®	Low
Amitriptyline	Elavil®	Nonspecific ECG changes reported.
Atazanavir	Reyataz®	
Azithromycin	Zithromax®	
Chloral hydrate	Noctec®	
Ciprofloxacin	Cipro®	
Citalopram	Celexa®	
Clomipramine	Anafranil®	
Desipramine	Pertofrane®	QT prolongation, VF/sudden death reported
Diphenhydramine	Benadryl®, Nytol®	
Dolasetron	Anzemet®	Granisetron < Ondansetron < Dolasetron
Doxepin	Sinequan®	
Dronedarone	Multaq®	
Escitalopram	Lexapro®, Cipralex®	
Felbamate	Felbatrol®	
Flecainide	Tambocor®	
Foscarnet	Foscavir®	
Fosphenytoin	Cerebyx®	
Fluconazole	Diflucan®	IV > PO
Fluoxetine	Prozac®, Sarafem®	1 in 10,000 ventricular arrhythmias reported
Galantamine	Reminyl®	
Gatifloxacin	Tequin®	
Gemifloxacin	Factive®	
Granisetron	Kytril®	Granisetron < Ondansetron < Dolasetron
Imipramine	Norfranil®	Nonspecific arrhythmias reported
Indapamide	Lozol®	
Isradipine	Dynacirc®	
Itraconazole	Sporanox®	
Ketoconazole	Nizoral®	
Lapatinib	Tykerb®	
Levofloxacin	Levaquin®	Lower risk than that of similar agents
Lithium	Lithobid®, Eskalith®	
Moexipril/HCTZ	Uniretic®	

Moxifloxacin	Avelox®	
Nicardipine	Cardene®	
Nilotinib	Tasigna®	
Nortriptyline	Pamelor®	Nonspecific arrhythmias reported
Octreotide	Sandostatin®	
Ofloxacin	Floxin®	
Ondansetron	Zofran®	Granisetron < Ondansetron < Dolasetron
Oxytocin	Pitocin®	
Paliperidone	Invega®	
Paroxetine	Paxel®	Lower risk than TCA's
Perflutren lipid microspheres	Definity®	
Protriptyline	Vivactil®	
Quetiapine	Seroquel®	QT prolongation
Ranolazine	Ranexa®	
Risperidone	Risperdal®	QT prolongation, sudden death reported
Ritonavir	Norvir®	
Sertraline	Zoloft®	Lower risk than TCA's
Solifenacin	VESIcare®	
Sunitinib	Sutent®	
Tacrolimus	Prograf®	
Tamoxifen	Nolvadex®	
Telithromycin	Ketek®	
Tizanidine	Zanaflex®	
Trazodone	Desyrel®	
Trimethoprim-Sulfa	Sulfa®, Bactrim®, Bactrim DS®	Low
Trimipramine	Surmontil®	
Vardenafil	Levitra®	
Venlafaxine	Effexor®	1 :1000 risk of arrhythmia reported
Voriconazole	VFend®	
Ziprasidone	Geodon®	QT prolongation, 1:1000 risk of arrhythmia

Note: the above list is not all-inclusive.

References:

Al-Khatib SM, Allen LaPointe NM, Kramer JM, Califf RM. What Clinicians Should Know About the QT Interval. *Journal of the American Medical Association* 2003;289:2120-2127.

Crouch MA, Limon L, Cassano AT. Clinical Relevance and Management of Drug-Related QT Interval Prolongation. *Pharmacotherapy* 2003;23:887-908.

Kies SJ, Pabelick CM et al. Anesthesia for Patients with Congenital Long QT Syndrome. *Anesthesiology* 2005;102:204-210

Li EC, Esterly JS, Pohl S, Scott SC, McBride BF. Drug-Induced QT-Interval Prolongation: Considerations for Clinicans. *Pharmacotherapy* 2010;30:684-701.

Roden DM. Drug-Induced Prolongation of the QT Interval. *The New England Journal of Medicine* 2004;350:1013-1022.

http://www.azcert.org/medical-pros/druginteractions.cfm Accessed 5/13/11

Appendix II: ECOG Performance Status

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix III: Patient Medication Diary

Name _____ Study No. MC1483

Patient No. _____

Please complete this diary on a daily basis. You will take the study medication (midostaurin) twice a day and you should take the medicine at about the same time in the morning and in the evening each day. Do not miss any capsules. Midostaurin capsules should be administered orally, twice daily at the same time every day and together with food.If the pills are thrown up, this should be noted on your diary but you should not take another pill until your next scheduled dose.
Complete non-shaded regions if you are taking midostaurin on days 8-21.
Complete all regions if you are taking midostaurin daily.

Day	Date (mm/dd/yy)			midostaurin	
		Time taken	Meal time	Dose in mg	Number of tablets
1		a.m.	a.m.		
		p.m.	p.m.		
2		a.m.	a.m.		
		p.m.	p.m.		
3		a.m.	a.m.		
		p.m.	p.m.		
4		a.m.	a.m.		
		p.m.	p.m.		
5		a.m.	a.m.		
		p.m.	p.m.		
6		a.m.	a.m.		
		p.m.	p.m.		
7		a.m.	a.m.		
		p.m.	p.m.		
8		a.m.	a.m.		
		p.m.	p.m.		
9		a.m.	a.m.		
		p.m.	p.m.		
10		a.m.	a.m.		
		p.m.	p.m.		
11		a.m.	a.m.		
		p.m.	p.m.		
12		a.m.	a.m.		
		p.m.	p.m.		
13		a.m.	a.m.		
		p.m.	p.m.		
14		a.m.	a.m.		
		p.m.	p.m.		

Day	Date (mm/dd/yy)			midostaurin	
		Time taken	Meal time	Dose in mg	Number of tablets
15		a.m.	a.m.		
		p.m.	p.m.		
16		a.m.	a.m.		
		p.m.	p.m.		
17		a.m.	a.m.		
		p.m.	p.m.		
18		a.m.	a.m.		
		p.m.	p.m.		
19		a.m.	a.m.		
		p.m.	p.m.		
20		a.m.	a.m.		
		p.m.	p.m.		
21		a.m.	a.m.		
		p.m.	p.m.		
22		a.m.	a.m.		
		p.m.	p.m.		
23		a.m.	a.m.		
		p.m.	p.m.		
24		a.m.	a.m.		
		p.m.	p.m.		
25		a.m.	a.m.		
		p.m.	p.m.		
26		a.m.	a.m.		
		p.m.	p.m.		
27		a.m.	a.m.		
		p.m.	p.m.		
28		a.m.	a.m.		
		p.m.	p.m.		

Participant's Signature: _____ Date: _____

Appendix IV
Acute Myeloid Leukemia WHO 2008 Criteria

Acute myeloid leukemia and related precursor neoplasms, and acute leukemias of ambiguous lineage (WHO 2008)

Categories

Acute myeloid leukemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
- APL with t(15;17)(q22;q12); *PML-RARA**
- AML with t(9;11)(p22;q23); *MLLT3-MLL*†
- AML with t(6;9)(p23;q34); *DEK-NUP214*
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- *Provisional entity: AML with mutated NPM1*
- *Provisional entity: AML with mutated CEBPA*

Acute myeloid leukemia with myelodysplasia-related changes‡

Therapy-related myeloid neoplasms§

Acute myeloid leukemia, not otherwise specified (NOS)
- Acute myeloid leukemia with minimal differentiation
- Acute myeloid leukemia without maturation
- Acute myeloid leukemia with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- Acute erythroid leukemia
  - Pure erythroid leukemia
  - Erythroleukemia, erythroid/myeloid

Acute megakaryoblastic leukemia

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis (syn.: acute myelofibrosis; acute

Appendix V

SAE REPORT
PROCESS IMMEDIATELY

TO: INTEGRATED MEDICAL SAFETY
NOVARTIS PHARMACEUTICALS CORPORATION
FAX: [redacted]

FROM:_____

PHONE:( )_____**FAX:( )**_____

NUMBER OF PAGES (INCLUDING COVER SHEET):_____

(If you encounter problems with the fax transmission please call [redacted] *)*

Please complete the following to avoid unnecessary delay in processing your SAE report:

INVESTIGATOR NAME: _____

CENTER NUMBER: _____

TRIAL DRUG: _____

STUDY/PROTOCOL NUMBER: _____

PATIENT ID/NUMBER: _____

ARGUS CASE ID NUMBER (FOLLOW-UP CASES) _____

COMMENTS: _____

_____

THIS DOCUMENT CONTAINS IMPORTANT SAFETY INFORMATION.
IF FAX IS RECEIVED IN ERROR, PLEASE FORWARD TO
[redacted]