A Phase 2 study of WEE1 Inhibition with AZD1775 alone or combined with Cytarabine in Patients with advanced Acute Myeloid Leukemia, Myelodysplastic Syndrome and Myelofibrosis

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Study # S17-01816
NCT # NCT03718143

Drug Availability
Supplied Investigational Agents: AZD1775
Commercial Agents: Cytarabine (cytosine arabinoside or AraC)

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

Initial version: February 6, 2018
Amended: August 24th, 2018
Amended: October 26, 2018
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Statement of Compliance

This study will be conducted in accordance with the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), 21 CFR Parts 50, 56, 312, and 812 as applicable, any other applicable US government research regulations, and institutional research policies and procedures. The International Conference on Harmonisation ("ICH") Guideline for Good Clinical Practice ("GCP") (sometimes referred to as "ICH-GCP" or "E6") will be applied only to the extent that it is compatible with FDA and DHHS regulations. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training

PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Phase 2 study of WEE1 Inhibition with AZD1775 alone or combined with Cytarabine in Patients with advanced Acute Myeloid Leukemia, Myelodysplastic Syndrome and Myelofibrosis

Protocol Number: s17-01816

This study will be conducted in compliance with the clinical study protocol (and amendments), International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guidelines for current Good Clinical Practice, and applicable regulatory requirements.

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Signature

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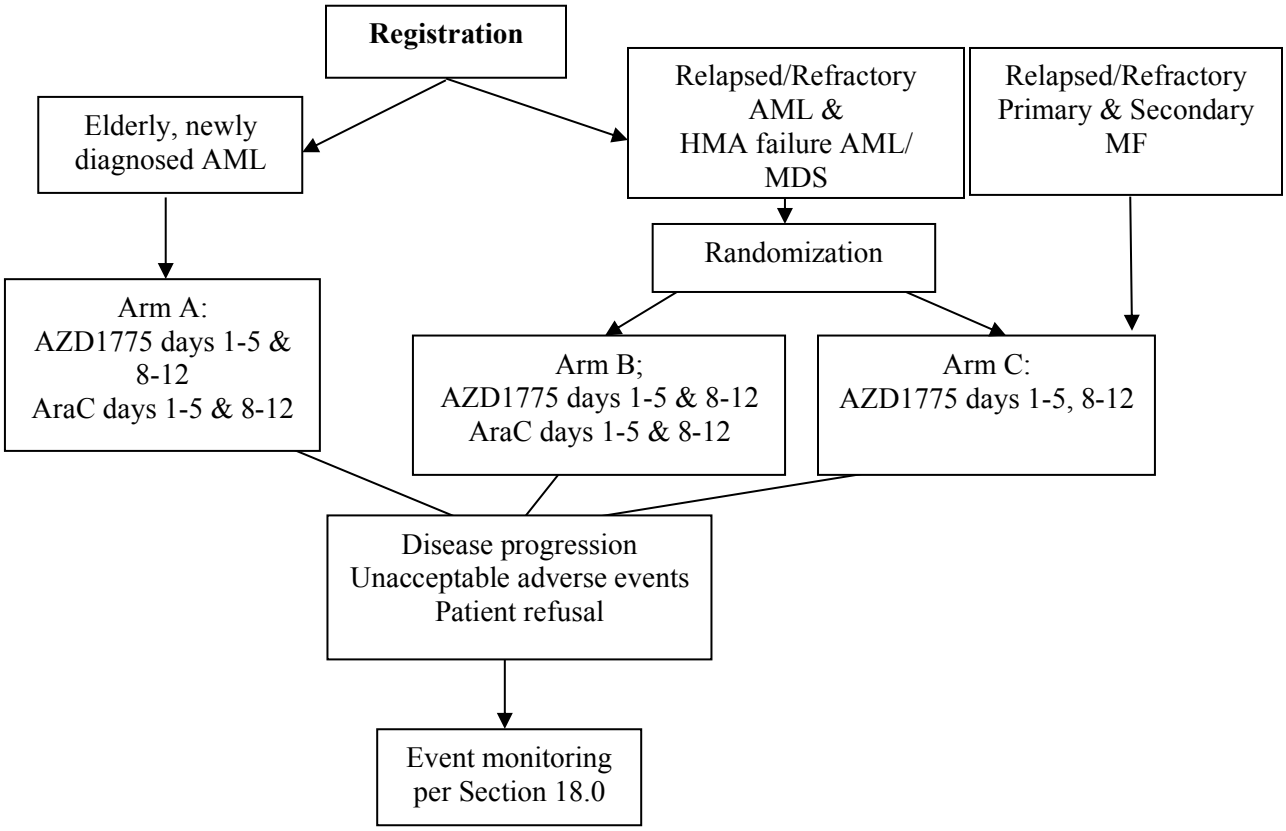
Date

Index

Schema



If a patient is deemed ineligible or a does not start first dose of treatment, please refer to Section 13.0 for follow-up information.

Cycle length=28 days
NOTE: The Safety portion of this trial will monitor six patients in each arm (combination and single agent) and observe them for a minimum of 28 days to assess toxicities.
Primary & Secondary MF: Primary Myelofibrosis (PMF) and Secondary MF after Polycythemia Vera (PV) and Essential Thrombocytosis (ET) (post-PV/ post-ET MF)

Generic name: AZD1775, Adavosertib Brand name(s): n/a Availability: Provided by AstraZeneca	Generic name: Cytosine arabinoside Brand name(s): Cytosar, ® Availability: Commercially available

1.0 Background

1.1 Acute Myeloid Leukemias (AML), Myelodysplastic Syndrome (MDS) and Myelofibrosis (MF)

Despite progress in the treatment of AML and MDS, most adult patients with AML and advanced/progressive MDS still do very poorly with current therapy and many die from their disease (Abe et al. 2008). Patients with primary refractory or relapsed AML have a particularly poor outcome, as well as MDS patients who are refractory, progress on or relapse after hypomethylating agent (HMA) based therapies (Duong et al. 2013, Prébet et al. 2011, Jabbour et al. 2010).

Acute myeloid leukemia patients who fail to achieve a complete remission (CR) with first induction therapy have a dismal outcome and only a small percentage of patients are alive at 1 year (Bai et al 2008). Current therapy is also inadequate for relapsed leukemias with a true long-term cure rate of less than 10% (Bai et al. 2008). Recently, comparable clinical activity and outcomes between HMAs and cytotoxic chemotherapy has been demonstrated in secondary, elderly and unfavorable cytogenetics AML in first line therapy (Quantas-Cardama et al. 2012 and Fenaux et al. 2010). Thus, many experts feel that these patients are candidates for lower intensity treatment as first line intervention.

The outcome of patients with advanced myelodysplastic syndrome (MDS) in the intermediate and IPSS intermediate-2, and especially high-risk category is almost as poor as for patients with acute leukemia. Median survival in this group is 4-5 months (Schanz et al. 2012 and Greenberg et al. 1997). The two approved HMAs Azacytidine (AZA) and Decitabine (DAC) have activity, however CR rates are less than <10-18% and overall responses (CR, PR and clinical benefit such as hematological improvements) approach at a maximum 40-50% in the first line treatment setting in MDS (Fenaux et al 2009 and Lubbert et al 2011).

Responses and survival in MDS patients having failed or progressed on or after HMA treatment is very poor with a median survival of 4.3-5.8 months and a 1-year survival of 17-29% in the largest three studies to date (Duong et al. 2013, Prébet et al. 2011, Jabbour et al. 2010). Accordingly HMA failure MDS represents one of the largest patient groups in need for novel agents and investigational therapies. In fact, apart from allogeneic transplant for which most patients do not qualify, investigational regimens were as good and better than cytotoxic chemotherapy after HMA failure (Prébet et al. 2011).

Azacitidine (AZA) and Decitabine (DAC) are often used as lower intensity, outpatient treatments in elderly AML patients not fit for induction treatment. Responses are comparable to somewhat lower than in treating MDS patients with CR/CRi rates ranging from 7-18% (Fenaux et al. 2010 and Kantarjian et al. 2012). Thus, there is likewise a great demand for improvement of alternative lower intensity, outpatient regimens and new combinations for elderly AML patients. Interestingly, in several earlier studies low-dose s.c. Cytarabine (AraC) alone or with growth factor support exhibited quite encouraging response rates of CR and PR of 18% and 8% respectively (Aul & Schneider 1989). Several studies also have been reported on the potential activity of low-dose AraC (AraC) in MDS (Visani et al. 2004). However, if the natural history of the disease is changed is unknown and there is significant room for improvements in therapeutic options for these patients. In summary, available data demonstrates the clinical activity of HMAs and AraC specifically in elderly AML and MDS patients, providing additional clinical justification, in addition to our pre-clinical data, to combine AZD1775 with AraC as one of the treatment arms in this protocol.

In conclusion, improvements in therapy for elderly AML patients, patients with relapsed/refractory AML as well as advanced MDS patients, particularly those who failed HMA treatments are urgently needed.

Investigational therapies are one of the recommended therapeutic choices for these patients due to the lack of effective standard salvage treatments. Pre-clinically, inhibition of WEE1 kinase is one of the most potent sensitizers to AraC, identified in large-scale RNAi screens. Sensitization potential between WEE1 inhibtion and AraC was best at lower AraC concentrations as we have published (Tibes et al. 2012), and hence lower dose AraC will be used in the combination arm as proposed in this protocol. The design of this trial offers relapsed and progressive AML and MDS patients novel treatment options in the form of either single agent AZD1775 or in combination with AraC, and thereby will investigate for the first time the clinical activity of WEE1 inhibition in AML and MDS.

Myeloproliferative neoplasms (MPN) - Primary (PMF) and Secondary Myelofibrosis: MPNs are clonal stem cell malignancies classified as Philadelphia chromosome negative myeloproliferative neoplasms (MPN) by the World Health Organization (WHO) (Vardiman et al., 2009). Myelofibrosis is divided into Primary Myelofibrosis (PMF) and Secondary or so called post-Polycythemia Vera (PV) and post-Essential Thrombocythemia (ET) MF, which is evolution of preceeding ET and PV into MF. Post-PV/ET MF occurs in around 5-15% of PV and ET patients (Tibes et al 2012) and resembles the clinical picture of PMF (Tibes et al, 2012).

Patients with MF suffer from severe constitutional symptoms, progressive hepatosplenomegaly, peripheral blood cytopenias often requiring transfusion (Tibes et al, 2012) and an increased risk of leukemia transformation, termed MPN-Blast Phase (BP), which clinically resembles acute leukemia (Kundranda et al, 2012). At progression PV and ET proceed through an accelerated phase (MF-AP) which upon further progression can lead to MPN-BP. Currently treatment options for MF patients are determined by risk assessment of individual patients by prognostic scoring systems that are based on various clinical parameters including age, leukocyte count, hemoglobin level, platelet count, monocyte count, peripheral blast count, presence of splenomegaly, constitutional symptoms and degree of bone marrow fibrosis (BMF) (Tibes et al, 2012). Patients that are symptomatic can be treated with the JAK2 inhibitor Ruxolitinib (Tibes et al, 2012a). Patients under the age of 65-70 without significant co-morbidities and intermediate/high risk disease are considered candidates for allogeneic stem cell transplant (allo-SCT) (Tibes et al, 2012), which is the only modality offering a potential cure although at significant risk of transplant related mortality (TRM) as well as complications (morbidity and mortality) from graft versus host disease (GVHD) and other long term complications (Kundranda et al, 2012). Therefore, patients older than 65-70 years or with substantial co-morbidities are considered not to be candidates for allo-SCT and upon JAK2 failure or intolerance become candidates for experimental therapies as propsoed in this protocol.

For patients not candidates for allo-SCT, patients with accelerated MF and/or those failing JAK2 inhibitor therapy there are no standard approved treatments. Cytotoxic induction chemotherapy has no role for those patients not canduidates/ proceeding to allo-SCT (Tibes et al, 2012). These advanced MF patients have poor outcome to current therapies with response rates < 5-10% and median survivial of < 6-12 months. Hydroxyurea is commonly given for count (WBC) control but does not alter the disase course as a single agent. Therefore novel therapeutic approaches are urgently needed for this disease.

1.2 Overview of the WEE1 pathway and DNA damage and Cell cycle inhibition

1.21 Background on Cytarabine, DNA Damage Repair and Cell Cycle Checkpoints

Cytarabine (AraC) has been the most widely used and is still the overall most active drug in AML (Rowe 2009). It forms the backbone of most AML and MDS induction and consolidation regimens, and has activity at low doses given subcutaneously both in AML and MDS (Bolwell et al. 1987, Kantarjian et al 2012).

AraC is an S-phase (cell cycle) specific agent that undergoes conversion and phosphorylation to a tri-phosphate form with subsequent incorporation into DNA of dividing cells. This usually triggers activation of the intra-S phase checkpoint a genotoxin-activated signaling pathway that stabilizes stalled replication forks and slows cell cycle progression by blocking the firing of late-acting DNA replication origins (Dimitrova & Gilbert 2000, Morita 1976, Grant 1998). AraC incorporation leads to single stranded DNA damage that later is converted to double strand DNA damage ultimately leading to cell cycle arrest and repair of damaged DNA (Do et al. 2013). Many of these processes are either directly regulated by WEE1 kinase, i.e. cell cycle arrest via CDK1/2, as well as WEE1 kinase plays a central role in the networks of DNA repair initiation, i.e. via its effect on CHEK1 or PLK1. Thus WEE1 kinase has a central role in many checkpoint and DNA damage mediated processes (Langerak & Russell 2011, Perry & Kornbluth 2007).

Interfering with cell cycle checkpoints and DNA damage repair (DDR) in combination with agents that cause DNA single or double strand breaks has been proposed as a promising concept in cancer therapy and captures a potential synthetic lethal molecular interaction. Advanced leukemias are genomically highly unstable, with cell cycle checkpoints and DDR pathways impaired causing these cells to rely on a fewer number of checkpoints, and highly reliant on the later stage in the cycle cycle at the G2/M transition (Cavelier et al. 2009, Didier et al. 2008). Thus, interfering with cell cycle checkpoints and DNA damage repair (DDR) in combination with agents that cause DNA single or double strand breaks such as AraC has been proposed as a promising concept in cancer therapy and captures a potential synthetic lethal molecular interaction (Tibes et al. 2012).

1.22 Inhibition of WEE1 kinase by AZD1775

WEE1 kinase is an evolutionary conserved kinase regulating late G2/M cell cycle checkpoints, directing cells either towards cell cycle arrest allowing time for DNA repair or proceeding with progression into mitosis. However, emerging data indicates that WEE1 kinase activates the intra S-phase checkpoint as well and interferes with DNA damage response through various processes. WEE1 kinase acts through and is the main kinase phosphorylating and regulating Cdc2 (CDK1), which in complex with Cyclin B is a master regulator of mitotic entry at G2/M. However, WEE1 is also the main kinase phosphorylating CDK2 (assembles with cyclin A) and exerts a prominent function in G1/S phase and the intra S-phase checkpoint (Perry & Kornbluth 2007).

Based on two unbiased RNAi screens and subsequent validation studies, inhibition of WEE1 kinase was identified as one of the most potent sensitizers to AraC in AML cells (Tibes et al 2012, Porter et al. 2012). We postulate that WEE1 kinase is the essential kinase that governs the “escape pathway” in malignant myeloid cells under cellular stress with cytotoxic agents, particularly AraC. Therefore inhibition of WEE1 kinase by AZD1775 with AraC is a rational combination in aggressive myeloid malignancies and leukemias. In addition, AZD1775 had single agent activity and its anti-leukemic activity alone or in combination is independent of p53 mutation and function in AML (Van Linden et al. 2013 and Tibes, unpublished observation).

1.23 Rational of WEE1 inhibition and combination with Cytarabine (AraC)

AraC is the backbone of therapy for myeloid leukemias. It is used in regimens for lymphoid leukemias as well as for patients with advanced MDS. Pre-clinically WEE1 inhibition sensitized cells to several cytotoxic agents including AraC. In Phase 1 and 2 ongoing clinical trials in solid tumor patients, the only in class Wee1 inhibitor AZD1775 is well tolerated with platinum compounds and gemcitabine providing a therapeutic window even at full standard doses of cytotoxic chemotherapies. We have generated

preliminary data that shows potent sensitization with synergy of AZD1775 and combined with AraC in vitro and ex vivo (Tibes et al. 2012). Other groups have shown potent activity in vivo mouse models as well (Porter et al. 2012). In addition WEE1 is highly expressed in myeloid leukemias (Tibes et al. 2012). Based on these data we hypothesize that the WEE1 kinase inhibitor AZD1775 alone and in combination with AraC will have strong synergistic clinical activity with manageable toxicity (given the already existing clinical data of tolerability in solid tumors) in patients with advanced myeloid malignancies. We further postulate that there will be single agent anti-leukemic activity of AZD1775 providing a rationale to compare AZD1775 single agent vs. in combination with AraC in patients with MDS and AML that would otherwise have limited therapeutic options remaining.

The molecular pathogenesis of MPNs and MF involves high replicative stress (Chen et al, 2014 and 2015). In MF, recent data indicates that PARP inhibitors may have activity (Pratz et al 2016 and 2017). WEE1 inhibition by AZD1775, similarly to PARP inhibitors effectively targets cancers with high replication stress (Pfister et al 2015). We have generated preliminary data that AZD1775 alone is active and when combined with HU exhibits strong sensitization in pre-clinical models (Tibes, unpublished data). Given the lack of effective therapeutic regimens in advanced, JAK2 failure MF patients we plan to include these patients in the protocol treatment.

1.3 Overview of AZD1775

The following overview of AZD1775 (Section 1.3 and 1.4) is based on the knowledge available at the time this protocol was first finalized and is based on Edition 12 of the Investigator's Brochure, Edition 12, dated 18 February 2015, with a data cut-off date of 11 November 2014. For more detailed and up-to-date information, please consult the current Investigator's Brochure.

AZD1775 is a highly selective, adenosine-triphosphate (ATP) competitive, small-molecule inhibitor of the WEE1 kinase that sensitizes tumour cells to cytotoxic agents and is being developed for the treatment of advanced solid tumours with p53 pathway deficient malignancies. Inhibition of the DNA damage checkpoint kinase WEE1 potentiates genotoxic chemotherapies by abrogating cell-cycle arrest and eliminating the opportunity for proper DNA repair to occur. From a therapeutic standpoint, inhibition of checkpoint kinases that mediate cell-cycle arrest may force tumour cells to continue cell division before chemically induced DNA damage is repaired, eventually causing apoptosis or mitotic catastrophe (Medema and Macurek 2012).

The primary objective of the clinical development of AZD1775 is its use as a chemosensitizing drug in combination with a cytotoxic agent (or combination of agents) for treatment of advanced tumors. In vitro experiments demonstrate that AZD1775 has synergistic cytotoxic effects when administered in combination with various DNA damaging agents that have divergent mechanisms of action. In studies with matched ovarian cell lines (p53 WT and shRNA p53 knockdown), AZD1775 enhanced cell death induction by gemcitabine in p53-deficient but not in p53 positive control cells. AZD1775 also demonstrates synergistic effects on cell death induction when used in combination with cisplatin and carboplatin in a p53-dependent manner. Cervical cancer cells with HPV induced inactivation of p53 demonstrated chemosensitization to cisplatin and topotecan by AZD1775.

The ability of AZD1775 to affect tumour growth as monotherapy or to enhance the antitumor effects of gemcitabine, carboplatin, cisplatin, capecitabine, 5-fluorouracil, and gamma irradiation was evaluated in immunocompromised host animals bearing human xenograft tumors.

The anti-tumor effect of AZD1775 dosed as monotherapy was investigated in the A427 non small-cell lung cancer nude mouse xenograft model. Daily treatment with AZD1775 led to 51% tumour regression (n=10) and mean body weight loss did not exceed 5% over the course of the study. AZD1775 single agent treatment also led to tumour growth inhibition in additional xenograft models: 92% TGI (Day 28) in SKMES1 model of non-small-cell-lung cancer (NSCLC), 13% regression (day 11) in LoVo colorectal cancer model and 64% TGI(day 19) in NCI-H2122 NSCLC.

The anti-tumour effect of AZD1775 in combination with gemcitabine was investigated in the WiDr (human colorectal adenocarcinoma) nude rat xenograft model. Several schedules of gemcitabine + AZD1775 were explored. A 10 mg/kg dose of AZD1775 significantly enhanced the anti-tumour effect of gemcitabine in WiDr tumours with % treated/control (T/C) = -2%.

The anti-tumour effect of AZD1775 in combination with carboplatin was investigated in the HeLa-luc (human cervical adenocarcinoma) nude rat xenograft model. AZD1775 dose-dependently enhanced the anti-tumour effect of carboplatin tumors with %T/C = 85, 39 and 28% at doses of 10, 20 and 30 mg/kg, respectively.

The anti-tumour effect of AZD1775 in combination with carboplatin or cisplatin was also investigated in the HeLa-luc model. These experiments showed that AZD1775 dose-dependently enhanced the anti-tumour effect of cisplatin with %T/C = -5 and -16% at doses of 10 and 20 mg/kg respectively, compared to or cisplatin alone (24% T/C)

AZD1775 enhanced the anti-tumour efficacy of 5-FU and capecitabine when used in combination with these agents, as well; and experiments with nude mouse xenograft models of A549 (p53 wild type) and Calu-6 (p53 null) NSCLC cell lines showed enhanced antitumour growth effect of radiotherapy preferentially in p53 mutant xenograft tumors. Please refer to the AZD1775 Investigator Brochure (IB) for more detailed information regarding these experiments and findings.

1.31 Pharmcodynamics

Inhibition of CDC2 (Y15) phosphorylation and induction of Histone H3 (Ser10) phosphorylation were observed upon Wee1 inhibition *in vitro*. *In vivo* PD effects ofAZD1775 were evaluated using the WiDr xenograft nude rat model. AZD1775 (0.5, 1.0,
3.0 and 7.0 mg/kg/hr) was intravenously infused for 8 hrs, 24 hrs after administration of gemcitabine (50 mg/kg, IV). PD marker analyses were performed on tumor tissue isolated immediately after the infusion. Continuous infusion of AZD1775 caused reduction of phospho-CDC2 (Y15) in WiDr xenograft tumor tissue in a dose-dependent manner. The EC50 value was 0.28 μM, and about 80% inhibition was achieved at 1.0 mg/kg/hr (0.45 μM at 8hr). Similar dose dependency was observed in the CEA (induction of phospho-Histone H3 [Ser10]) in tumor tissue. EC50 value was 0.21 μM, and maximal effect was observed at approximately 1.0 mg/kg/hr. These data suggest that phopsho-CDC2 (Y15) and phospho-Histone H3 (Ser10) could be useful as AZD1775 PD biomarkers in tumors.

Similar PD marker changes were observed in surrogate tissues, such as skin hair follicle and peripheral blood cells in the presence or absence of the DNA damaging agent gemcitabine. Strong pCDC2 (Y15) immunopositivity was observed in skin hair bulb in the hair follicle. In combination with gemcitabine (50 mg/kg, IV: 24 hr before AZD1775 dosing), AZD1775 (0.5, 1.0 and 3.0 mg/kg/hr x 8 hrs, IV-infusion)

dose-dependently decreased these signals. An almost complete reduction of phospho-CDC2 signal was achieved at 3.0 mg/kg/hr. Phospho-CDC2 (Y15) signal in peripheral blood cells were also reduced in a dose dependent manner with significant reduction at 1.0 and 3.0 mg/kg/hr. These results suggest that hair follicles and blood cells are surrogate tissues in which phospho-CDC2 (Y15) can be used as a marker to predict PD/efficacy in tumors treated with gemcitabine.

Similar dose dependent reduction of phospho-CDC2 (Y15) by AZD1775 (0.5, 1.0 and 3.0 mg/kg/hr x 8 hrs, IV-infusion) was observed without gemcitabine pretreatment in both skin hair follicles and tumors. Thus, these PD markers may be available to predict PD/efficacy in tumors in the presence or absence of DNA damaging agents.

1.32 Nonclinical pharmacokinetics and metabolism

The pharmacokinetics of AZD1775 were evaluated in male Sprague-Dawley rats and Beagle dogs following intravenous (IV) and oral administration. AZD1775 exhibited high plasma clearance in rats and dogs (57.3 and 50.8 mL/min/kg, respectively). The terminal half-life (T1/2) of the compound was short in both species (1.6 and 1.1 hr in rats and dogs, respectively). The oral bioavailability was 59.7% in rats and 33.6% in dogs.
AZD1775 (1 μM) was moderately bound to plasma proteins from rat, dog and human, with the unbound fractions being 23.2, 40.0, and 39.5%, respectively. Metabolism was the major route of elimination of AZD1775 in rat and dog. The major metabolic pathway of AZD1775 in human liver preparations was oxidative metabolism. All metabolites observed in human liver preparations were also formed in the rat and dog. Oxidative metabolism of AZD1775 was mediated predominantly by cytochrome P450 (CYP) 3A4 and FMO3. AZD1775 was a weak reversible inhibitor of CYP2C8, CYP2C9, CYP2C19 and CYP3A4. In addition, AZD1775 was a time-dependent inhibitor of CYP3A4. Collectively, these data indicate that the pharmacokinetics of AZD1775 could be altered if AZD1775 is coadministered with CYP3A4 inhibitors and/or inducers, and depending on AZD1775 therapeutic plasma concentrations, there is also some potential for drug drug interactions when coadministered with CYP3A4 substrates.

1.33 Toxicity and safety Studies with AZD1775

In rats, the toxicologic profile of AZD1775 was evaluated using 4 separate dosing schedules; single-dose, once weekly for three weeks, and daily for 7 consecutive days or one month. A recovery (treatment-free period) was included in each study design. With each of these schedules, the toxicologic profile for physical signs, hematological changes, and gross and histomorphological findings were expected based on the cytotoxic mechanism of action of AZD1775. The major organs affected were proliferation dependent organs such as lymphoid and hematopoietic organs and gastrointestinal tract. Evidence of reversibility of all changes, based on drug-related effects observed in early death rats, was generally demonstrated by the end of the 2-week recovery period.

In the fifteen-day oral toxicity study, conducted in rats dosed once weekly for three weeks (Study Days 1, 8, and 15), no mortality or severe toxicity was observed at 300 mg/kg/day, however treatment-related body weight changes and hematological changes were observed. The magnitude of change of absolute reticulocyte counts and white blood cell parameters observed after the first dose were generally similar to those after the third dose, indicating that additive toxicity was not seen after 3 weekly intermittent doses. A trend toward recovery was observed for many of these changes following the 14 day recovery period, however recovery of hematological changes appeared to be delayed. Since the histomorphologic examination of the bone marrow revealed normal cellularity at the completion of the 14 day recovery, it is expected that hematological changes will fully recover as was seen in dogs. The magnitude of the decreased WBC and erythroid parameters were close to those observed in the previous single dose

toxicity study in rats. No histological findings were noted at the completion of the 14 day recovery period in the 300 mg/kg/day once weekly group.

In a single dose oral toxicity study, severe irreversible toxicity (mortality) was seen in 1 female out of 10 female rats after a single dose at 300 mg/kg (1800 mg/m2). In a consecutive 7-day repeat dose study, expected toxicity of hematopoietic organs and the gastrointestinal tract were observed and associated with mortality at 75 mg/kg/day and 300 mg/kg/day. At 25 mg/kg/day (14.2 μM/hr), all animals survived to scheduled necropsies and all observed toxicities were demonstrated to be reversible during the 2-week recovery period. In a 1 month rat toxicity study, toxicity of hematopoietic organs (including bone marrow, spleen, thymus, mesenteric lymph nodes, Peyer's patches) were observed at ≥10 mg/kg/day in females and at 25 mg/kg/day in males. Serum biochemical changes were observed at 25 mg/kg/day only and consisted mainly of very slight to slight decreases in total protein, albumin, and globulin and very slight increases in alanine aminotransferase (ALT) and alkaline phosphatase (ALP) in females whereas in males, the changes were limited to a slight decrease in globulin. Very slight to slight liver hepatocellular vacuolation, very slight centrilobular degeneration and slight cardiomegaly were observed at ≥10 mg/kg/day in females (except for cardiomegaly observed in females at 25 mg/kg/day only) and at 25 mg/kg/day in males; these findings in the liver and heart were considered to be correlated with anemia. At 25 mg/kg/day (25 μM/hr in females and 10 μM/hr in males), all animals survived to scheduled necropsies. In general, findings at 25 mg/kg/day were more marked in females compared to males, and all findings showed a trend towards recovery following a 4-week recovery period.

In dogs, similar dosing schedules as studied in rats were evaluated (single dose, once weekly for three weeks, and daily for 7 consecutive days or one month). Severe irreversible toxicity was not observed at the highest dose tested of 36 mg/kg (720 mg/m2) after a single dose and 3-intermittent doses (mean area under the plasma concentration time curve [AUC] from time 0 to 24 hours postdose [AUC0-24hr] for sexes combined = 17.4 μM/hr and 17.6 μM/hr, respectively). As reported in rats studies, similar hematologic changes were observed in dogs as was reported in rats; notably decreases in reticulocytes. In both the single-dose and 3 intermittent dose studies, reticulocyte counts returned to baseline following the 14-day recovery period and histomorphologic examination revealed normal cellularity in the bone marrow in these studies. In dogs receiving AZD1775 for 7 days, 15 mg/kg/day (9.5 μM/hr) was well tolerated and demonstrated expected toxicities to hematopoietic organs and the gastrointestinal tract. During a 2-week recovery period, test article-related changes recovered or showed a trend towards reversibility. In a 1-month dog repeat dose study, dose levels of 3 mg/kg/day and 10 mg/kg/day were administered daily for about 1 month. Dose dependant toxicity of hematopoietic organs (including bone marrow, thymus, lymph nodes, Peyer's patches), gastrointestinal tract, testes as well as serum biochemical changes (very slight or slight decreases in total protein, albumin, and globulin) were observed. At 10 mg/kg/day (3.60 μM/hr), all animals survived to scheduled necropsies. All findings showed a trend towards recovery following the 4-week recovery period.

AZD1775 was negative in the Microbial Mutagenesis Assay but positive in *in vitro* Chromosomal Aberrations Assays and in vivo micronucleus assay. These positive results in the chromosomal aberration assay were not unexpected based on the mechanism of action of AZD1775.

Combination treatment with AZD1775 and 5-FU was administered to tumor-bearing female nude rats for up to 5 days with several administration schedules. Test article related hematological changes (decreases in erythroid parameters, reticulocytes, leukocytes, and/or platelets) were observed with the combination treatment with AZD1775 plus 5-FU. There were no remarkable differences in the severity of these changes across the different AZD1775 administration schedules in combination with 5-FU.

These preclinical observations were expected based on the intended pharmacologic action (cytotoxicity) of the compound. The toxicity profile of AZD1775 in rats and dogs following 1 month of daily dosing was generally consistent with the toxicity profile previously observed in studies of shorter duration. Observations in rat and dog toxicology studies are generally monitorable and with evidence of reversibility within a 4-week recovery period were demonstrated to be reversible following a 2 week recovery period. These studies support continued clinical trials in subjects with advanced stage cancer.

1.4 Clinical Experience with AZD1775

The following overview of the clinical experience with AZD1775 is based on the knowledge available at the time this protocol was written and is based on Edition 16 of the Investigator's Brochure, , dated January 2018, with a data cut-off date of 11 November 2017. For more detailed and up-to-date information, please consult the current Investigator's Brochure.
As of 11 November 2017, a total of approximately 713 patients have been exposed to AZD1775 in AstraZeneca-sponsored or Merck-sponsored clinical studies. In addition, approximately 559 patients have also received AZD1775 as part of externally-sponsored scientific research. These patients include those who have received single doses per cycle as high as 1300 mg of AZD1775 as monotherapy, 325 mg of AZD1775 in a single-dose in combination with chemotherapy, and 325 mg twice a day (BID) in a multiple-dose regimen in combination with chemotherapy.The completed or terminated early studies include:

- PN001 (NCT00648648) (except for Part 3): a first-time-in-patients (FTIP), Phase I, dose-escalation study evaluating AZD1775 both as monotherapy and combination therapy with gemcitabine, cisplatin, or carboplatin in adult patients with advanced solid tumours

- PN004 (NCT01357161): a Phase II study evaluating AZD1775 combined with carboplatin and paclitaxel in patients with platinum-sensitive p53-mutant ovarian cancer

- PN005 (NCT01047007): a Phase I, dose-escalation study evaluating AZD1775 as monotherapy (Part 1), combination therapy with 5-FU (Part 2), and combination therapy with 5 FU plus cisplatin (Part 3) in adult Japanese patients with advanced solid tumours was terminated early due to portfolio prioritization in oncology at Merck after 3 patients had been enrolled in Part 1 and 8 patients had been enrolled in Part 2. Part 3 was not initiated.

- PN008 (NCT01076400): a Phase I/IIa, dose-escalation study evaluating AZD1775 in combination with topotecan plus cisplatin in adult patients with cervical cancer was terminated early due to portfolio prioritization in oncology at Merck after 7 patients had been enrolled in the dose-escalation part of the study. The Phase IIa part was not initiated.

- D6011C00001 (NCT02087176; SCRI LUN 262): a lead-in Phase II multicentre, randomised, double-blind study comparing AZD1775 plus docetaxel with placebo plus docetaxel in previously treated patients with non-small-cell lung cancer (NSCLC)

- D6011C00002 (NCT02087241; SCRI LUN 261): a Phase II study of AZD1775 plus pemetrexed and carboplatin followed by a randomised comparison of pemetrexed and carboplatin with or without AZD1775 in patients with previously untreated stage IV non-squamous NSCLC

Ongoing:

- D6010C00004 (NCT02272790; SCRI GYN 49): a multicentre Phase II study of AZD1775 plus either paclitaxel, gemcitabine, carboplatin, or pegylated liposomal doxorubicin in patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer

- D6010C00005 (NCT02511795; SCRI REFMAL 384): a Phase I study evaluating AZD1775 in combination with olaparib in refractory solid tumours.

- D6011C00003 (NCT02341456): a Phase Ib dose-finding study evaluating AZD1775 as monotherapy and in combination with carboplatin and paclitaxel in adult Asian patients with advanced solid tumours

- D6015C00001 (NCT02482311; SCRI REFMAL 383): a Phase I, dose escalation, safety and pharmacokinetic study of AZD1775 monotherapy (Schedule 1) in patients with advanced or metastatic solid tumours

- D6015C00002 (NCT02617277; SCRI REFMAL 412): a Phase I study assessing the safety, tolerability, and pharmacokinetics of AZD1775 in combination with MEDI4736 in patients with advanced solid tumours

- D6015C00003 (NCT02610075; SCRI REFMAL 398): a Phase Ib study to determine the maximum-tolerated dose (MTD) of AZD1775 monotherapy (Schedule 2) in patients with locally advanced or metastatic solid tumours.

- NCT01748825: A Phase I Study of Single-agent AZD1775 (MK-1775), a Wee1 Inhibitor, in Patients With Advanced Refractory Solid Tumors.

1.41 Clinical Safety

Several clinical studies with AZD1775 alone and in combination with (mostly full dose) cytotoxic chemotherapy have been conducted.

The RP2D of AZD1775 monotherapy has been established as 300mg QD day1-5, and 8-10 in week 1 and 2 of a 3 week schedule.

The MTDs of AZD1775 when administered with chemotherapy are presented in the table below:

Maximum-tolerated doses of AZD1775 when administered in combination with chemotherapy

Chemotherapy	Dose Frequency	AZD1775 (mg)
Gemcitabine 1000 mg/m$_2$ on Day 1 weekly for 3 consecutive weeks out of every 4 weeks	Single-dose	200
Cisplatin 75 mg/m2 on Day 1 every 21 days	Single-dose	200
Carboplatin AUC 5 on Day 1 every 21 days	Single-dose	325
Gemcitabine 1000 mg/m2 on Day 1 weekly for 3 consecutive weeks out of every 4 weeks	Multi-dose	175 QD x2 days

Cisplatin 75 mg/m2 on Day 1 every 21 days	Multi-dose	200 BID x 2.5 days
Carboplatin AUC 5 on Day 1 every 21 days	Multi-dose	225 BID x 2.5 days

BID = twice daily; QD = once daily

Based on the safety data from the completed AZD1775 clinical studies and preliminary data from ongoing studies adverse drug reactions to AZD1775 monotherapy include: anaemia, neutropenia, thrombocytopenia, QTc prolongation, gastrointestinal events such as dyspepsia, diarrhoea, nausea and vomiting (with or without dehydration or serum electrolyte decreases), as well as decreased appetite. In addition, the following events are also considered expected during treatment with AZD1775 in combination with cytotoxic chemotherapy: febrile neutropenia, leukopenia, stomatitis, asthenia, fatigue, mucosal inflammation and myalgia.

Based on information emerging during the clinical development programme of AZD1775, potential risks where a causal relationship with AZD1775 monotherapy has not been established include asthenia/fatigue, febrile neutropenia, gastrointestinal haemorrhage, lymphopenia/lymphocyte count decreased, leukopenia/WBC count decreased, myalgia, stomatitis, sepsis and transaminases elevation.

In addition, the following events are also considered potential risks for AZD1775 in combination with cytotoxic chemotherapy: tachycardia and pancytopenia.

Refer to the IB for AZD1775 for information on the potential benefits and assessment of potential and known risks.

1.42 Clinical Efficacy

The table below shows the efficacy outcome in Study PN001 by treatment arm.

Study PN001 Efficacy

Treatment	Dose Frequency	Patients Treated (N)	Patients Evaluable [N (%)]	PR* (N)	SD (N)	PD (N)	NE
AZD1775 in combination with gemcitabine	Single-dose	14	12 (85.7)	1 c	8	2	1
AZD1775 in combination with cisplatin	Single-dose	13	12 (92.3)	1 c 1 u	7	3	
AZD1775 in combination with carboplatin	Single-dose	16	15 (93.8)	1 c 1 u	3	9	1
AZD1775 in combination with gemcitabine	Multi-dose	67	55 (82.1)	1 c 2 u	35	17	

AZD1775 in combination with cisplatin	Multi-dose	45	38 (84.4)	3 c 4 u	16	15	
AZD1775 in combination with carboplatin	Multi-dose	46	44 (95.6)	2 u	25	16	

* confirmed and unconfirmed
NE=not evaluable, c=confirmed, u=unconfirmed

In Study PN001, of 176 evaluable patients who received AZD1775 (either single or multiple doses) as monotherapy or in combination with gemcitabine, cisplatin, or carboplatin, a partial response (PR) (confirmed and unconfirmed) was observed in 17 (9.7%) patients, and stable disease (SD) was observed in 94 (53.4%) patients (AZD1775 Investigator's Brochure[IB])In Study PN001, 9 patients received AZD1775 monotherapy. Single ascending doses of AZD1775 up to 1300 mg were well tolerated; the maximum tolerated dose (MTD) was not established.

In Study PN004, all patients were treated at the 225 mg AZD1775 BID 2.5 day dose level in combination with paclitaxel and carboplatin. Of the 14 evaluable patients by RECIST v1.1 in Part 1, there were 11 PRs (6 confirmed and 5 unconfirmed), and 3 SDs; 7 patients were evaluable by CA-125 with 3 CRs and 4 PRs. Final data for Part 2 is not available as of the cut-off date for this protocol.

In Study PN005, patients in Part 1 received single-cycle BID dosing of AZD1775 for 5 days at 1 of 2 dose levels as monotherapy. A cohort of 3 patients was enrolled at the starting dose level of AZD1775 65 mg BID and no serious adverse events (SAEs) were experienced.
No complete responses (CRs) or PRs were observed in either of Studies PN005 or PN008 at the time that they were terminated.

In Study PN011, patients received single-agent AZD1775 PO BID over 2.5 days per week for 2 weeks in 3-week treatment cycles. Twenty-five patients were enrolled to determine the MTD using a 3+3 design. The MTD was established at 225 mg by mouth (PO) BID for 5 doses on Weeks 1 and 2 of a 3-week schedule. Six patients with BRCA-mutated solid tumours were enrolled at the MTD. Partial responses were confirmed in two of the patients carrying BRCA mutations (ovarian cancer patient and head/neck cancer patient). Paired tumor biopsies were obtained from 5 patients treated at the MTD at baseline and after the 5th AZD1775 dose to determine the levels of pY15-Cdk and γH2AX. The biopsies showed a decrease in pY15-Cdk levels (2/5 paired biopsies). The same biopsies were analyzed for increases in γH2AX, an indicator of DNA damage. Three of the 5 biopsy pairs showed an increase in γH2AX levels. DNA damage response was observed in this study through provided paired tumor biopsies (Do et al 2015).

In Study D6011C00001, 32 patients with NSCLC were treated with 225 mg AZD1775 BID over 2.5 days in combination with docetaxel (75 mg/m2 IV) administered on Day 1 followed by pegfilgrastim on Day 4 of each 21-day cycle. The 3 patients (9.4%) that achieved PR by RECIST v1.1 had TP53 mutations. Twenty-one patients (65.6%) had SD and 10 (47.6%) of these patients had TP53 mutations. The planned Interim Analysis of 32 patients in the single cohort lead-in (Part A) suggested that toxicities associated with AZD1775 given in combination with docetaxel were greater in frequency and severity than with docetaxel alone.
Additionally, the analysis revealed that it was very unlikely the target response rate would be reached in this study and a decision was made to terminate enrolment.

In Study D6011C00002, 14 patients with NSCLC were treated with 225 mg AZD1775 BID over 2.5 days in combination with pemetrexed 500 mg/m2 IV and carboplatin AUC 6 IV, both administered on Day 1 of each 21-day cycle. Enrolment was stopped because of the introduction of new therapies for the treatment of first-line NSCLC, such as immunotherapy, which resulted in challenges in patient recruitment. In addition, the planned Interim Analysis of Study D6011C00001 revealed that it was very unlikely that the target response rate would be reached, and increased gastrointestinal and hematologic toxicities associated with AZD1775 were observed.

1.43 Clinical Pharmacokinetics and pharmacodynamics

Clinical Pharmacokinetics

The PK data of AZD1775 following a single oral administration showed a moderate rate of absorption with a Tmax occurring at 3 to 4 hours. Post-peak plasma concentrations declined essentially in a mono-exponential manner with a t1/2 in the region of 10 hours. Exposure as measured by maximum plasma drug concentration observed (Cmax) and area under the curve (AUC 0-∞) increased in a dose-proportional manner over the dose range of 325 to 1300 mg. The urinary excretion of AZD1775 was investigated after single-oral-dose monotherapy at 325, 650, and 1300 mg of AZD1775. The mean percent of total AZD1775 excreted unchanged in urine over a 24-hour period was 5.15% to 11.9%, which is comparable to what was observed in preclinical species (urinary excretion as unchanged drug in rats and dogs were ~8.6% and 11.8% of the dose, respectively, over a 48-hour collection interval). The mean renal clearance of AZD1775 at 325 mg was approximately 2.30 L/hour (38.3 mL/minute), below that expected due to filtration alone (based on an AZD1775 unbound fraction of 39.5% and a typical glomerular filtration rate of 120 mL/minute) of47.4 mL/minute, indicating that net reabsorption appeared to be taking place. Overall, the results suggest that urinary excretion is not the major route of AZD1775 elimination

Following single (100 to 325 mg) and multiple dose administrations of AZD1775 (25 to 325 mg BID and 100 to 200 mg once daily [QD]) with carboplatin, cisplatin, and gemcitabine, plasma exposure of AZD1775 was consistent with predictions based on the single-dose regimen. The median Tmax values were between 1.02 and 4.25 hours. Given a t1/2 of approximately 10 hours, steady-state was expected to be achieved after approximately 3 days of AZD1775 treatment in adult patients. Accumulation ratios for AZD1775 BID doses (geometric mean ratio = Day 3/Day 1) for the area under the plasma-concentration time curve from time 0 to 8 hours post dose ($AUC_{0\text{-}8hr}$), Cmax, and plasma drug concentration observed at 8 hours post dose (C_{8hr}) averaged 0.991 to 3.82, 0.928 to 3.32, and 1.01 to 2.98, respectively, across tested AZD1775 BID doses in combination with gemcitabine, cisplatin, and carboplatin.

Preliminary investigation of drug-drug interactions in Study PN001 suggest a 40% increase in the exposure of AZD1775 in the presence of aprepitant (moderate CYP3A4 inhibitor), but no effect with the concomitant administration of steroids (moderate CYP3A4 inducers).

Preliminary studies also suggested that the Pre-marketed Oral Formulation (PMF) of AZD1775 was similar to that of the Fit-For-Purpose (FFP) formulation.

Preliminary PK data from a Japanese combination study with AZD1775 and 5-fluorouracil (5-FU)5FU suggests that the pharmacokinetics of AZD1775 in Japanese and Caucasian patients were similar, however, further work is ongoing.

Pharmacodynamics evaluation
PN001: Skin biopsies were obtained from patients in all 3 parts of this study in order to evaluate the pharmacodynamic effects of AZD1775 in a surrogate tissue. Formalin-fixed and paraffin- embedded skin samples were analysed by immunohistochemical staining for the presence of total and phosphorylated levels of the WEE1 kinase substrate CDC2 (CDK1). Since CDC2 is expressed and phosphorylated in a cyclical manner and only observed in proliferating cells in the epidermis, the data was reported as the percent of CDC2-positive cells that were also pCDC2 positive. Post treatment values obtained from this scoring method were divided by the same value derived from the matched pre-treatment biopsy to generate a post/pre ratio to reflect the changes in pCDC2 observed at the time of the biopsy (see IB v16 for additional details).

Additional pharmacodynamic inhibtion has been observed in a monotherpy study run by the NCI. Paired tumor biopsies were obtained at baseline and 2 to 5 hours after the 5th dose of the first week of administration of drug. Dramatic reductions in pY15-Cdk levels (67%, 84%, and 90% compared to baseline) were found in 3 of 5 paired tumor biopsies with 2 of those patients also demonstrating concurrent evidence of DNA damage response based on increased levels of γH2AX level on post-treatment tumor biopsy (Do et al., JCO 33: 3409-3415 (2015)

1.5 Study Design and Treatment

This study is a phase II study testing the clinical efficacy of combined AZD1775 with AraC or single agent activity of AZD1775 in three patient strata: Elderly(> 60 years) newly diagnosed AML patients (Arm A) will only receive the combination; whereas relapsed/refractory AML patients and HMA failure MDS patients will be allocated to either the combination (Arm B) or single agent AZD1775 (Arm C). The study will have a run in safety cohort of six patients in each of the three arms to determine the safe use of combined AraC /AZD1775 or single agent AZD1775 in the patient populations. This will be followed by an expansion phase of up to 20 and 21 eligible patients in each arm respectively where elderly patients with newly diagnosed AML will receive a combination of AZD1775 and AraC (Arm A) while patients with relapsed or refractory AML or HMA failure MDS will be allocated to receive either AZD1775 with AraC (Arm B) or AZD1775 alone (Arm C). An early toxicity check will be conducted to determine safety and tolerability. If indicated, dose levels will be reduced. The study will continue to enroll the rest of the patients at the tolerated dose.

1.51 Rationale for AraC and AZD1775 Dosing Schedule, Dose Selection and Dosing Arms:

Dose and Schedule of AraC: AraC is a pyrimidine nucleoside analog that functions as an antimetabolite in a cell cycle specific manner. When given in high doses and in combination with other cytoreductive agents AraC can be too toxic in the elderly patients and those with relapsed/refractory disease. Subcutaneously administered low-dose AraC (defined as 5 to 10 mg/m$_2$/d or 20mg fixed dose twice daily) for 10-12 days has been employed for specific AML subpopulations since 1979, with complete remission (CR) rates generally around 10-20% at maximum (Cheson et al. 1986). It is frequently used as a comparator arm in large phase 3 trials or in combination studies with other agents (Kantarjian et al. 2012, Fenaux et al. 2009). Clinically, AraC can be given at low, intermediate and high dose concentration schedules. The strongest pre-clinical ex vivo and in vitro sensitization effects to AZD1775 occurred at

low to moderate AraC concentrations of 9-120 nanoMolar (nM) (Tibes et al.2012). Whereas, antagonism was seen at very high concentrations (AraC > 1000nM), concentrations that clinically resemble high dose AraC dosing schedules. As the mechanism is not yet fully understood, we postulate that for maximum anti-leukemic activity of combined AraC and AZD1775, there has to remain a low level proliferation with incorporation of AraC into the DNA of dividing leukemia cells upon concurrent inhibition of WEE1 kinase. This results in abrogation of the DNA repair machinery (Tibes, ASCO 2014) and cell death/apoptosis originating directly from the damaged DNA. Therefore, we propose to use AraC in a twice daily s.c. schedule that can achieve concentrations of up to 50-100nM of AraC, comparable to the pre-clinical data.

Dose and Schedule of AZD1775: The optimal concentrations of AZD1775 in combination with AraC are in the range of 100-600nM based on in vitro and ex vivo data (Tibes et al, Blood 2012). Pharmacokinetic data for AZD1775 is available from the ongoing solid tumor Phase 1 trial. AZD1775 at once or twice daily dosing up to 200 to 225 mg orally (po) in combination with full doses of Gemcitabine, Cisplatin or Carboplatin was well tolerated (Schellens et al. 2011, Leijenet al. 2010, IB AZD1775, Jan.. 2018). The half-life of AZD1775 is ~9 hrs and C trough for AZD1775 is up to 570nM, with an unbound concentration of 225nM. Preliminary population PK model simulations by Astra Zeneca (Robert Godin, personal communication, AZD1775 Lead) suggest that once daily dosing of 200 mg AZD1775 for 5 days will result in a median plasma trough total concentration level of 172 nM (range: 8-740 nM) for AZD1775. The unbound concentration will be 67 nM (3-292 nM). This would be in the range at which pre-clinically single agent activity and sensitization has been observed (Tibes et al, Blood 2012). In the ongoing Phase 1 Study at the National Cancer Institute (and REFMAL 398, see IB) alternative dosing was explored. NCT01748825Arm B explored the MTD of once daily dosing of AZD1775. The DLT dose level was reached at 400mg daily on a 5-2-5 schedule (5 days on and 2 days off for 2 weeks every 21 days), and the MTD was 300mg AZD1775 (Takebe, 2018). On a 5/2 schedule, 300 mg daily dose provides the greatest cover over the targeted concentration range (500-1000 nM) and is predicted based on preclinical data to result in good clinical activity. On that schedule 18 pateints have/ are currently being treated for 2-14 cycles as of the presentation (ASCO 2018, Takebe 2018). Thus, AZD1775 at 300mg on a 5days on -2 days off - 5 days on days schedule every 21 days is well tolerated in advanced cancer patients and these data provide a rationale for the single agent AZD1775 dosing schedule for Arm C and the pilot MF patient cohort in this protocol.

AZD1775 dosing and cycle length: In ongoing Phase 1 solid tumor single agent AZD1775 trial at the National Cancer Institute (NCT01748825 and REFMAL 384, see IB), current information of toxicity and tolerability supports the initial AZD1775 dosing to be 300mg QD on a 5 days on 2 day off schedule for 2 weeks every on a 21 days (3 weeks) scheduled as proposed for Arm C. For AraC there is a clinical rationale for 10 and 12 day dosing schedules if given subcutaneously. AZD1775 at 200-225mg BID x 5 doses was tolerated with full dose (strength) chemotherapy in solid tumor patients (Leijens, JCO 2016). Therefore, taken the safety and tolerability data from various studies with AZD1775, as well as our preclinical data of optimal sensitization with concurrent AraC and AZD1775 treatment, the proposed AZD1775 dose in combination with AraC is AZD1775 at 200mg once daily on a 5-2-5 schedule every 4 weeks (28 days), the latter to account and mirror the commonly used clinical s.c. AraC cycle length of 4 weeks. However, it should be noted that cycle length is often 4-6 weeks for s.c. AraC, which will be reflected in the dose adjustment and toxicity study criteria.

1.52 AZD1775 alone vs. AZD1775 plus AraC

AZD1775 ex vivo and in vitro has single agent activity against myeloid malignant cells from relapsed/refractory AML and HMA failure MDS patients as well as MF. Pre-clinical data provides support for concurrent exposure to both agents at lower AraC and moderate AZD1775 concentrations and

these dosing concentrations are hypothesized to have the optimal biological effect. Further, the available clinical trial data of AZD1775 alone or with full dose cytotoxic chemotherapies is showing good tolerability without excessive cytopenias [cytopenias are less concern for the patient population under study in this protocol]. Clinical trials, including single investigational agents are recommended standard interventions for the patient population in this protocol. Therefore patients with relapsed or refractory AML or HMA failure MDS will be allocated to, either AZD1775 or AZD1775 plus AraC treatment. For patients with newly diagnosed AML, AraC should in most cases be part of the upfront therapeutic regimens, therefore newly diagnosed untreated elderly AML patients will only be allocated to the combination treatment Arm A of AZD1775 plus AraC.

1.53 Biologically effective dose

Ideally current trial designs incorporate a biologically effective dose in assessing responses in relation to safety, toxicity and maximum tolerated doses. However, for AZD1775 even though inhibition of one of WEE1 kinases' direct substrate CDK1 was used in some studies as a readout of effective target engagement, p-CDK1 Y15 inhibition was not complete and varied (Leijens, JCO 2016). In addition the biology around WEE1 kinase and its' inhibition are not fully elucidated and other target/ substrates of WEE1 kianse are either known (i.e. CDK2) or are starting to be discovered. Thus, there is currently no single marker and/ or a reliable readout of effective WEE1 kinase inhibition. Conseqeuntly, conventional DLT and MTD criteria, PK information from ongoing and previous trials as well as preclinical data (for target dose/ concentration of AZD1775) in leukemias will be used in this protocol. The proposed correlative studies are aimed at addressing and identifying pharmacodynamic and predictive biomarkers of WEE1 kinase inhibition and AZD1775 response.

2.0 Goals

2.1 Primary Goals

2.11 To estimate the clinical efficacy of AZD1775 in combination with AraC in patients with newly diagnosed AML by assessing complete response (CR plus CRi) rates

2.12 To estimate the clinical efficacy of AZD1775 alone or in combination with AraC in patients with relapsed/refractory AML and hypomethylating agent failure MDS by assessing complete response (CR plus CRi) rates

2.13 To evaluate the clinical efficacy (best overall response including clinical improvement) of AZD1775 in patients with advanced MF defined as intermediate and high risk MF (primary or secondary MF)

2.2 Secondary Goals

2.21 To determine the safety and tolerability of AZD1775 alone or combined with AraC in the study population.
2.22 To estimate additional measures of clinical benefit (i.e. hematological improvements, transfusion requirements, spleen size reduction).
2.23 To measure the duration of response of AZD1775 alone or combined with AraC.
2.24 To measure time to response of AZD1775 alone or combined with AraC.
2.25 To measure time to progression of AZD1775 alone or combined with AraC.

2.26 To measure overall survival of AZD1775 alone or combined with AraC.
2.27 To measure time to AML (for MDS, MF subjects) of AZD1775 alone or combined with AraC

2.3 Correlative Research

2.31 To determine the pharmacokinetics (PK) of AZD1775 alone or combined with AraC in the study population

2.32 To conduct correlative research studies characterizing underlying molecular events and solidifying putative mechanism of action in vivo and to identify potential pharmacodynamic/biomarkers of response to AZD1775 alone or combined with AraC

2.33 To evaluate quality of life (QOL) and patient-reported symptoms in subjects treated with AZD1775 alone or combined with AraC.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Patient population (histological or cytologically confirmed diagnosis):
Dose **escalation** part of trial for combined AraC + AZD1775 (Arm A)

- untreated elderly (>60 years) AML if in the poor-risk cytogenetic group (please reference Appendix V).
  Note: previous therapy with a hypomethylating agent (HMA) for a diagnosis of MDS is allowed

Dose **expansion** part of trial for combined AraC + AZD1775 (Arm A)

- untreated elderly (>60 years) AML if in the intermediate and poor-risk cytogenetic group (please reference Appendix V)

  Note: previous therapy with a hypomethylating agent (HMA) for a diagnosis of MDS is allowed

- relapsed or refractory AML (≥ 18 years)

- any MDS (≥ 18 years) having failed or been intolerant to prior hypomethylating agent (HMA) treatment.
  - Failure is defined as any disease progression while on HMA, relapse after HMA treatment or no response after 4 cycles of 5-Azacitidine or decitabine
  - Patients with isolated 5q-/5q- syndrome must have failed, not tolerated, or progressed on lenalidomide in addition to having failed or been intolerant to HMA treatment.

Note: Patients with CMML and MDS/MPN overlap are allowed if meeting other study eligibility criteria.

- advanced progressive MF, defined as intermediate and high risk primary and secondary MF, or any other MF failed or intolerant to JAK2 inhibitor therapy requiring medical therapy

  Note:
  - If appropriate, patients can have failed other prior therapies for their disease (i.e. JAK2 inhibitor, interferon, hydroxyurea or IMIDs). Patients may have failed more than one JAK2 inhibitor and JAK2 inhibitor must not have been the most recent treatment (e.g. other therapies as last therapy prior to study given after failure of previous JAK2 inhibitor).
  - Primary (PMF) and secondary MF (post PV/post ET) are allowed.

Failure/ intolerance of Ruxolitinib is defined as loss of optimal response in a responder to Ruxolitinib, based on growth of the spleen *[appearance of a new splenomegaly that is palpable at least 5 cm below the LCM, or a ⩾100% increase in palpable distance, below LCM, for baseline splenomegaly of 5–10 cm, or a 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm],* loss of symptom improvement [*MPN-SAF*], worsening cytopenias *[currently or previously treated with ruxolitinib for at least 28 days and either required RBC transfusion on ruxolitinib, or required a dose adjustment of ruxolitinib to less than 20 mg twice a day and also had anaemia; grade 3 thrombocytopenia]* or intolerable side effects [*in the assessment of the treaing physician*]. Further increase of blood or marrow blasts to > 5% if previously < 2% and > 10% if previously < 7% qualify as progression to Ruxolitinib.

NOTE: For all patient groups, therapy as part of a plan as a bridge to transplant is allowed.

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

- Total bilirubin ≤ 1.5 mg/dL (except Gilbert's syndrome or known hemolysis or leukemic infiltration)
- AST (SGOT) and ALT (SGPT) ≤ 2.5 x Upper Limit normal (ULN) or < 5 x ULN if organ involvement
- Alkaline Phosphatase < 5 x ULN
- Serum creatinine ≤1.5 x ULN, or measured creatinine clearance (CrCl) ≥45 mL/min as calculated by the Cockcroft-Gault method (confirmation of creatinine clearance is only required when creatinine is >1.5 x institutional ULN)

  $$\text{CrCl (glomerular filtration rate [GFR])} = \frac{(140-\text{age}) \times (\text{weight/kg}) \times F_a}{(72 \times \text{serum creatinine mg/dL})}$$

  [a] where F= 0.85 for females and F=1 for males

3.14 ECOG Performance Status (PS) 0, 1 (Appendix I).

3.15 Ability to provide informed written consent and be able to adhere to the study visit schedule and other protocol requirements.

3.16 Willing to return to enrolling institution for follow-up (during the Active

Monitoring Phase of the study).

3.17 Willing to provide blood and bone marrow aspirate samples for correlative research purposes

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

3.19a Female patients who are not of child-bearing potential and fertile females of childbearing potential who agree to use adequate contraceptive measures from 2 weeks prior to the study and until 1 month after study treatment discontinuation, who are not breastfeeding, and who have a negative serum or urine pregnancy test within 3 days prior to the start of study treatment.

3.19b Male patients should be willing to abstain or use barrier contraception (i.e., condoms) for the duration of the study drug exposure and for 3 months after study treatment discontinuation.

3.19c Patients who have undergone stem cell transplantation (SCT), autologous or allogeneic, are eligible provided that they are > 60 days from stem cell infusion, have GVHD ≤ grade 1 and are off immunosuppressive agents for > 28 days at time of registration.

3.2 Exclusion Criteria

3.21 Uncontrolled intercurrent illness including, but not limited to, active uncontrolled infection, known positive for active infectious hepatitis, type A, B or C (past infection allowed), or psychiatric illness/social situations that would limit compliance with study requirements.

Note: ongoing infection controlled on antibiotics/antifungal/antiviral medications are allowed.

3.22 Any of the following prior therapies:

- Cytotoxic Chemotherapy ≤14 days prior to registration
- Immunotherapy ≤14 days prior to registration
- Biologic therapy (i.e. antibody therapies) ≤14 days prior to registration
- Radiation therapy ≤14 days prior to registration
- Targeted therapies (i.e. kinase inhibitors, ≤7 days or 5 half-life's whichever is longer)
- For steroids or other non-cytotoxics (exception, HU) given for blast count control, patient must be off for > 24 hrs before starting therapy. NOTE: Hydroxyurea (HU) is allowed for blast count control throughout study
- Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm ≤ 28 days prior to registration
- Patients with persistent toxicities of ≥ Grade 1 from prior AML treatment (including chemotherapy, kinase inhibitors, immunotherapy, experimental agents, radiation, or surgery).

3.23 Active uncontrolled CNS leukemia. NOTE: Positive (cyto)pathology is allowed and patient can receive intrathecal chemotherapy

3.24 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy. NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, are eligible for this trial.

3.25 Any previous treatment with AZD1775 or allergic reactions to excipients of AZD1775.

3.26 Acute Promyelocytic Leukemia (APL, M3) unless failed treatment will all available therapies known to be active for treatment of APL.

3.27 Major surgery ≤ 28 days prior to registration

3.28 Clinically significant heart disease, including the following:

- Active severe angina pectoris within 3 months prior to registration
- Acute myocardial infarction within 3 months prior to registration
- New York Heart Association classification IV cardiovascular disease or symptomatic class III disease (Appendix III).

Note: patients with any of the above may be allowed after discussion amongst the investigators including the principal investigator

3.29 AML patients who are suitable for and willing to receive intensive chemotherapy

3.30
a Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.30b Subject has had prescription or non-prescription drugs or other products known to be sensitive CYP3A4 substrates or CYP3A4 substrates with a narrow therapeutic index, or to be moderate to strong inhibitors / inducers of CYP3A4 which cannot be discontinued two weeks prior (alternatively 5 half lives if T1/2 is known) prior to Day 1 of dosing and withheld throughout the study until 2 weeks after the last dose of study drug (Appendix VI).

NOTE: Co-administration of aprepitant or fosaprepitant during this study is prohibited.

Note: Individiual drugs exerting CYP interactions as listed in tables in Appendix VI may be continued on a case by case basis if felt essential for patient managment, after discussions and discretion of the treating physician.

The preferred azole anti-fungal medication is Fluconazole (alternatively Posaconazole) which can be given during treatment with AZD1775 (section 9.5).

3.29c Pateints may not be on an inhibitor of BCRP as outlined in Appendix VI.

NOTE: AZD1775 is an inhibitor of breast cancer resistance protein (BCRP). The use of statins including Atorvastatin which are substrates for BCRP are therefore prohibited and patients should be moved on to non-BCRP alternatives.

3.29d Not willing to avoid grapefruit, grapefruit juices, grapefruit hybrids, Seville oranges, pummelos, and exotic citrus fruits from 7 days prior to the dose of study medication and during the entire study due to potential CYP3A4 interaction with the study medication. NOTE: Orange juice is allowed.

3.29e

Mean resting corrected QTc interval using the Fridericia formula (QTcF) >450 msec/male and >470 msec/female (as calculated per institutional standards) obtained from 3 electrocardiograms (ECGs) 2-5 minutes apart at study entry, or congenital long QT syndrome

3.30 Herbal preparations/medications are generally not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7-14 days prior to first dose of AZD1775. If there is no known potential interaction between an herbal medication and AZD1775, the protocol principal investigator can give a waiver to continue such medication, with the expection of St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng, that are not allowed at any stage.

4.0 Test Schedule

Table 4.1: Test Schedule for Elderly Newly Diagnosed and Relapsed/Refractory AML patients

		Active Monitoring Phase				
Tests and procedures	≤14 days prior to registration	≤7 days prior to registration	Cycle 1 Days 1, 4, 8, 15, & 28(±3 days)[5, , 16]	Cycles 2 & 3 Days 1, 15, and 28 (± 3 days)[5, , 16]	Cycles 4+ and Beyond Day 1 (±3 days)[5, 16]	EOS[2]
History and exam, wt, PS, vitals	X		X	X	X	X
Height	X					
Adverse event assessment	X		X	X	X	X
Hematology group WBC ANC Hgb PLT		X	X[A]	X[B]	X[9]	X
Chemistry group: sodium, potassium, calcium, creatinine, bicarbonate, glucose, chloride, albumin, BUN, alkaline phosphatase, AST, ALT, total protein, total bilirubin, LDH		X	X[A]	X[B]	X	X
TLS monitoring (for selected AML patients): BUN, calcium, CO2, chloride, creatinine, glucose, potassium, sodium, uric acid, phosphorus			X[13]			
PT/PTT and D-dimer			X[18]			
Serum pregnancy test[1]		X		X	X	
Bone marrow biopsy and aspirate procedure (cytogenetics or FISH)[14]	X[11]		X[3]	X[3]	X[3]	X[10]
Bone marrow aspirate research specimens (see Section 14.0)[R]	X[8]		X[7]	X[7]	X[7]	X[6]
Blood specimens (see Section 14.0)[R]	X[4, 8]		X[4]	X[4]	X[4]	X[4]

Saliva Sample, see Section 14.0) R	X					
Patient Questionnaire Booklet12	X		X15	X15	X15	X15
ECG (12 lead)17		X	XC	X	X	X

1. For women of childbearing potential only. Day 1 of each cycle
2. 30 days (+/-3days) post last dose of study drug
3. For AML patients: marrow aspirates and biopsies will be done after cycle 1 (at physician's discretion), after cycles 2 and 4, and then at physician discretion). In addition, bone marrow should be performed at time of suspected CR/CRi and/or disease progression and at physician discretion as clinically indicated. Note: Bone Marrow Aspirate and biopsy may be avoided aftercycle 4 as determined by study chair or treating physician (i.e. if determined to not yield information that would change clinical management).
4. Blood specimens for research sampling to be collected as defined in Section 14.
5. Day 1 assessments do not need to be repeated if pre-registration or Day 28 assessments completed within 72 hours of Day 1.
6. Only if an EOS marrow sample is collected as part of standard of care
7. Research bone marrow samples are to be collected at the same time when a marrow is done as part of patient's standard of care, including research marrow samples should be drawn at time of marrow for suspected CR/CRi and/or disease progression.
8. To be collected on all patients at baseline. If no baseline marrow samples obtained, the peripheral blood research sample becomes mandatory to participate in study. Bone marrow aspirate specimens must be collected and submitted per section 14.0. If bone marrow performed at end of study as part of patient's standard of care, collect sample per section 14.0.
9. After 2 cycles, CBC frequency may be reduced at treating physician's discretion but needs to be performed at least once per cycle.
10. Progression marrow can be used as EOS marrow if patient is taken off trial based on the results. Additional EOS bone marrow can be omitted if a progression marrow was done, or an EOS marrow can be done at physician discretion and is optional.
11. ≤ 28 days prior to registration; for patients with an outside marrow biopsy within 4 weeks of study start, outside results can serve as baseline after review at NYU.
12. Patient questionnaire booklet must be used; copies are not acceptable for this submission. Booklet should be completed by patient prior to review of treatment response and discussions of patient's general health since last treatment evaluation.
13. For patients at high risk of tumor lysis syndrome (TLSTLS labs will be performed at least twice during the first week of therapy, when maximum TLS risk is highest. . Additional monitoring will be done on a case by case basis.
14. Either conventional cytogenetics or FISH panel (or both based on physician discretion) for AML to be performed at baseline. If diploid cytogenetics at baseline, subsequent cytogenetic studies may be omitted unless disease progression is suspected. For FISH based cytogenetic assessments, an entire AML FISH panel should be performed at baseline, while on subsequent marrows only positive specific FISH abnormalities/probes need to be repeated unless disease progression is suspected, in which case a full AML FISH panel or instead conventional cytogenetics should be performed.
15. Booklets to be completed at end of all cycles.
16. Prior to the start of treatment.
17. ECG in triplicate on day1 of each cycle, for cycle 1, ECGs will be conducted at least weekly.
18. To be tested on C1D1 prior to treatment.

A. For AML patients, CBC and blood chemistries will be collected at least twice weekly for Cycle 1
B. For AML patients, CBC and blood chemistries will be collected weekly for Cycle 2
C. For cycle 1, ECGs will be conducted at least weekly.
R Research funded (see Section 19.0).

Table 4.2: Test Schedule for HMA failure MDS/ AML patients

		Active Monitoring Phase				
Tests and procedures	≤14 days prior to registration	≤7 days prior to registration	Cycle 1 Days 1, 8, 15, & 28(± 3 days)[12, 10]	Cycle 2 Days 1, 15, and 28 (± 3 days)[10, 12]	Cycles 3+ and Beyond Day 1 (±3 days)[10, 12]	EOS[2]
History and exam, wt, PS, vitals	X		X	X	X	X
Height	X					
Adverse event assessment	X		X	X	X	X
Hematology group WBC ANC Hgb PLT		X	X	X	X	X
Chemistry group: sodium, potassium, calcium, creatinine, bicarbonate, glucose, chloride, albumin, BUN, alkaline phosphatase, AST, ALT, total protein, total bilirubin, LDH		X	X[A]	X[B]	X	X
Serum Erythropoietin level	X					
Serum pregnancy test[1]		X		X	X	
Bone marrow biopsy and aspirate procedure (cytogenetics or FISH[9])	X[6]			X[3]	X[3]	X[7]
Blood specimens (see Section 14.0)[R]	X[4,13]		X[4]	X[4]	X[4]	X[4]
Saliva Sample (see Section 14.0) [R]	X					
Bone marrow aspirate research specimens (see Section 14.0)[R]	X[6, 13]			X[5]	X[5]	X[5]
Patient Questionnaire Booklet[8]	X				X[8]	X
ECG (12 lead)[11]		X	X[C]	X	X	X

1. For women of childbearing potential only Day 1 of each cycle
2. 30 days (+/-3days) post last dose of study drug
3. Marrow biopsies only to be done at End of cycle 2, End of cycle 4, at time of suspected CR/CRi and thereafter at physician discretion as clinically indicated (i.e. disease progression).

4. Blood specimens for research sampling to be collected as defined in Section 14.
5. Research marrow samples (aspirates) to be done at times of clinical standard of care marrow tests at End of cycle 2, End of cycle 4, at time of suspected CR/CRi or disease progression and thereafter at physician discretion as clinically indicated. A sample will be obtained at end of study (EOS) if a bone marrow is performed as part of patient's standard of care; sample will be collected per section 14.0
6. ≤ 28 days prior to registration; for patients with an outside marrow biopsy within 4 weeks of study start, outside results can serve as baseline after review at NYU.
7. Bone marrow at end of study is only to be done at physician discretion and is optional. Progression marrow can be used as EOS marrow if patient is taken off trial based on the results.
8. Patient questionnaire booklet must be used; copies are not acceptable for this submission. Booklet should be completed by patient prior to review of treatment response and discussions of patient's general health since last treatment evaluation. Booklets to be completed at baseline, cycles 3, 6, 9, and EOS.
9. Either conventional cytogenetics or FISH panel (or both based on physician discretion) for MDS should be performed at baseline. If diploid cytogenetics at baseline subsequent cytogenetic studies may be omitted unless disease progression is suspected. For FISH based cytogenetic assessments, an entire MDS FISH panel should be performed at baseline, while on subsequent marrows only positive specific FISH abnormalities/probes need to be repeated unless disease progression is suspected.
10. Prior to the start of treatment.
11. ECG in triplicate on day1 of each cycle,
12. Day 1 assessments do not need to be repeated if pre-registration or Day 28 assessments completed within 72 hours of Day 1.
13. To be collected on all patients at baseline. If no baseline marrow samples obtained, the peripheral blood research sample becomes mandatory to participate in study. If collected bone marrow aspirate specimens must be collected and submitted per section 14.0. If bone marrow performed at end of study as part of patient's standard of care, collect bone marrow sample per section 14.0.

A For AML patients, CBC and blood chemistries will be collected at least twice weekly for Cycle 1. TLS labs will be performed at least twice during the first week of therapy

B For AML patients, CBC and blood chemistries will be collected weekly for Cycle 2

C For cycle 1, ECGs will be conducted at least weekly.

R Research funded (see Section 19.0).

Table 4.3: Test Schedule for MF patients

		Active Monitoring Phase				
Tests and procedures	≤14 days prior to registration	≤7 days prior to registration	Cycle 1 Days 1, 15, & 28(± 3 days)[12, 10]	Cycle 2 Days 1, 15, and 28 (± 3 days)[10, 12]	Cycles 3+ and Beyond Day 1 (±3 days)[10, 12]	EOS[2]
History and exam, wt, PS, vitals	X		X	X	X	X
Height	X					
Adverse event assessment	X		X	X	X	X
Hematology group WBC ANC Hgb PLT		X	X	X	X	X
Chemistry group: sodium, potassium, calcium, creatinine, bicarbonate, glucose, chloride, albumin, BUN, alkaline phosphatase, AST, ALT, total protein, total bilirubin, LDH		X	X	X	X	X
Serum Erythropoietin level	X					
Serum pregnancy test[1]		X		X	X	
Bone marrow biopsy and aspirate procedure (cytogenetics or FISH[9])	X[6]			X[3]	X[3]	X[7]
Blood specimens (see Section 14.0)[R]	X[4,13]		X[4]	X[4]	X[4]	X[4]
Saliva Sample (see Section 14.0) [R]	X					
Bone marrow aspirate research specimens (see Section 14.0)[R]	X[6, 13]			X[5]	X[5]	X[5]
Patient Questionnaire Booklet[8]	X		X[8]	X[8]	X[8]	X
ECG (12 lead)[11]		X	X	X	X	X

1. For women of childbearing potential only Day 1 of each cycle
2. 30 days (+/-3days) post last dose of study drug
3. Marrow biopsies only to be done at End of cycle 2, End of cycle 4, at time of suspected CR/CRi and thereafter at physician discretion as clinically indicated (i.e. disease progression).

4. Blood specimens for research sampling to be collected as defined in Section 14.
5. Research marrow samples (aspirates) to be done at times of clinical standard of care marrow tests at End of cycle 2, End of cycle 4, at time of suspected CR/CRi or disease progression and thereafter at physician discretion as clinically indicated. A sample will be obtained at end of study (EOS) if a bone marrow is performed as part of patient's standard of care; sample will be collected per section 14.0
6. ≤ 28 days prior to registration; for patients with an outside marrow biopsy within 8 weeks of study start, outside results can serve as baseline after review at NYU.
7. Bone marrow at end of study is only to be done at physician discretion and is optional. Progression marrow can be used as EOS marrow if patient is taken off trial based on the results.
8. Patient questionnaire booklet must be used; copies are not acceptable for this submission. Booklet should be completed by patient prior to review of treatment response and discussions of patient's general health since last treatment evaluation. Booklets to be completed at end of all cycles.
9. Either conventional cytogenetics or FISH panel (or both based on physician discretion) for MDS should be performed at baseline. If diploid cytogenetics at baseline subsequent cytogenetic studies may be omitted unless disease progression is suspected. For FISH based cytogenetic assessments, an entire MDS FISH panel should be performed at baseline, while on subsequent marrows only positive specific FISH abnormalities/probes need to be repeated unless disease progression is suspected.
10. Prior to the start of treatment.
11. ECG in triplicate on day1 of each cycle. NOTE: for cycle 1, ECGs will be conducted at least weekly.
12. Day 1 assessments do not need to be repeated if pre-registration or Day 28 assessments completed within 72 hours of Day 1.
13. To be collected on all patients at baseline. If no baseline marrow samples obtained, the peripheral blood research sample becomes mandatory to participate in study. If bone marrow aspirate specimens obtained must be collected and submitted per section 14.0. If bone marrow performed at end of study as part of patient's standard of care, collect peripheral blood sample instead per section 14.0.

R Research funded (see Section 19.0).

5.0 Grouping Factors:

5.1 Grouping Factor

Study Stage: 1=Safety Portion vs 2=Expansion Portion

5.2 Grouping Factor

Disease type: 1=Elderly newly diagnosed AML (assigned treatment Arm A) vs 2=Relapsed/refractory AML vs 3=HMA failure MDS/ AML vs 4=MF

NOTE: HMA failure MDS patients include MDS, CMML and MDS/MPN overlap patients.
NOTE: Disease type groups 2 and 3 are randomized to arm B or C. Disease type 4 only receives single agent (Arm C)

6.0 Enrollment Procedures

The inclusion and exclusion criteria in this study should not have a negative effect on the enrollment of the desired populations.

Target enrollment at NYU Langone Health for this study is a minimum of 40 patients over 3 years. The target accrual goal for the run in safety is each 6 patients in the single (Arm C) and combination Arms (Arms A and B); once the safe use of combined AraC/AZD1775 or single agent AZD1775 is determined, the study will expand to 20-21 subjects in each arm distributed over the study duration of 3 years. An explorative cohort of MF patients (n=7) will be assigned to single agent AZD1775 treatment as in Arm C, however, these patients will not be counted into the statistical analysis for Arm C. Patients will be recruited from the physician participating in this study.

Consenting, screening, and treatment will take place at the NYU Langone Health PCC or participating sub-sites under the supervision of the Site PI. Prospective subjects will receive detailed information regarding this study; its investigational nature, required study procedures, alternative treatments, risks and potential benefits of the study. They will also receive the informed consent document to read. All questions are answered by the PI and qualified research personnel.

The Principal Investigator(s) or their representatives will:

1. Obtain signed and dated informed consent from the potential subject before any study specific procedures are performed (can be obtained by study investigators).

2. Determine patient eligibility; see Section 3.1 and 3.2

3. Submit registration to NYU Langone Health Perlmutter Cancer Center CTO

4. Receive registration confirmation from the NYU Langone Health Perlmutter Cancer Center CTO, including a unique study identification number assigned to the patient that will be distributed to the study team upon registration of the patient.

Recruitment and consenting will take place in a private area such as an exam room to protect the patient's privacy. The informed consent process and documentation follows the established procedures of the NYU Langone Health Perlmutter Cancer Center Clinical Trials Office.

6.1 Use of DataCore/Epic Information for Recruitment Purposes

Although, primary recruitment will be done via participating physicians contacting potential participants; recruitment will also be done utilizing EPIC.
Any recruitment information sent by email will utilize Send Safe email.

Once potential subjects have been identified, the study team will notify the treating physician (TP) that they have patients eligible to participate. Should the potential subjects agree, the study team will provide the subjects with information regarding the next steps for participation.

If a subject requests information regarding opting out of further recruitment for all research, subjects will be directed to contact research-contact-optout@nyumc.org or 1-855-777-7858.

6.2 Registration Procedures

6.21 General Guidelines

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU Langone Health PCC Clinical Trials Office. The following materials must be submitted to the CTO for subject registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated eligibility checklist

3. All supporting documentation verifying each eligibility criterion has been met

Registration will occur within 48 hours of research coordinator receipt of all of the above documents. A written confirmation of enrollment including a unique study identification number assigned by the research coordinator will be disbursed to the study team upon registration.

Once eligibility is verified, a unique patient study number will be issued within 48 hours of receiving all required registration material. The patient will not be identified by name. This is the point, at which, the patient is considered accrued on study.

6.22 Multi-Site Surveillance

As the lead investigator in a multi-site trial, the Principal Investigator is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial's quarterly Data and Safety Monitoring report to the DSMC to include minutes from monthly PI teleconferences. Each participating site will be responsible for submitting the results and recommendations from the DSMC's quarterly reviews to their IRB of record at the time of continuing review. Additionally, the NYU Langone Health PCC Clinical Trial Office, Quality Assurance Unit will provide a remote extensive monitoring including real-time review of all eCRFs to ensure completeness and compliance with the protocol (100% source documentation verification). Additionally, a first subject audit is to be completed within four weeks of enrollment.

6.23 Patient Registrations at Additional Sites

Enrollment at additional sites can begin once each site's IRB has approved this protocol, a copy of each site's IRB approval, Citi training certificates, Medical Licenses and signed CVs are provided to NYU Langone Health Perlmutter Cancer Center (PCC) Clinical Trials Office. Once, all required documents are provided to NYU Clinical Trials Office an activation notification will be sent to the PI and research coordinator of that site. Central registration for this study will take place at NYU Langone Health PCC Quality Assurance Unit (PCC-QAU@nyumc.org).

Each patient must sign and date an informed consent form before undergoing any study specific procedures unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, each site must notify the NYU Langone Health PCC Quality Assurance Unit and forward a copy of the signed consent to NYU Langone Health PCC Clinical Trials Office within 24 hours.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU Langone Health PCC Clinical Trials Office. The following materials must be submitted to the Quality Assurance Unit at NYU Langone Health via email (PCC-QAU@nyumc.org):

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met.

Registration will occur once the Senior Research Nurse for Quality Assurance conducts a central review of the submitted materials. Once eligibility is verified, a unique subject study number will be issued within 48 hours of receiving all required registration material. This number is unique to the participant and must be written on all data and correspondence for the participant. The NYU Langone Health PCC CTO will return a signed eligibility confirmation worksheet email with the subject's unique study number.

The subject will not be identified by name. This is the point, at which, the patient is considered accrued on study. Protocol treatment should begin within designated timeframe; issues that would cause treatment delays should be discussed with the overall PI, Dr. Tibes. All screen failures/ineligible subjects, as well as subject's who withdraw consent prior to initiation of protocol therapy must be submitted to the CTO in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

Subjects must not start any protocol procedures prior to registration; each participating institution will order the study agent through NYU Investigational Pharmacy.

Each site is responsible for reporting all unexpected problems involving risks to participants or others to NYU Langone PCC Clinical Trials Office and to their IRB as per site institutional policy.

Please email all SAEs to NYUPCCsafetyreports@nyumc.org, Dr. Tibes, and the NYU Langone Health CTO QA specialist.

6.3 Safety & Expansion Portions

6.31 Correlative Research

6.311 A mandatory correlative research component is part of this study, the subject will be automatically registered onto this component (see Section 3.17 and 14.0).

6.32 At the time of registration, the following will be recorded:

- Subject has/has not given permission to store and use his/her sample(s) for future research of Acute Myeloid Leukemia or Myelodysplastic Syndrome at NYU Langone Health.
- Subject has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Subject has/has not given permission to give his/her sample(s) to researchers at other institutions.

6.33 Treatment on this protocol must commence at a participating institution, NYU Langone Health, under the supervision of a hematologist.

6.34 Treatment cannot begin prior to registration and must begin ≤ 14 days after registration.

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

6.36 All required baseline symptoms (see Section 10.3) must be documented and graded.

6.37a Study drug is available on site.

6.37b Blood draw kit is available on site.

6.37c Subject questionnaire booklet is available on site; copies are not acceptable for this submission.

6.37d Randomization Procedures

6.37d1 After the subject has been registered into the study, the values of the grouping factors will be recorded. An elderly newly diagnosed AML subject will be allocated to arm A. A relapsed/refractory AML or HMA failure MDS/ AML subject will be randomized to treatment group arm B or arm C. MF patients will be allocated to Arm C but not included in the statistical analysis for Arm C, rather descriptive response rates will be summarized separately.

- Elderly (age 60+) newly diagnosed AML subjects assigned to Arm A: AZD1775 days 1-5, 8-12 and AraC days 1-5, 8-12
- Relapsed/Refractory AML and HMA failure MDS/ AML subjects randomized to Arm B: AZD1775 days 1-5, 8-12 and AraC days 1-5, 8-12 or Arm C: AZD1775 days 1-5, 8-12.
- MF patients allocated to Arm C

7.0 Protocol Treatment

7.1 Pre-Treatment Requirement

7.11

All patients will receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO QD or granisetron (Kytril) 1 mg PO QD prior to each dose of AZD1775. If nausea and vomiting continue, a second dose of antiemetics can be taken 8 hours later if necessary. In addition, dexamethasone 4 mg PO may be given with each AZD1775 dose unless contraindicated or not well-tolerated. Dexamethasone or the 5-HT3 antagonist may be given by IV route as needed.
Promethazine (Phenergan), prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy.
Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known DDIs.
Patients should be encouraged to maintain liberal oral fluid intake.
Suitable alternative medications may be used, with adequate justification, in those studies where the use of any of the above medications might interfere with other study procedures or are deemed insufficient.

7.2 Treatment Plan for AZD1775 combined with AraC (Arms A and B)

7.21 Safety Portion

The safety portion of this trial will consist of a limited dose escalation and subsequently assess the safe combination dose of AZD1775 with standard AraC s.c.twice daily dosing. A limited safety run in dose escalation of AZD1775 will be performed as outlined in Table 7.21. Three subjects from either arm will be treated and and observed for a minimum of 28 days to assess toxicities. Toxicity and DLT/ MTD criteria will follow a classical three by three dose escalation toxicity assessment:

In the run-in portion of the trial, 3 patients who are eligible for the trial will be treated at dose level 0 (AZD1775 200 mg PO once daily and AraC 20 mg s.c.twice daily days 1-5 & 8-12) and observed for a minimum of 28 days. If there are no DLT defining toxicities, the following 3 patients will be treated at dose level 1 (AZD1775 250 mg PO once daily and AraC 20 mg s.c. twice daily days 1-5 & 8-12). If there are no DLT defining toxicities at dose leve 1, the next 3 will be treated at dose level 2 (AZD1775 300 mg PO once daily and AraC 20 mg s.c. twice daily days 1-5 & 8-12). If there are no DLTs in the first 3 pateints at dose level 2, an additional 3 patients will be treated. If </+ 1/6 patients at dose level 2 expereince DLT, the Expansion portion (cohort) of the trial will be opened for the remaining patients.
If 1/3 patient experiences a DLT at a given dose level, an additional 3 patients will be enrolled at this dose level. If there are no further DLTs (maximum of </= 1/6 patients with DLT at any given dose level) this dose level will be defined as the MTD dose level and advanced to the Expansion portion of the study. If 2/3 patients experience a DLT, dose will be de-escalated by one dose level and an (additional) 3 patients treated at the next lower dose level, unless six pateints have been treated already and there were </= 1/6 DLT, than this level will be defined as MTD dose level and advanced to the Expansion portion. If >/= 2/6 patients experience at any dose level, then enrollment into that study arm will be placed on hold, and a meeting of all participating investigators, the NYU DSMC Medical Monitor, the Astra Zeneca Trial/ Program Lead will be called to determine how best to proceed, as well as available PK data will be reviewed.
If DLT occurs at dose level 0, study will be de-escalated to dose level -1 (AZD1775 150 mg PO once daily and AraC 20 mg s.c. twice daily days 1-5 & 8-12). If </= 1/3 patients have DLT another 3 patients will be enrolled and if </= 1/6 patients have DLT, than this level will be

defined as MTD dose level and advanced to the Expansion portion. If 2/3 patients at dose level -1 have DLT, the combination will be deemed as not tolerable in combination with LD-AraC.

NOTE: the Safety/ Escalation portion and MTD determination for Arm A (newly diagnosed/ untreated AML) and Arm B (relapsed/ refractory AML, HMA failure MDS) as outlined above will be performed together with patients from both Arms eligible. .

Table 7.21: Safety run in dose escalation

Dose Level	***AZD1775***[2]	***Cytarabine (AraC)*** [1]
-1	150 mg PO once daily days 1-5 & 8-12	20 mg SC twice daily days 1-5 & 8-12
0	200 mg PO once daily days 1-5 & 8-12	20 mg SC twice daily days 1-5 & 8-12
1	250mg PO once daily days 1-5 & 8-12[1]	20 mg SC twice daily days 1-5 & 8-12
2	300 mg PO once daily days 1-5 & 8-12	20 mg SC twice daily days 1-5 & 8-12

[1] AraC dose is a fixed dose of 20 mg s.c. per a single dose twice daily.
[2] AZD1775 should be taken either 2 hours before or 2 hours after a meal.

7.22 Expansion Portion

The Expansion portion of this trial will commence for Arms A and B as soon as the Safety portions for BOTH arms are completed. The MTD/ Expansion cohort dose can be differernt for Arm A and B.

Table 7.22: Dose for Expansion cohort

Agent	Dose	Route	Day(s)	ReRx
AraC[1]	20 mg	SC twice daily	1-5 & 8-12[2]	Every 28 days
AZD1775	MTD (from escalation portion)	PO once daily	1-5& 8-12[2]	Every 28 days

[1] AraC dose is a fixed dose of 20 mg s.c. per a single dose twice daily.
[2]AZD1775 should be taken either 2 hours before or 2 hours after a meal.

7.3 Treatment Plan for AZD1775 single agent (Arm C)

7.31 Safety Portion

The Safety portion of this trial will treat and monitor up to six subjects in the arm and observe them for a minimum of 21 days to assess toxicities. The Safety portion will first treat 3 patients at a single dose AZD1775 of 300mg daily (dose level 0) on days 1-5 and 8-12 for 21 days. If 0/3 patients experience DLT, another 3 patients will be treated. If </= 1/6 patients have DLT, 300mg will be the tolerated dose (MTD) and advanced to the Expansion portion of the study. If </= 2/6

patients have DLT, dose will be de-escalated to dose level -1 (AZD1775 250mg daily on days 1-5 and 8-12 for 21 days) and 3 patients treated. If </= 1/3 patients have DLT another 3 patients will be treated. If </= 1/6 patients have DLT, 250 mg AZD1775 will be the tolerated dose (MTD) and advanced to the Expansion portion of the study. If </= 2/6 patients have DLT at dose level -1 (250 mg AZD1775) dose will be further de-escalated to dose level -2 (AZD1775 200mg daily on days 1-5 and 8-12 for 21 days) and 3 patients treated. If </= 1/3 patients have DLT another 3 patients will be treated. If </= 1/6 patients have DLT, dose level -1 (200 mg AZD1775) will be the tolerated dose (MTD) and advanced to the Expansion portion of the study.
If </= 2/6 patients have DLT at dose level -2 (200 mg AZD1775) dose will be further de-escalated to dose level -3 (AZD1775 150 mg daily on days 1-5 and 8-12 for 21 days) and 3 patients treated. If </= 1/3 patients have DLT another 3 patients will be treated. If </= 1/6 patients have DLT, dose level -3 (150 mg AZD1775) will be the tolerated dose (MTD) and advanced to the Expansion portion of the study. If </= 2/6 patients have DLT at dose level -3 (150 mg AZD1775) **or** if >/= 2/6 patients experience DLT at any dose level, then enrollment into that dose level will be placed on hold, and a meeting of all participating investigators, the NYU DSMC Medical Monitor, the Astra Zeneca Trial/ Program Lead will be called to determine how best to proceed, as well as available PK data will be reviewed.

Table 7.31 Single agent AZD1775 (Arm C)

Dose	**AZD1775**[1]
0	300 mg PO once daily days 1-5 & 8-12 every 21 days
-1	250 mg PO once daily days 1-5 & 8-12 every 21 days
-2	200 mg PO once daily days 1-5 & 8-12 every 21 days
-3	150 mg PO once daily days 1-5 & 8-12 every 21 days

[1]AZD1775 should be taken either 2 hours before or 2 hours after a meal.

7.32 Expansion Portion

The Expansion portion of this trial will commence for Arm C as soon as the Safety Portion is completed.

Starting Dose

Agent	Dose	Route	Day(s)	ReRx
AZD1775[1]	MTD	PO once daily	1-5 & 8-12,	Every 21 days

[1]AZD1775 should be taken either 2 hours before or 2 hours after a meal.

7.33 Hydroxyurea (HU)

For patients randomized to Arm C single agent AZD1775, HU may be added after the first cycle of therapy at the physicians discretion after discussion with the PI. HU dose should be started according to clinical judgement at 500-1000mg/ day and titrated for additional myelosuppression as needed. Note: for patients with Myelofibrosis, HU can be given during cycle 1 at the previously tolerated dose.

7.4a Toxicity Assessment for Safety Portion: DLT definition and RP2D

Toxicity will be measured per NCI-CTCAE version5.0. DLT is defined as an adverse event occurring during the first cycle of treatment that is not clearly related to the subject's underlying disease and that meets one of the following:

- Grade 3 or higher toxicity as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 not clearly resulting from the underlying leukemia and that does not resolve to ≤ Grade 2 within 24 hours with the following exceptions;
    - Grade 3 fatigue, asthenia, fever, anorexia, or constipation;
    - Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization;
    - infection, bleeding or other expected direct complication of cytopenias due to active underlying disease;
    - Grade 3 or 4 tumor lysis syndrome (TLS) if it is successfully managed clinically and resolves within 7 days without end-organ damage;
    - Grade 3 or 4 isolated electrolyte abnormalities that last < 72 hours.
- Grade 3 AST, ALT or alkaline phosphatase will be considered dose limiting if it last > 72 hours
- treatment-related deaths are dose limiting
- confirmed Hy's law cases are dose limiting

NOTE: Myelosuppression will not be considered in evaluating toxicity in subjects with acute leukemias or similar advanced myeloid malignancies (MDS, MF) except where bone marrow (BM) hypoplasia occurs for >42 days with BM cellularity <5% in the absence of residual leukemia/disease.

7.4.b RP2D for the combination of AZD1775 with Cytarabine; DLT, MTD and Biological dose

Despite a lack of a clear biomarker/ PD marker for WEE1 kinase inhibition, based on preclinical data an effective pharmacological dose is up to the range of 750 nM, possibly higher to maximally 1000 nM. From recent PK data (REFMAL 984 and NCI study), daily dosing for 5 days for one or two weeks with AZD1775 was determined as the RP2D, that yielded an AUC (0-8 hrs) of ~8000nM. Therefore we would expect that 300mg AZD1775 daily would yield around 600-800 to maximally 1000 nM concentrations of AZD1775 in the first 8 hours.
For the combination arms (Arms A and B) in the Escalation portion we will escalate dose starting at AZD1775 200 mg daily on a 5-2-5 schedule. We will escalate up to/ until

a) the current MTD/ RP2D of 300 mg daily (5-2-5 schedule) is reached at acceptable toxicity (AEs) regardless of preclinical PK efficacy
b) DLT defining toxicities/ AEs are observed
c) clinical efficacy is observed that would meet the primary response endpoint already below the currnet RP2D of 300 mg AZD1775 daily
d) Clinical PK (AUC) of AZD1775 reaches approx. > 1000 nm/ hr

We will accomplish above goals with real-time assessment of safety, efficacy, PK and/or PD in each chohrt.

7.5 MTD Determination

This MTD determination applies to the Safety Portion. MTD for the safety portion will be defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of subjects (at least 2 of a maximum of 6 subjects).

7.51 Three subjects will be treated at a given dose level combination and observed for one cycle to assess toxicity (accrual will be suspended while the 3 subjects are treated and observed – only applicable to the dose escalation cohort/ part of study).

7.52 If DLT is not seen in any of the 3 subjects or in 1 of 3 subjects, 3 new subjects will be accrued. and treated at the same dose level (accrual will be suspended while the 3 subjects are treated and observed). If DLT is seen in 2 or 3 of 3 subjects treated at a given dose level, then the next 3 subjects will be treated at the next lower dose level, if only 3 subjects were enrolled and treated at this lower dose level.

7.53 After enrolling 6 subjects on a specific dose level, if DLT is observed in 1 or less subjects, then the combination dose will be considered safe for the expansion phase. If DLT is observed in at least 2 of 6 subjects, then the MTD will have been exceeded and defined as the previous dose unless only 3 subjects were treated at the lower dose level. In that case, 3 additional subjects will be treated at this lower dose level.

7.55 If a subject fails to complete one cycle of treatment for reasons other than dose-limiting toxicity defined adverse events, the subject will be regarded as non-informative for estimating the MTD and an additional subject will be treated at the current dose level.

7.6 Dose escalation (intrapatient) will not be allowed for a subject.

7.7a For this protocol, the subject must return to the consenting institution for evaluation at least once per cycle.

7.7b Local Medical Doctor (LMD)
When it has been determined that a patient's malignant disease is stable or objective tumor regression has been observed and the patient is tolerating therapy without excessive toxicity, after the first cycle of treatment, the standard of care drug AraC may be administered by the patient's Local Medical Doctor

(LMD). However, study drug AZD1775 can only be dispensed by an investigator or investigational site of the study. The registering physician retains responsibility for the patient.

In this case, a written statement outlining drug dosage, method of administration, follow-up tests required, and telephone number to call to discuss any questions with the responsible investigator must be sent with the patient to provide necessary information to the LMD, post cycle 1 of treatment therapy. The LMD will be required to supervise the administration of the study drugs as stipulated in the protocol and provide written documentation that the drug was administered.

8.0 Dosage Modification Based on Adverse Events - If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Dose modifications apply to the treatment given in the preceding cycle and are based on adverse events observed since the prior dose. Dose modification recommendations listed below are general guidelines, and appropriate dose adjustments for patient safety should be done if needed per treating physician discretion.

ALERT: *ADR reporting may be required for some adverse events. See Section 10.0.*

8.1 Dose Modification

Individual drugs can be dose reduced as per the table below depending on the adverse event attribution. The dose reductions outlined in table 8.11 should first generally apply to AraC. If, however, the AE is at least possibly related to AZD1775, then AZD1775 can be reduced first as indicated in Table 8.11. After cycle 2, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed.

8.11 AZD1775 combined with AraC (Arms A and B)

Dose	***AZD1775*** *[reduce AZD1775 first if at least possibly attributed to AZD1775]*	***Cytarabine (AraC)***
0	300 mg PO once daily days 1-5 & 8-12	20 mg SC twice daily days 1-5 & 8-12
-1	250mg PO once daily days 1-5 & 8-12[1]	20 mg SC twice daily days 1-5 & 8-12[2]
-2a	200 mg PO once daily days 1-5 & 8-12	20 mg SC twice daily days 1-5 & 8-12[2]
-2b	200 mg PO once daily days 1-5 & 8-12	10 mg SC twice daily days 1-5 & 8-12[2]

[1]If toxicity is clearly attributable to AZD1775, AZD1775 will be reduced to 250mg PO daily (days 1-5, 8-12) with continued AraC 20 mg SC twice daily days 1-5, 8-12. [2]AraC may be decreased to 10 mg SC twice daily at physicians discretion based on myelosupression, tolerance and clinical benefit..
NOTE: intermediate dose levels may be explored based on PK, PD and clinical efficacy parameters and evaluation under future amendments based on PK, PD and safety assessments.

8.12 AZD1775 single agent (Arm C)

Dose	AZD1775
0*	300 mg PO once daily days 1-5 & 8-12
-1	250 mg PO once daily days 1-5 & 8-12
-2	200 mg PO once daily days 1-5 & 8-12
-3	150mg PO once daily days 1-5 & 8-12

*Presumed starting dose of Expansion Portion.
Note: Further dose modifications such as intermittent dosing or proloned longer dosing can be made under future amendments.

8.2 A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- AZD1775 or AraC related adverse event that may have occurred has resolved to ≤ Grade 2 severity, except hematological adverse events for WBC, ANC, Platelets and Hemoglobin, or per table 8.32 guidelines.

If these conditions are not met on scheduled Day 1 of a new cycle, the subject will be evaluated as clinically indicated (i.e. weekly but at least every other week) and the new cycle of treatment will not be initiated until the adverse event has resolved as described above. **Treatment can be continued on the drug that is not associated with the adverse event at the start of the following cycle and the drug associated with the adverse event may be reintroduced when the adverse event resolves to ≤ Grade 1 if the treating physician feels that the patient will derive benefit from continued AraC or AZD1775 alone.**

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for the remainder of the study

8.3 Dose modification table for adverse events felt to be at least possibly related to AZD1775*** or AraC

Non-hematologic toxicity management guidelines
Substantial acute toxicities should be managed as medically indicated and with temporary suspension of investigational product, as appropriate. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treatment physician.
Dose reductions of AZD1775 should be consideredif toxicity is considered to be at least possibly related to AZD1775, i.e. in monotherapy studies or in combination studies if relationship cannot be wholly attributed to the combination agent (each combination agent should be considered on an individual basis). Dose re-escalation is not permitted.
In general, if a patient experiences a G1/G2 non-hematological toxicity, no dose modification is required (except QTc prolongation, see Table 8.31). If a patient experiences a G3 or G4 non-hematological toxicity which is not attributable to the disease or disease related processes under investigation, dosing will be interrupted and/or the dose reduced and

supportive therapy administered as required. Any patient who develops a Grade 3 or 4 non-hematologic toxicity that does not resolve to ≤ Grade 1 within 21 days should be removed from the study treatment unless approved by the Medical Monitor and Study Chair.
No more than two dose reductions will be allowed for any patient. Patients requiring further dose reduction due to toxicity must discontinue study treatment. Dose re-escalation is not allowed. If the patient has concurrent neutropenia and thrombocytopenia, please follow the most conservative guidance in the table below and discuss with Medical Monitor as needed.
If haematological parameters do not recover within 21 days, the patient should be removed from the study treatment.

Table 8.31

Electrocardiogram QT corrected interval prolonged	
QTc Value (triplicate)[a]	AZD1775
QTc 450-480 ms (males) or 470-480 (females)	Hold. Once QTc interval has returned to pretreatment status and correction of possible electrolyte imbalance has been made, resume at next lower dose level.
QTc 481-500 ms	Hold. Seek cardiologist advice, patient may resume at next lower dose level if cardiologist agrees.
QTc ≥ 501 ms	Discontinue treatment. Seek cardiologist advice
Shift from baseline of ≥ 60ms	Discontinue treatment. Seek cardiologist advice

Table 8.32

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified*** ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
BASED ON INTERVAL ADVERSE EVENT***			
Blood and Lymphatic System Disorders	Febrile neutropenia ≥ Grade 3	AZD1775	May omit dose until fever has resolved or returned to baseline. Dose to be restarted at same dose level or treating physician may discuss possible dose reduction (per Table 8.12) with the Study Chair. If clinical benefit is derived, AZD1775 may be continued if the infection is managed andcontrolled with appropriate medical intervention (i.e.antibiotics) and the patient is felt to derive benefit from the treatment with AZD1775 *(Rationale: AML, MDS and MF patients may have persistent and/ or prolonged neutropenia and will only recover if underlying disease is adequately treated]*.

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Investigations	Neutrophil & Platelet count decrease ≥ grade 4 NOTE: only applicable for patients with absolute neutrophil count (ANC) of ≥ 1000mm3 and platelet count > 100,000/mm3 at baseline (i.e. MDS or ME patients)	AZD1775	Omit dose until ANC and/or platelets have recovered to ≤ grade 2. If clinical benefit is derived, AZD1775 may be continued if not recovered to ≤ grade 2 after discussion of treating physician and study chair. For a second event reduce by 1 dose level (Table 8.12) For a third event discontinue from treatment. *[If clinical benefit is derived, AZD1775 may be continued per physician assessment and after discussion with Study Chair and Medical Monitor (NYU DSMC)]*
Investigations	Creatinine increased Grade 2	AZD1775	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease by 1 dose level (Table 8.12) *[If clinical benefit is derived, AZD1775 may be continued if the renal function is elevated but stable]*
		AraC	Continue treatment at current dose level
	Creatinine increased Grade 3 and 4	AZD1775	Omit dose until resolved to ≤ grade 1, then decrease dose by 1 dose level
		AraC	Omit dose until resolved to ≤ grade 1, then decrease dose by 1 dose level
Investigations	Blood bilirubin increased ≥ Grade 3	AZD1775	Omit dose until resolved to ≤ grade 1, then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease by 1 dose level
		AraC	Continue treatment at next lower dose level
	Blood bilirubin increased Grade 4	AZD1775	Omit dose until resolved to ≤ grade 1, then decrease dose by 1 dose level

→ → *Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0* unless otherwise specified* ← ←			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
		AraC	Continue treatment at Dose level -1once resolved to ≤ Grade 1
	Alanine aminotransferase (ALT) increased and/or Aspartate aminotransferase (AST) increased Grade 3	AZD1775	Omit dose until resolved to ≤ grade 1 or baseline then: • If resolved in ≤ 7 days, then maintain dose level • If resolved in > 7 days, then decrease dose by 1 dose level
		AraC	Continue treatment at next lower dose level
	Alanine aminotransferase (ALT) increased and/or Aspartate aminotransferase (AST) increased Grade 4	AZD1775	Omit dose until resolved to ≤ grade 1 or baseline, then decrease dose by 1 dose level
		AraC	Continue treatment at dose reduced AraC of 10mg s.c. twice daily days 1-5 & 8-12
Cardiac Disorders	Cardiac disorders – Other ≥ Grade 4	AZD1775	Omit dose and discontinue patient from study
Other Non-Hematologic events	Grade 3	AZD1775	Omit drug and follow patient at least weekly or at least every other week until adverse event has resolved to grade ≤ 2, restart drug at next lower dose level. Contact protocol chair anda medical monitor if resumption of AZD1775 at previous dose may be clinically indicated
Other Non-Hematologic events	≥ Grade 4	AZD1775	Omit drug and follow patient at least weekly or at least every other week until adverse event has resolved to grade ≤ 2, restart drug at next lower dose level. For a repeated Grade 4 event discontinue patient from study
AT TIME OF RETREATMENT (at beginning of each next cycle)			
Non Hematologic	All Non-Hematologic Toxicities Grade ≥ 4 (With the exception of nausea, vomiting or diarrhea controlled with appropriate medications.)	AZD1775	Hold AZD1775 and AraC. Re-check patient weekly or at least every other week. When event returns to ≤ grade 2, resume AZD1775 and/ or AraC treatment at next lower dose level. For a repeated Grade 4 event present/ recurred at beginning of each next cycle patient will be discontinued from therapy.

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** Use the following to describe actions in the Action column:

- Omit = Treatment is not given for the day that is omitted, but treatment may resume once the adverse

event has resolved as mandated in Table 8.2. For example, if treatment is omitted on Day 8, but the adverse event has resolved by Day 10, treatment may resume on Day 10 to complete the cycle. Missed doses will not be made up.

- Hold/Delay = Treatment can be made up as part of this cycle
- Discontinue = Treatment is totally stopped

***AraC can be continued each cycle regardless of dose hold or adjustments for AZD1775, if patient is presumed to derive clinical benefit from the intervention.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event including abnormal laboratory values must be followed by their treating physician as clinically indicated.
The maximum time allowed for treatment interruption due to toxicity is 4 weeks from the intended dosing day for the combination arms (Arm A and B) and 3 weeks for the single agent AZD1775 arm (Arm C) . If interruption is > 4 and 3 weeks for Arms A, B and C respectively, continuation of treatment may be allowed on a case by case basis (i.e. clinical benefit) as determined by the treating physician in discussions with the Medical Monitor (NYU DSMC) and the Stuyd Chair. However, any discontinued patient will continue to be followed for toxicity. Dose interruptions should be reported on the appropriate Dosage Administration CRF.

9.0 Ancillary Treatment/Supportive Care/Concomitant Medications

9.1 Diarrhea

Due to frequent reports of diarrhea with AZD1775 administration, anti-diarrhoeal treatment with loperamide (Imodium) is required at the **first** onset of diarrhea according to American Society of Clinical Oncology (ASCO) guidelines. Oral loperamide 4mg should be administered at the first onset of diarrhoea and then 2mg every 2 hours until patient is diarrhea-free for at least 12 hours. The first dose of loperamide could be lowered to 2mg if the diarrhea is recurrent and if, in the opinion of the treating physician, the diarrhoea is not severe. The dose of loperamide should not exceed 16mg in a 24-hour period.
Patients should be instructed to notify the Investigator or research staff of the occurrence of bloody or black stools, symptoms of dehydration, fever, inability to take liquids by mouth, and inability to control diarrhoea within 24 hours of using loperamide or other prescribed anti-diarrheal medications
If diarrhea is severe (i.e., requiring intravenous [IV] rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalised for IV hydration and correction of electrolyte imbalances.
Nausea and vomiting
All patients must receive a 5-HT3 antagonist, ondansetron (Zofran) 8 mg PO QD or granisetron (Kytril) 1 mg PO QD prior to each dose of AZD1775. If nausea and vomiting continue, a second dose of antiemetics can be taken 8 hours later if necessary. In addition, dexamethasone 4 mg PO may be given with each AZD1775 dose unless contraindicated or not well-tolerated. Dexamethasone or the 5-HT3 antagonist may be given by IV route as needed.
Promethazine (Phenergan), prochlorperazine (Compazine), and benzodiazepine may still be used as additional adjunctive treatments during AZD1775 therapy.
Please note: aprepitant [Emend] and fosaprepitant are not permitted due to known DDIs.
Patients should be encouraged to maintain liberal oral fluid intake.
Suitable alternative medications may be used, with adequate justification, in those studies where the use of any of the above medications might interfere with other study procedures or are deemed insufficient.

Febrile neutropenia
Patients experiencing febrile neutropenia with significant symptoms should be managed in a hospital setting according to standard procedures, with the urgent initiation of IV antibiotic therapy. Patients with febrile neutropenia without symptoms should be managed according to standard guideline.

Routine use of colony-stimulating factors (G-CSF or GM-CSF) is not recommended. Prophylactic use of colony-stimulating factors should be discussed with the study chair. Therapeutic use in patients with serious neutropenic complications may be considered at physician discretion. Recombinant erythropoietin to maintain adequate hemoglobin levels is discouraged and only allowed after discussion with the study chair.

9.2 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, anti-emetics received from the first administration of study drugs until 30 days after the final dose are to be recorded in the medical record. For more severe diarrhea (i.e. Grade 3 or 4) supportive measures such as hydration and anti-diarrheals are recommended according to instutitional practice guidelines and as deemed appropriate by the medical situation (i.e. IV rehydration as in- or outpatient, antibiotics).

9.3 Anti-emetic therapy (excluding aprepitant) may be used in accordance with standard practice and/or the discretion of the investigator.

9.4 Hydroxyurea is allowed during the trial to control blast counts/WBC if the patient is felt to derive benefit from study treatment.

9.5 Antifungal treatment on protocol: The preferred azole anti-fungal medication is Fluconazole, (alternatively Posaconazole may be given (same below criteria apply for posaconazole) which can be given during treatment with AZD1775 at the treating physician's discretion, however with dose reductions of AZD1775 as outlined below. Based on the DDI simulations with Fluconazole (moderate inhibitor), there is an approximately 35% increase in AZD1775 exposure. Therefore if Fluconazole (or Posaconazole) are given the following AZZD1775 dose reductions need to be followed:

AZD1775 200 mg dose → reduce to AZD1775 150 mg
AZD1775 250mg dose → reduce to AZD1775 200 mg
AZD1775 300mg dose → reduce to AZD1775 250mg

10.0 Safety and Adverse Events

10.1 Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

Adverse Event

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if <u>any one of the following</u> conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.2 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

As outlined in Section 10.8, adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

10.3 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported within 5 days of PI notification are those that are:

- related to study participation,
- unexpected, and
- Harmful or have the potential to cause harm (see definitions, section 10.1)

Events should be reported using the NYU CTO Medical Events Form.

Adverse events that do not fit the above immediately reportable criteria must still be reported to the IRB at each annual review, either in a summary or tabular format.

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the study sponsor. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are SAEs will be reported to the IRB and to the DSMC/study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DSMC/study sponsor within 24 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within 5 days of the IR's receipt of the report of the problem from the investigator.

Serious adverse event reporting will begin in conjunction with the date of informed consent. Any SAEs occurring prior to study drug administration that the investigator believes may have been caused by a protocol procedure must be reported immediately to the Sponsor or its designee and recorded on the case report form.

> All fatal or life-threatening adverse events must be immediately reported to the Principal Investigator, via appropriate reporting mechanism and the NYU Langone Health IRB by telephone or e-mail. Within 24 hours of the event, the Serious Adverse Event Form must be emailed to NYUPCCsafetyreports@nyumc.org whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

All other serious adverse events must be reported to the sponsor and DSMC within 24 hours by email (NYUPCCsafetyreports@nyumc.org) or fax (212-263-0715) . The Serious Adverse Event Form can be emailed to the principal investigator and Clinical Trials Office (NYUPCCsafetyreports@nyumc.org) or it can be faxed (212-263-0715), this documentation will be forwarded to the DSMC's appointed medical moniotr within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known.

Current contact information shall be maintained at the site within the regulatory binder.

All serious adverse events (SAEs) will be evaluated by the DSMC if meeting the requirements for expedited reporting, the study Sponsor(NYU Langone Health) will report serious adverse events to all regulatory authorities with jurisdiction over ongoing trials with the study drug, this will be done in accordance with standard operating procedures and policies of the IRB, DSMC and FDA.

10.31 **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 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.311 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 5.0. 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 Section 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

10.312 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). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI.

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.

10.313 Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are not recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

10.314 Any serious adverse event occurring after the patient has provided informed consent, has started taking the study medication, and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication). The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.

10.4 Investigator reporting: notifying the study sponsor

Since multiple sites may be participating, the following describes events that must be reported to the study sponsor (NYU Langone Health PCC) and Astra Zeneca in an expedited fashion.

The following describes events that must be reported to the study sponsor in an expedited fashion.

Initial Report: within 24 hours:
The following events must be reported to the study sponsor (NYU Langone Health PCC) by email within 24 hours of awareness of the event using the NYU CTO Medical Events Form:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

The investigator shall maintain a copy of the Medical Events Form on file at the study site. All report forms must be signed and dated by the Principal Investigator. If the Principal Investigator is not available at the time of the initial report, then the form can be submitted by a Sub-Investigator. This form should be reviewed by the Principal Investigator, whom sign/date initial report upon return.

Report to:

NYUPCCsafetyreports@nyumc.org

AND

Raoul Tibes, MD, PhD
NYU Hematology Associates
240 East 38th Street, 19th Floor
New York, NY 10016
646-501-8205
Email: *raoul.tibes@nyumc.org*

Events of Clinical Interest (any medical event that is deemed significant via Principal Investigator's expertise, but does not apply to SAE categories) will be reported within 2-5 days, or as per study Sponsor specifications.

Follow-up report:
As a follow-up to the initial report, the investigator shall provide further information, as applicable, on the unanticipated event or the unanticipated problem in in the form of a written narrative. This should include any other diagnostic information that will assist in the understanding of the event.

Other Reportable events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

- ***Withdrawal of IRB approval***
  An investigator shall report to the sponsor a withdrawal of approval by the investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

10.5

10.5 Investigator reporting: notifying the collaborator

- **Reporting of SAEs to AstraZeneca**
  Investigators **must** report to the Overall PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

  All SAEs have to be reported, whether or not considered causally related to AZD1775, or to the study procedure(s). All SAEs will be recorded in the eCRF.

  If any SAE occurs in the course of the study, then investigators or other site personnel must inform NYU Langone Health PCC immediately; procedures for reporting to AstraZeneca will be followed as per outlined below.

  SAE information will be sent via secure e-mail connection or via fax. The standard paper SAE Report with supporting relevant source documents (e.g. history and physical [H&P], hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed to evaluate the event) will be attached and sent via:

  Send SAE report and accompanying cover page by way of Email to

  AEMailboxClinicalTrialTCS@astrazeneca.com
  or by fax to AstraZeneca's designated fax line: US: 302-886-4114, ex-US +46 31 776 37 34

  Transmission of the SAE report Form should be confirmed by the site personnel submitting the report.

  Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to PI and AstraZeneca as soon as it is available; these reports should be submitted using the SAE Report Form. Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB) according to the policies of the responsible IRB. For fatal or life- threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately.
  AstraZeneca or their representative will provide Regulatory Authorities, Ethics Committees (ECs), IRBs and PIs with clinical safety updates/reports according to local requirements.

  Overall Investigator to ensure that all the necessary information is provided to the AstraZeneca Safety Department **within 1 calendar day** of initial receipt of the information for fatal and life threatening events and **within 5 calendar days** of initial receipt of the information for all other SAEs.

EVENT TYPE	REPORTING PROCEDURE

Other Grade 4 or 5 Events and/or Any Hospitalizations During Treatment Not Otherwise Warranting an Expedited Report	Complete a Notification Form*: Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form electronically via the MCCC Remote Data Entry System or paper form within 5 working days of the date the clinical research associate (CRA) is aware of the event(s) necessitating the form. If an expedited written report has been submitted, this form does not need to be submitted.

* This form is not required for those adverse events listed in section 10.31

10.61 Special Situations for Expedited Reporting

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

An expedited report or notification form may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will supercede the standard Expedited Adverse Event Reporting Requirements (Note: These adverse events must still be reported through the routine reporting mechanism [i.e. Nadir/adverse events form]; see footnote 1):

NOTE: These only apply to those events that are not attributed to AZD1775 (Unlikely or Unrelated as defined in Section 10.3).

System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported[1]
General disorders and administrations site conditions	Fatigue	Grade 3
Gastrointestinal Disorders	Nausea	Grade 3
	Vomiting	
	Diarrhea	
Investigations	Neutrophil count decreased	Grade 3 and Grade 4
	White blood cell count decreased	
	Platelet count decreased	
Blood and lymphatic system disorders	Anemia	Grade 3 and Grade 4
	Febrile Neutropenia (in AML patients only)	Grade 3 and 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, detailed in Section 10.4 .

10.6 Other Required Reporting

10.61 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 abnormities 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 AstraZeneca database as specified in 21 CFR 312.64(b).

10.62 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 (incl 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.

10.63 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 must be reported.
- Any malignancy possibly related to cancer treatment should also be reported via the routine reporting mechanisms outlined in each protocol.

10.64 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.

10.7 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYU Langone Health IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record. The NYU IRB address is:

NYU School of Medicine IRB
1 Park Avenue, 6th Floor
New York, NY 10016

Report promptly, but no later than 5 working days:
Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

Other Reportable events:
The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

Reporting Process
The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation). The contact information for submitting IND safety reports is noted below:

Email: NYUPCCsafetyreports@nyumc.org

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's study file.

It is the responsibility of the study sponsor to notify all participating investigators of any adverse event that meets the FDA 15-day reporting requirement criteria as note above. The same materials and timeline used to report to the FDA are used for notifying participating investigators.

All Internal SAEs reported by the CTO, occurring to patients on clinical trials that are not monitored by any other institution or agency, are reported via email: NYUPCCsafetyreports@nyumc.org and reviewed within 48 hours by the medical monitor. Based on the review, one of three determinations will be made:

- SAE report is considered to be adequate
- Queries for clarification to PI regarding treatment attribution and/or resolution of SAE or completeness of other information. The committee may request a cumulative review of all SAEs on the study to date.
- Request for full DSMC committee review of protocol at the next scheduled meeting.

The DSMC Coordinator will record the committee's decision and incorporate it into the study summary for the next scheduled study review.

10.8 Required Routine Reporting

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v5.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
General disorders and administrations site conditions	Fatigue	X	X
	Fever (Pyrexia)	X	X
Blood and lymphatic system disorders	Anemia	X	X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	# of stools	X	
	Diarrhea		X

Investigations	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
	AST Increased	X	X
	ALT Increased	X	X

10.81 Submit via appropriate NYU Case report forms (i.e., paper or electronic, as applicable) all AEs regardless of attribution to study treatment.

10.811 Grade 5 AEs (Deaths)

10.8131 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.8132 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.

11.0 Treatment Evaluation Guideline

Note: Novel combinations in AML/MDS may be expected to result in different response kinetics than "conventional" cytotoxic regimens. Thus initial blast % increase may not accurately reflect later stage responses. AraC, when given may lead to differentiation. There will be no pre-specified number of cycles and patients can remain on study as long as they tolerate the combination and/or derive clinical benefit.

11.1 AML response criteria

11.11 Complete hematologic response (CR)
Less than 5% blasts in a non-hypocellular marrow with a granulocyte count ≥ 1.0, and a platelets count of ≥ 100 with complete resolution of
extramedullary disease and absence of peripheral blood blasts.

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)

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

11.13 Partial remission (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.

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

11.15 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.

11.2 MDS and CMML response criteria

Category	**Hematologic Response** **Response Criteria (responses must last at least 4 weeks)**[a]
Complete remission (CR)	Bone marrow: ≤5% myeloblasts with maturation of all cell lines. If present, persistent dysplasia will be noted (dysplastic changes should consider the normal range of dysplastic changes.) Peripheral blood: • Hemoglobin (Hgb) ≥11 g/dL (untransfused, patient not on erythropoietin) • Neutrophils ≥1.0 x 10^9/L (not on myeloid growth factor) • Platelets ≥100 x 10^9/L (not on a thrombopoietic agent) • Blasts 0%;
Partial remission (PR)	All CR criteria (if abnormal prior to treatment), except: Bone marrow blasts decreased by ≥50% compared with pretreatment but still >5%. Cellularity and morphology not relevant.
Marrow CR	Bone marrow: ≤ 5% myeloblasts and decrease by ≥50% over pretreatment if > 10% at baseline Peripheral blood: if hematologic improvement (HI) responses, they will be noted in addition to the marrow CR
Stable disease (SD)	Failure to achieve at least PR, but no evidence of progression for >8 weeks.
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to an MDS FAB subtype more advanced than pretreatment after 6 months/cycles of therapy
Relapse after CR or PR	At least one of the following: • Return to pretreatment bone marrow blast percentage • Decrement of ≥50% from maximum remission/response levels in granulocytes or platelets • Reduction in hemoglobin concentration by ≥1.5 g/L or transfusion dependence if previously had become transfusion independent for > 8 weeks[c]
Cytogenetic response	Complete: Disappearance of the chromosomal abnormality without appearance of new ones Partial:

	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: • Less than 5% blasts: ≥50% increase in blasts to >5% blasts • 5%-10% blasts: ≥50% increase in blasts to >10% blasts • 10%-20% blasts: ≥50% increase in blasts to >20% blasts • 20%-30% blasts: ≥50% increase in blasts to >30% blasts Any of the following: • At least 50% decrement from maximum remission/response levels in granulocytes or platelets • Reduction in hemoglobin concentration by ≥2 g/dL • Transfusion dependence if previously had become transfusion independent for > 8 weeks[c]
a For a designated response (CR, PR), relevant response criteria must be noted on at least 2 successive determinations at least 1 week apart after an appropriate period following therapy (e.g., 1 month or longer). c In the absence of another explanation, such as acute infection, gastrointestinal bleeding, hemolysis, etc.	

Hematologic Improvement*	**Response Criteria (responses must last at least 8 weeks)[a]**
Erythroid response (pretreatment, Hgb < 11 g/dL)	Hgb increase by ≥1.5 g/dL Relevant reduction of units of red blood cell (RBC) transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for an Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation.
Platelet response (pretreatment, < 100 x 10^9/L)	Absolute increase of ≥ 30 x 10^9/L for patients starting with >20 x 10^9/L Increase from < 20 x 10^9/L to >20 x 10^9/L and by at least 100%
Neutrophil response (pretreatment, < 1.0 x 10^9/L)	At least 100% increase and an absolute increase >0.5 x 10^9/L.
Progression or relapse after HI	At least 1 of the following: • At least 50% decrement from maximum response levels in granulocytes or platelets • Reduction in Hgb by ≥1.5 g/dL • Transfusion dependence[b]
* Pretreatment count averages of at least 2 measurements (not influenced by transfusions) ≥1 week apart (modification) a For a designated response (CR, PR, HI), relevant response criteria must be noted on at least 2 successive determinations at least 1 week apart after an appropriate period following therapy (e.g., 1 month or longer). b In the absence of another explanation, such as acute infection, gastrointestinal bleeding, hemolysis, etc.	

11.3 Response Criteria for MF

Response categories	Required criteria (for all response categories, benefit must last for ≥12 weeks in order to qualify as a response)
Complete Remission (CR)	*Bone marrow:* * Age-adjusted normocellularity; <5% blasts; ≤Grade 1 myelofibrosis**, AND *Peripheral blood:* Hemoglobin ≥100 g/L and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells***, AND *Clinical:* Resolution of disease symptoms; Spleen and liver not palpable; No evidence of EMH
Partial Remission (PR)	*Peripheral blood:* Hemoglobin ≥100 g/L and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells***, AND *Clinical:* Resolution of disease symptoms; Spleen and liver not palpable; No evidence of EMH **OR** *Bone marrow:* * Age-adjusted normocellularity; <5% blasts; ≤Grade 1 myelofibrosis**, AND *Peripheral blood:* Hemoglobin ≥85 but <100 g/L and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥50 but <100 x 10^9/L and <UNL; <2% immature myeloid cells***, AND *Clinical:* Resolution of disease symptoms; Spleen and liver not palpable; No evidence of EMH
Clinical improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia or neutropenia‡
Anemia response	*Transfusion-independent patients:* a ≥20 g/L increase in hemoglobin level† *Transfusion-dependent patients:* becoming transfusion-independent††
Spleen response§	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable§§, OR A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%§§ *A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response* *Confirmation by MRI or CT showing ≥35% spleen volume reduction is recommended (but not required)*
Progressive disease¥	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM, OR A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5 to 10 cm, OR A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm, OR Leukemic transformation confirmed by a bone marrow blast count of ≥20%, OR A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 x 10(9)/L that lasts for at least two weeks
Stable	Belonging to none of the above listed response categories

disease	
Relapse	No longer meeting criteria for at least CI after achieving CR, PR or CI, OR Loss of anemia response persisting for at least one month, OR Loss of spleen response persisting for at least one month

Key: UNL, upper normal limit; LCM, left costal margin; MRI, magnetic resonance imaging; CT, computed tomography; EMH, extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven non-hepatosplenic EMH) ;

*Baseline and post-treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

**Grading of myelofibrosis is according to the European classification (*Thiele et al. Haematologica 2005;90:1128*) . It is underscored that the consensus definition of "a complete remission bone marrow" is to be used only in those patients where all other criteria, including resolution of leukoerythroblastosis, are met. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histological remission.

***Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells is allowed.

‡See table for definitions of anemia response, spleen response and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in hemoglobin level from pre-treatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pre-treatment baseline, in platelet count or absolute neutrophil count, according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. In addition, assignment to clinical improvement (CI) requires a minimum platelet count of ≥25,000 x 10(9)/L and absolute neutrophil count of ≥0.5 x 10(9)/L

†Applicable only to patients with baseline hemoglobin of <100 g/L. In patients not meeting the strict criteria for transfusion-dependency at the time of study enrollment (see below), but have received transfusions within the previous month, the pre-transfusion hemoglobin level should be used as the baseline

††Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to study enrollment, for a hemoglobin level of <85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥85 g/L.

§In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy

§§Confirmation of spleen or liver responses by imaging studies is recommended (but not required), where a ≥35% reduction in spleen volume, asassessed by magnetic resonance imaging (MRI) or computed tomography (CT), is required. Furthermore, a≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

¶Symptoms are evaluated by the Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPN-SAF TSS).17 The MPN-SAF TSS is assessed by the patients themselves and includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as

good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-to-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

Confirmation by MRI or CT is recommended (but not required) to confirm progressive disease assignment for splenomegaly, where a ≥25% increase in spleen volume from baseline is required for confirmation. Baseline values for both physical examination and imaging studies refer to pre-treatment baseline and not to post-treatment measurements.

11.4. Symptom Assessment Package for MF

Given there is no currently validated instrument of patient-reported outcomes (PRO) for serial administration in patients with ET or PV to be used in a clinical trial setting we have adopted a standard validation approach used for new PRO instruments. The new PRO instrument to be tested (MPN-SAF) and a well validated questionnaire for assessing health related quality of life will be given to patients at baseline and prior to treatment on cycles 3, 6, and 9, and at study discontinuation. The symptom assessment package of instruments will be completed by enrolled patients on-site at the time of their study visits.

MPN-SAF: The MPN-SAF (Appendix IV) was created to address the constellation of symptoms most frequent in MPN patients based on the results of our internet based survey of 1179 MPN patients ((PV (N=405); ET (N=304); MF (N=456))(2). Our survey demonstrated that the vast majority of the MPN patients have very significant fatigue compared to age matched published data. Given the central importance of this symptom, and need for accurate measurement on a trial, the previously validated Brief Fatigue Inventory (BFI) is included as item 1-9 (3), and a composite score is generated for the BFI (the score is the mean result of all 9 items). Items 10-13 address spleen related symptoms (early satiety, abdominal pain), inactivity, and cough. Items 14-18 address the central MPN symptoms of night sweats, pruritus, bone pain, fever, and weight loss. Although some of these symptoms are more frequent in PMF, they are still present in significant numbers of ET and PV patients and are of relevance in this trial given the high risk patients included on study will also include those who already have mild features of post ET/PV MF respectively. Item 19 includes a single item overall quality of life measure. Items 10-16 and 19 are measured on a linear analog scale assessments (LASA). The LASA methodology has proven very valid in the past (4). Additionally, the lack of a composite score overall for the MPN-SAF is a positive attribute for this instrument for serial assessment in a clinical trial for MPN patients as individual symptoms may respond (or worsen) independently with therapy.

The MPN-SAF has previously been validated for use at a single time point(5) by co-administration with previously validated instruments. Measurement of individual symptoms which existed on other validated instruments was highly correlated with single item results on the MPN-SAF. Additionally, patient anonymous feedback demonstrated the MPN-SAF was easy to understand. Additionally patients were questioned to respond to any major symptoms which were not included in the MPN-SAF, and no symptom was mentioned by more than one patient demonstrating the relatively comprehensive nature of the instrument for MPN patients.

EORTC-QLQ C30 (Appendix V): The EORTC-QLQ-C30 version 3.0 (6) is included as our main instrument for co-validation on these trials, and redundant capture of information for impact of protocol therapy on patient's symptoms, mood, and quality of life. The initial EORTC QLQ-C36 questionnaire, later shortened and validated with 30 questions, has the following advantages namely being a) cancer specific b) multidimensional in structure c) appropriate for self-administration d) applicable across a range of cultural settings. This instrument has been thoroughly validated for serial use in cancer clinical trial setting. This instrument although highly valid for a portion of the symptom changes we wish to capture with this trial, never-the-less is not as comprehensive for MPN.

12.0 Descriptive Factors

12.1 Transfusion Dependent: Yes vs No

12.2 MDS subcategory: MDS vs MDS/MPN overlap vs CMML

12.3 Previous cytotoxic chemotherapy: yes vs no

12.4 AML subcategory: without prior HMA vs prior HMA

12.5 HMA failure: refractory vs relapsed vs progressed on HMA

12.6 AML: De novo vs secondary AML

12.7 AML: newly diagnosed vs relapsed/refractory

12.8 MF: with or without HU

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who have not developed PD will continue treatment per protocol.

13.2 Patients who develop PD while receiving therapy will go to the event monitoring phase. This phase consist of obtaining follow up/survival data for up to 5 years by phone and medical record review of subjects.

13.3 Patients who go off protocol treatment for reasons other than PD will go to the event monitoring phase per Section 18.0.

13.4 If a patient in the initial safety portion fails to complete 28 days of treatment for reasons other than dose-limiting toxicity defined adverse events, the patient will be regarded as uninformative in regard and an additional patient will be treated; however, all toxicity information will be utilized in the analysis.

13.5 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 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.

13.6 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 endpoint 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. Event monitoring will be required per Section 18.0 of the protocol.

13.7 A patient is deemed ascreen failure 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

Body Fluid Biospecimen Submission

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

Correlative Study (Section for more information)	**Mandatory or Optional**	**Blood or Body Fluid being Collected**	**Type of Collection Tube (color of tube top)**	**Volume to collect per tube (# of tubes to be collected)**	**Baseline**	**Cycle 1 Day 2 (+/- 1 Day)**	**Cycle 1 Day 5 (+/- 1 Day)**	**Cycle 2 Day 5 (+/- 2 Day) & Day 5 of Subsequent Odd Cycles**	**At time of bone marrow after cycles 1 (AML only), 2 and 4[3] (+/- 3 days)**	**EOS**	**Process at site? (Yes or No)**	**Temperature Conditions for Storage /Shipping**
Biomarkers	Mandatory	Whole Blood	1 x Red top 2 x Na Heparin Green top	10 mL (3)	X	X[1]	X	X	X	X	Yes	Cold Pack
Biomarkers	Mandatory	Bone marrow aspirate (if no marrow obtained whole blood becomes mandatory)	Heparinized Green top	4 mL (2)	X[4]				X	X[2]	Yes	Cold Pack
Saliva Sample	Mandatory	Saliva	n/a	n/a	X						No	ambient
Pharmacokinetics	Mandatory	Plasma	Lavender Top	2 ml			Pre-Dose, 1, 2, 4, 6, & 8 hrs post-dose[5]	Pre-Dose			Yes	-20^{o}C

1. Only to be done in those patients with circulating tumor cells in their blood
2. End of study bone marrow sample is optional and to be collected only if bone marrow performed as part of patient's standard of care.

3. Bone marrow aspirates will be done at times of standard clinical marrow tests. Follow Tables 4.1. (AML) and 4.2. (MDS) for study schedule. In brief after cycle 1 (for AML only, at physician's discretion can be omitted, see Table 4), after cycles 2 and 4, and then at physician discretion, an at relapse/ progression. Note: there is a +/- 3 day window for marrow biopsies.
4. This is only mandatory IF a BM biopsy has not been done within 4 weeks of study start for MDS and AML and 8 weeks for MF patients.
5. Post-dose pks have a 10% window as follows: 1hr post-dose ± 6min; 2hr post-dose ± 12 min; 4hrs post-dose ± 24 min; 6hrs post-dose ± 36 min; 8 hrs post-dose ± 48 min.

NOTE: marrow bisopies will not be done soley for the purpose of drawing a research sample , but should be performed to coincide at times of standard clinical marrow biopsies/aspirates.

14.2 Collection and Processing

14.21 Biomarkers: Process on site. Send all samples in original tubes to Center for Biospecimen Research & Development lab per section 14.32.

14.22 Pharmacokinetics: Samples are collected at the time intervals presented in the protocol. Whole blood will be collected in 2 mL BD Vacutainer tubes containing K2EDTA (lavender top) as anti-coagulant for the analysis of AZD1775. Following collection, gently invert the samples 10 times and immediately place on ice. Within 30 minutes of blood collection centrifuge at 1500 xg, at 4°C for 10 minutes. From each blood sample, transfer roughly equal volumes into a total of two 1.8 mL polypropylene cryovials using a disposable polypropylene pipette. Store plasma samples at -20°C in an upright position within 30 minutes of plasma preparation and keep frozen at this temperature until shipment and during shipment.

Labels will be provided. Tubes should be labeled with the following information: Study, Subject ID, Visit, Draw Time, and Biological Matrix (e.g., blood or plasma). When applying the label, place the label in a vertical position. Do not wrap the label around the tube horizontally. Place the label as close to the cap as possible, but do not adhere the label to the cap of the tube. Do not cover any written information with the label.

14.3 Shipping and Handling

14.31 Kits will be used for this study for the pharmacokinetics.

14.32 Shipping Specimens

14.321 For Biomarkers including saliva: Verify ALL sections of the Specimen Submission Forms (i.e. blood, bone marrow, saliva – see Forms Packet) are completed and filled in correctly.

For Pharmacokinetics: Ship the aliquots frozen on dry ice. The samples must be securely packed in boxes to avoid breakage during transit, double-bagged to contain leaks, and where applicable, packed with a sufficient quantity of dry ice to ensure they remain frozen for at least 72 hours.

Samples should be placed in a courier box with a paper copy of the Sample Inventory. Samples should be boxed up with each subject's samples in profile order and listed in the same order on the Sample Inventory for ease of checking at the bioanalytical laboratory (Covance Central Laboratory Services).

Once the courier has collected the samples, the sample receiver at Covance should be notified via email of the courier name, airway bill number, expected delivery date/time and shipment contact. An electronic sample inventory (Excel format, Request file) should also be attached to this email.

14.322 Transport specimens immediatelyto:

For Biomarkers:

Center for Biospecimen Research & Development
Medical Science Building
550 First Avenue, Berg 3rd Fl.,
Rm. 381 New York, NY 10016
cbrd@nyumc.org
Tel: 646-501-4268

For Phamacokinetics: Ship specimens via Priority Overnight service, Monday – Wednesday ONLY, to:

Covance Central Laboratory Services
Special Handling
Attn: Phyllis Sellars
8211 SciCor Drive
Indianapolis, Indiana 46214
Phone: 317-271-1200
Do not send samples the day before, the day of, or the observed day of a national holiday.

All specimens must be shipped Monday – Wednesday ONLY.

14.4 Suggested Correlative Studies and Experiments:

The correlative studies are designed based on the pre-clinical data in AML, MDS and other tumor types and the general mechanisms of WEE1 and AraC in pathophysiology of cancer and the diseases under study. These studies are suggestions at the time of protocol development. Specific assays may change based on the current knowledge at time of biomarkers analysis.

Patients will be asked in the informed consent to provide a research bone marrow aspirate and blood samples as outlined in the schedule of events. Research bone marrow and aspirates will be collected as outlined in Table 14.1 in conjunction with a patient's standard of care bone marrow biopsy or aspirate procedures. Peripheral blood research samples will be drawn at times of routine clinical draws, in parallel with the marrow biopsies as defined in Table 14.1.

Objectives and overview of correlative studies:

The below assays and studies to be performed are suggested at the time of protocol writing. Based on novel insights into the biology of WEE1 inihibition and AML/MDS that will arise during the protocol duration, below experiments may be adjusted to reflect the current state of the art knowledge.

1. WEE1 inhibition causes DNA damage and apoptosis. The degree of DNA damage in combination with AraC is unknown. Assessment of DNA damage induction by γH2AX and apoptosis by cleaved caspase 3 (CC3) as measured by flow cytometry on patient specimens at baseline and on follow up specimens, preferably on marrow aspirates, alternatively on peripheral blood samples will be conducted. Cell cycle distribution analysis and co-staining for total and phosphorylated CDK1/2 may be performed (using propidium iodide staining) at the same time points for samples with sufficient material.

2. Preclinical experiments (R.Tibes Lab) suggest that the damage and cell death induction is mainly/stronger in an earlier, leukemia "stem cell like" population. Therefore the "stemness" of a γH2AX/CC3 dual positive population will be assessed by co-staining for CD34+/38- and other hematopoetic/ leukemic stem cell surface markers in parallel with γH2AX/CC3 by multi-color flow cytometry. Alternatively, selection of CD34+/38- cells can be performed with subsequent staining for γH2AX/CC3.

3. In vitro we have shown that WEE1 protein expression may correlate with sensitivity to the AraC/AZD1775 combination. WEE1 protein expression levels in baseline marrow or peripheral blood may be assessed as well as WEE1 mRNA expression levels (could be deduced from RNAseq experiments below).

4. In unpublished work we have found a potential modulation of DNA damage response genes/proteins by WEE1 kinase inhibition. We will examine changes in total and phosphorylation forms of essential DNA repair proteins within the HR repair pathway, transcript genes changes under treatment with single agent AZD1775 and in the combination with AraC.

5. The role of myeloid specific mutations is unknown. Hence mutational/targeted sequencing of hematology/myeloid specific genes will be performed by targeted sequencing of gene panels or WES at baseline, at time of best response and at disease progression. Asaliva sample will be used as germline control.

6. It is hypothesized that AZD1775 activity is independent of mutated/functional p53, SETD2, ASXL-1 and RAS mutations status. Therefore all samples will be assayed by the NYU NGS for a 580 gene panel including pertinent mutations in hematological tumors. Potentially, induction of p21 in fresh samples will be assessed as a transcriptional readout of functional p53 status.

7. Next Generation Sequencing - RNA sequencing: WEE1 target genes are master transcriptional regulators. Therefore we will use next generation sequencing for RNA and microRNAs to assess transcriptional changes before, during and after therapy. Expression and differential regulation for the WEE1 published signature genes [claspin, FBXO5, MCM10, CCNE 1 and 2] in patient

specimens at baseline and follow up samples will be assessed, as well as p21 and HR pathway genes.

15.0 Drug Information

15.1 AZD1775

15.11 **Background**: AZD1775 is a highly selective, adenosine-triphosphate (ATP) competitive, small molecule inhibitor of Wee1 kinase, that is involved in regulation of intra-S and G2 cell cycle checkpoints through phosphorylation and inhibition of CDK2 and CDK1, respectively. AZD1775 has significant selectivity over other tested protein kinases. In vitro, AZD1775 inhibits Wee1 activity and induces DNA damage as well as G2 checkpoint escape in cell based assays. AZD1775 increases cytotoxicity when used in combination with DNA damaging agents, such as gemcitabine, cisplatin, carboplatin and topotecan, in p53-deficient cell lines. In vivo, AZD1775 was well tolerated and showed enhancement of anti-tumor efficacy by gemcitabine, carboplatin, cisplatin, 5-fluorouracil (5-FU) and capecitabine in nude rat xenograft tumor models. Similarly, in nude mouse xenograft models, AZD1775 treatment resulted in significant tumor growth inhibition at tolerated doses, and also enhanced the anti-tumor growth effect of gemcitabine, carboplatin, and radiation therapy.

15.12 **Formulation**: AZD1775 is currently available as dry filled capsules for oral administration containing AZD1775 with the following excipients: lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

15.13 **Preparation and storage**: Capsules are packaged in high density polyethylene (HDPE) bottles, and should be stored at room temperature, no more than 30° C. For further information, refer to the investigational product label. Provided by AstraZeneca.

15.14 **Administration:** 300 mg PO (or respective dose) once daily either 2 hours before or 2 hours after a meal

15.15 **Pharmacokinetic information**: The PK data of AZD1775 following a single oral administration showed a moderate rate of absorption with a Tmax occurring at 3 to 4 hours. Post-peak plasma concentrations declined essentially in a mono-exponential manner with a t1/2 in the region of 10 hours. Exposure as measured by maximum plasma drug concentration observed (Cmax) and area under the curve (AUC)0-∞ increased in a dose-proportional manner over the dose range of 325 to 1300 mg. Following single (100 to 325 mg) and multiple dose administrations of AZD1775 (25 to 325 mg BID and 100 to 200 mg once daily [QD]) with carboplatin, cisplatin, and gemcitabine, plasma exposure of AZD1775 was consistent with predictions based on the single-dose regimen. AZD1775 was moderately bound to plasma proteins in all species tested, with the unbound fractions (at AZD1775 concentration of 1 μM) in plasma from the rat, dog and human being 23.2, 40.0, and 39.5%, respectively. Binding

to plasma proteins was independent of AZD1775 concentration (0.1-10 μM) in the rat and human, but an increase in unbound fraction from 30.6% at 0.1 μM to 45.4% at 10 μM was observed in the dog. CYP3A4 is the major CYP isoform involved in the oxidative metabolism of AZD1775, to the N-demethylated product. In addition, studies with flavin-containing monooxygenase (FMO) enzymes indicated that FMO3 and FMO5 were involved in formation of the N-oxide derivative of AZD1775.

15.16 **Potential Drug Interactions**: The following treatments and all the medications listed in Appendix VI are prohibited while in this study. Any further questions regarding concomitant treatments should be referred to the sponsor:

- No other investigational therapy should be given to patients. No anticancer agents other than the study medications should be given to patients. If such agents are required for a patient, then the patient must first be withdrawn from the study.

- No formal clinical drug interaction studies have been performed with AZD1775. An exploratory assessment of the effect of aprepitant on AZD1775 exposure in oncology patients suggests that there is a drug interaction between AZD1775 and aprepitant, as exposure to AZD1775 increased by 40% when aprepitant was co-administered with AZD1775. The observed increase in AZD1775 exposure is likely the result of CYP3A4 inhibition by aprepitant. This increase in exposure is statistically significant. At the selected MTDs, this increase may also be of clinical importance. Therefore, concomitant treatment with aprepitant and fosaprepitant is not allowable per protocol until further evaluation.

  Potent or moderate inhibitors or inducers of CYP3A4, sensitive CYP3A4 substrates, and CYP3A4 substrates with a narrow therapeutic window should be avoided until additional data on drug-drug interaction becomes available (Appendix VI).

- *In vitro* data suggests that AZD1775 may also be a weak reversible inhibitor of CYP2C19. Caution should be exercised with concomitant administration of AZD1775 and agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range; refer to Appendix VI for a list of sensitive substrates of CYP2C19, or substrates of this enzyme with narrow therapeutic range.

- AZD1775 has been shown to be a weak inducer of CYP1A2 *in vitro* with a maximum measured response between donors of 39.9% to 93.1% (at 10 μM) and 18.6% to 32.5% (at 5 μM) of the positive control omeprazole (50 μM), respectively. Given the nature of the AZD1775 dosing schedule, however, the risk of induction in the clinic is considered low. No specific precautions or change in medications are recommended at this time, except to be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range.

- *In vitro* studies have shown that AZD1775 may be a substrate and inhibitor for human P-glycoprotein (P-gp). Caution should be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with AZD1775 (see Appendix VI).

- Recent *in vitro* transporter studies have shown AZD1775 to be an inhibitor of BCRP (IC50 5.1 μM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins. Modelling has predicted a substantial increase in the exposure of Atorvastatin when co-administered with AZD1775 and the **use of Atorvastatin is therefore prohibited** in the current study. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug (Appendix VI).

- AZD1775 has been shown to be an inhibitor or MATE1 and MATE2K transporters. A drug interaction with substrates of either transporter cannot be ruled out, the most important substrate known to date being **metformin**. Thus patients taking these medication should be carefully monitored for their glycemic control. Patients on metformin should be closely watched for elevated metformin levels that could put them at risk for hypoglycemia.

- Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 14 days prior to first dose of AZD1775.

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15.17 **Known potential toxicities**: Based on the preliminary safety data available, the most frequent adverse events observed were blood and lymphatic disorders (anemia, febrile neutropenia), gastrointestinal disorders (diarrhea, vomiting, nausea, abdominal pain, constipation), general disorders and administration site conditions (fatigue, fever, chills), and investigation findings (thrombocytopenia, neutropenia, hematology and serum chemistry).

15.18 **Drug procurement:** Drug will be provided by AstraZeneca.

15.2 Cytarabine (AraC)

15.21 **Background**: Cytarabine (cytosine arabinoside) inhibits DNA synthesis. Cytosine gains entry into cells by a carrier process, and then must be converted to its active compound, aracytidine triphosphate. Cytosine is a pyrimidine analog and is incorporated into DNA; however, the primary action is inhibition of DNA polymerase resulting in decreased DNA synthesis and repair. Cytarabine is specific for the S phase of the cell cycle (blocks progression from the G1 to the S phase).

15.22 **Formulation**: Commercially available for injection, powder for reconstitution: 100 mg, 500 mg, 1 gram, 2 gram

15.23 **Preparation, storage, and stability**: Store intact vials of powder at room temperature 15ºC to 30ºC (59ºF to 86ºF). Reconstitute with bacteriostatic water for injection. Reconstituted solutions are stable for up to 8 days at room temperature, although the manufacturer recommends use within 48 hours. Further dilution in 250-1000 mL of D5W or 0.9% NaCL is stable for 8 days at room temperature (25C). Note: Solutions containing bacteriostatic agents should not be used for the preparation of either high doses or intrathecal doses of cytarabine.

15.24 **Administration:** Low-dose cytarabine (LD-AraC) will be administered at a starting dose of 20 mg BID subcutaneously (sc) for 10 days of a 28-day cycle., with dosing adjustments as outlined in section 8.

15.25 **Pharmacokinetic information**:
Distribution: V_d: Total body water; widely and rapidly since it enters the cells readily; crosses blood-brain barrier with CSF levels of 40% to 50% of plasma level
Metabolism: Primarily hepatic; metabolized by deoxycytidine kinase and other nucleotide kinases to aracytidine triphosphate (active); about 86% to 96% of dose is metabolized to inactive uracil arabinoside.
Half-life elimination: I.V.: Initial: 7-20 minutes; Terminal: 1-3 hours.
Excretion: Urine (~80%) within 24 hours.

15.26 **Potential Drug Interactions**:
Decreased Effect: Cytarabine may decrease the effect of Flucytosine; cytarabine may decrease digoxin absorption.

15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information.
Warnings/Precautions: Potent Myelosuppressive agent
Common known potential toxicities, frequency not defined:
Other: Fever
Dermatologic: Rash
Gastrointestinal: Anal inflammation, anal ulceration, anorexia, diarrhea, mucositis, nausea, vomiting
Hematologic: Myelosuppression, neutropenia, anemia, thrombocytopenia, bleeding, leukopenia, megaloblastosis, reticulocytes decreased
Hepatic: Hepatic dysfunction, transaminases increased (acute)
Local: Thrombophlebitis

Less common known potential toxicities:
Cardiovascular: Chest pain, pericarditis
Central nervous system: Dizziness, headache, neural toxicity, neuritis
Dermatologic: Alopecia, pruritus, skin freckling, skin ulceration, urticaria
Gastrointestinal: Abdominal pain, bowel necrosis, esophageal ulceration, esophagitis, pancreatitis, sore throat
Genitourinary: Urinary retention
Hepatic: Jaundice
Local: Injection site cellulitis

Ocular: Conjunctivitis
Renal: Renal dysfunction
Respiratory: Dyspnea
Miscellaneous: Allergic edema, anaphylaxis, sepsis

Infrequent and/or case reports:
Amylase increased, aseptic meningitis, cardiopulmonary arrest (acute), cerebral dysfunction, cytarabine syndrome (bone pain, chest pain, conjunctivitis, fever, maculopapular rash, malaise, myalgia); exanthematous pustulosis, hyperuricemia, injection site inflammation (SubQ injection), injection site pain (SubQ injection), interstitial pneumonitis, lipase increased, paralysis, rhabdomyolysis, veno-occlusive liver disease

15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

16.0 Statistical Considerations and Methodology

16.1 Overview:

This study is a phase II screening study. It is divided into two portions. The safety portion is designed to determine the dose of the treatment agents. The expansion portion is designed to continue enrollment at the acceptable dose levels to determine efficacy of treatment in in the patient cohorts of the respective study criteria. (Arm A: AZD1775 days 1-5 & 8-12) and AraC days 1-5 & 8-12) and to make a selection of one of the two randomized arms for Relapsed/Refractory AML and HMA failure MDS/ AML patients (Arm B: AZD1775 days 1-5 & 8-12) and AraC days 1-5 & 8-12; Arm C: AZD1775 days 1-5, 8-12). In addition on Arm C single agent AZD1775, a cohort of n=7 MF patients will be treated to obtain pilot efficacy data. These MF patients will not be formally included in the statistical calculations for Arm C.

The purpose of this screening design is NOT TO ensure a high probability that the very best treatment is selected, but to ensure a low probability that a poor treatment is selected. In other words, at the conclusion of this trial, we cannot make a definitive conclusion about the superiority of one treatment compared to the other, but we can ensure that there is a small probability of bringing the inferior treatment forward.

16.2 Statistical Design and Analysis for the Primary Endpoint

16.21 Primary Endpoint

The primary endpoint of this trial is the rate of complete response (CR plus CRi). 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 at the study MTD will be evaluable for complete response, with the exception of patients who are determined to be a major treatment violation.

Treatment Responses will be assessed by standard criteria for the respective disease per NCCN guidelines or according to specific criteria from expert panels (i.e. the International Working Group Criteria for the response in acute myeloid leukemias). Response will be assessed by peripheral blood criteria at the end of each cycle and every other cycle (for MDS) thereafter (Burnett et al. 2007. Gileset al. 2005, Kantarijian et al. 2012, Fenaux et al. 2009).
Bone marrow tests to assess responses will be carried as outlined in the study tables Table 4.1 and 4.2.

16.22 Arm A: Efficacy and safety of AZD1775 + AraC in elderly newly diagnosed AML

Statistical Design, Analysis and Decision Rule

Efficacy and safety of AZD1775 + AraC will be tested in elderly patients with newly diagnosed AML using a single-arm single-stage binomial design. The primary endpoint will be the complete response rate, which will be defined as an objective status of CR or CRi. Complete response rate will be evaluated over all cycles of study treatment. The proportion of CR/CRi responses will be estimated by the number of CR/CRi responses divided by the total number of evaluable patients. Two-sided 95% confidence intervals will be computed using an exact binomial confidence interval. The frequency and relative frequency of individual response categories will also be computed. For a subject to be considered evaluable for statistical analysis, the subject must be eligible, provide consent, initiate treatment and not experience a major treatment violation during the first cycle of treatment.

The largest CR/CRi response proportion where the proposed treatment regimen would be considered ineffective in this population is 15% (Burnett et al. 2007. Gileset al. 2005, Kantarijian et al. 2012, Fenaux et al. 2009) and the smallest CR/CRi response proportion that would warrant subsequent studies with the proposed regimen in this patient population is 40%.

The following one-stage binomial design uses 21 patients to test the null hypothesis that the true CR/CRi response proportion in a given patient population is at most 15%.

Decision Rule: Enter 21 patients into the study. If 5 or fewer CR/CRi responses are observed in the first 21 evaluable patients, we will consider this regimen ineffective in this patient population. Otherwise, if 6 or more CR/CRi responses are observed in the first 21 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population. We anticipate accruing an additional 2 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Thus, the total maximum accrual to this arm is 23 patients.

Assuming that the number of CR/CRi responses is binomially distributed, the significance level within this arm is </=10% and the probability of declaring that this regimen warrants further studies (i.e., statistical power) under various

CR/CRi response proportions can be tabulated as a function of the true CR/CRi response rate as shown in the following table.

If the true CR/CRi rate is…	0.15	0.20	0.25	0.30	0.35	0.40
Then the probability of declaring that the regimen warrants further studies is…	0.08	0.23	0.43	0.64	0.80	0.90

16.23 Arm B and C: Efficacy and safety of AZD1775 in combination with AraC compared to AZD1775 alone in relapsed/refractory AML or HMA failure MDS and AML patients.

Statistical Design, Analysis and Decision Rule

Efficacy and safety of AZD1775 alone or with AraC will be tested in patients with relapsed/refractory AML and patients with HMA failure MDS using a flexible randomized phase II selection design. Patients will be randomized to AZD1775 alone or with AraC in a 1:1 fashion using a dynamic allocation procedure (Pocock & Simon 1975). The primary endpoint will be the complete response rate, which will be defined as an objective status of CR or CRi. Complete response rate will be evaluated over all cycles of study treatment. The proportion of CR/CRi responses will be estimated by the number of CR/CRi responses divided by the total number of evaluable patients (by arm). Two-sided 95% confidence intervals will be computed using an exact binomial confidence interval. The frequency and relative frequency of individual response categories will also be computed. Estimates will also be computed by arm separately for each disease. For a subject to be considered evaluable for statistical analysis, the subject must be eligible, provide consent, initiate treatment and not experience a major treatment violation during the first cycle of treatment.

The selected design is a flexible randomized phase II selection design (Sargent & Goldberg 2001). This study will randomize 40 evaluable patients (20 per arm). The minimum required number of CR/CRi responses for an arm to be considered as having evidence of efficacy is 3 (out of 20 evaluable patients). This decision rule is based on a single-arm single-stage binomial design testing the null hypothesis that the true CR/CRi response proportion in a given arm is at most 5% (Tawfik et al. 2014, Giles et al. 2005, Jabour et al. 2010, Prevet et al. 2011) with the smallest CR/CRi response proportion warranting subsequent studies being 25%.

In the event that both arms meet this decision rule for efficacy, the combination arm will be considered as having additional efficacy over the single-agent arm if the CR/CRi response rate on the combination arm is at least 10% greater than the single-agent arm. If the difference is <10%, then the trial is considered statistically ambiguous and the selection between the combination and single-agent arm will be allowed to include other factors (e.g., adverse event data) in addition to the CR/CRi response rate. We anticipate accruing an additional 4 patients (2 patients per arm) to account for ineligibility, cancellation, major

treatment violation, or other reasons. Thus, the total maximum accrual to Arm B is 22 patients and to Arm C is 22 patients.

Assuming that the number of CR/CRi responses is binomially distributed, the significance level for the single-arm decision rule requiring a minimum of 3 (out of 20 evaluable patients) within an arm is </=10% and the probability of declaring that a given arm's treatment regimen warrants further studies (i.e., statistical power) under various CR/CRi response proportions can be tabulated as a function of the true CR/CRi response rate as shown in the following table.

If the true CR/CRi rate is…	0.05	0.10	0.15	0.20	0.25
Then the probability of declaring that a given arm's treatment regimen warrants further studies is…	0.08	0.32	0.60	0.79	0.91

Probabilities for the combination arm being selected as the overall winner are provided in the following table.

CR/CRi rate (AZD1775 alone)	CR/CRi rate (AZD1775 + AraC)	Probability combo selected over single-agent arm
0.05	0.05	0.07
0.25	0.25	0.30
0.20	0.25	0.44
0.15	0.25	0.61
0.10	0.25	0.77
0.05	0.25	0.88

16.3 Sample Size, Accrual Rate, and Study Duration

This design is expected to accrue 18 patients to the safety portion with the possibility of enrolling up to 54 + 7 MF patients. Six patients in each of the safety arms will be treated at the MTD and thus will be eligible for primary endpoint analysis. An additional 15 AML patients in Arm A and 14 AML or MDS patients in both arm B and C will be enrolled per treatment arm in the expansion portion with the addition of another 2 per arm to account for ineligibility, cancellation, major treatment violation, or other reasons. Thus the final accrual may be as large as 102 + 7 MF pateints or as low as 67 + 7 MF patients (Arm A: 23; Arm B: 22; Arm C: 22 + 7 MF patients).

The anticipated accrual rate is 2-4 evaluable patients per month. Therefore, the accrual period is expected to be approximately 1.5-2.5 years. The primary endpoint will be evaluated approximately 2 years after the trial opens, or after the last patient accrued has been observed for at least 4 months. The total study duration is expected to be approximately 3.5 years.

16.4 Secondary Endpoints

16.41 Safety and tolerability data will be compiled. The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns (by arm, disease and overall). Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. The rate of grade 3 or higher non-hematologic adverse events, and the rate of grade 4 or higher adverse event (hematologic and non-hematologic) will be computed each with a 95% exact binomial confidence interval.

16.42 Summary statistics for clinical benefit (mean and standard deviations for continuous variables and frequencies and percentages for discrete variables) will be compiled for hematologic improvements and transfusion requirements.

16.43 Duration of response is defined for all evaluable patients who have achieved a response as the date at which the patient's earliest best objective status is first noted to be a CR/CRi response to the earliest date progression is documented. If a patient dies subsequent to the response without a documentation of disease progression, the patient will be censored at the last date disease was assessed. In the case of a patient failing to return for evaluations before a documentation of disease progression, the patient will be censored for progression on the date of last evaluation. The distribution of duration of response will be estimated using the method of Kaplan-Meier (1958).

16.44 Time to response/progression is defined as the time from registration to the earliest date of documentation of response/disease progression. If a patient dies without a documentation of disease progression the patient will censored at the last date disease was assessed. In the case of a patient starting treatment and then never returning for any evaluations, the patient will be censored for progression 1 day post-registration. The distribution of time to progression will be estimated using the method of Kaplan-Meier (1958).

16.45 Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier (1958).

16.46 Time to AML or death is defined for all evaluable patients with MDS and MF as the time from registration to leukemic transformation or death due to any cause. The distribution of time to AML or death will be estimated using the method of Kaplan-Meier (1958).

16.5 Exploratory Analysis

An exploratory analysis will be conducted, if there is indication, to determine any differences in study endpoints for subgroups of patients within each treatment arm as defined by the grouping factors (section 5.0), descriptive factors (section 12.0), dose level or any other patient demographics.

16.6 Correlative Research

16.61 Statistical analysis of pharmacokinetics and biomarkers will be primarily descriptive. Continuous biomarker levels will be explored in a graphical manner

including mean plots and plots of change and percent change from baseline and other summary measures. Any potential relationships between the baseline level or change in the level of each biomarker and clinical outcome such as overall response, 6-month progression and survival, and adverse event incidence will be further analyzed using Wilcoxon rank sum tests or logistic regression methods, as appropriate. Association between a dichotomized biomarker and overall response will be assessed using a chi-squared test. Comparisons with 1-sided p-values ≤0.10 are considered significant. As this correlative component is exploratory in nature, we have not adjusted for multiple comparisons.

16.62 Patient-reported outcomes will be assessed at baseline, cycles 3, 6, 9, and EOS.. MPN-SAF TSS was created to address the constellation of symptoms. The MPN-SAF includes 1 item measuring fatigue from the previously validated Brief Fatigue Inventory (BFI), as well as linear analog scales capturing early satiety, abdominal discomfort, inactivity, concentration problems, numbness/tingling in the hands/feet, night sweats, itching, bone pain, fever, and weight loss. The MPN-SAF TSS has previously been validated for use at a single time point by co-administration with previously validated instruments.

Quality of life will be assessed prior to review of treatment response and discussions of patient's general health since last treatment evaluation. QOL will be measured using the EORTC QLQ-C30, a 30-item patient-reported questionnaire about patient ability to function, symptoms related to the cancer and its treatment, overall health and quality of life, and perceived financial impact of the cancer and its treatment. 28 of the 30 items are measured on a 1-4 scale (1=not at all; 4=very much) with the remaining two items (overall health and overall quality of life) scored on a 1-7 numeric analogue scale (1=very poor; 7=excellent). The recall period for the EORTC QLQ-C30 is one week. The EORTC QLQ-C30 is the product of more than a decade of collaborative research and to date, more than 2200 studies using the EORTC QLQ-C30 have been registered with the EORTC (Fayers et al, 2001 [EORTC Scoring Manual]). The patient booklet containing this questionnaire will be administered to all willing patients via a paper booklet in clinic at baseline and on day 1 of every cycle starting with Cycle 2, and will be scored according to the published scoring algorithms.

Scale score trajectories over time and changes from baseline over time will be examined using repeated measures or growth curve models, as appropriate, stream plots and mean plots with standard deviation error bars overall. Scores and changes at each cycle will be statistically tested using paired t-tests, and standardized response means (i.e. effect sizes) (mean of the change from baseline scores at a given cycle, divided by the standard deviation of the change scores) will be interpreted (after applying Middel's (2002) adjustment) using Cohen's (1988) cut-offs: <0.20 = trivial; 0.20-<0.50 = small; 0.50-<0.80 = moderate; and >=/0.80 = large.

16.7 Early Safety Analysis

An early safety analysis will be performed after 6 patients have been accrued to each arm of the study and observed for one cycle. Accrual will be temporarily halted while these patients are evaluated. If 2 or more of the first 6 patients experience a DLT, as defined below, then the dose level will be reduced as defined in Section 8.0 and another six patients will be treated. If < 2/6 patients experience toxicities defined as DLT, then this dose level will be defined as the operational MTD and moved into the expansion portion. Further dose de-escalation to dose level -2 will follow the same guidelines.

Should additional modification be necessary, the study will be closed and evaluated by the study team regarding continuation. Upon determination of the safe dose level, the study will re-open for accrual.

16.8 Ongoing Safety Analysis

Ongoing safety monitoring will occur continuously; patient-level unacceptable toxicity will be defined as per DLT criteria (Section 7.4) and we will require a toxicity rate of of no more than 20%. Monitoring for toxicity will follow a Bayesian-based rule for the probability that the unacceptable toxicity rate exceeds a maximal tolerated level of 20%. We will use a flat Beta(1,1) prior. Early termination for toxicity will be based on a posterior probability above 80% (in parentheses) that the toxicity rate exceeds 20%. Termination will be considered if DLT occurs in: 2 of 6 patients (0.85), 3 of 9 patients (0.88), 4 of 12 patients (0.90), 5 of 15 patients (0.92), 6 of 18 patients (0.93), or 6 of 21 patients (0.87).

16.9 Inclusion of Women and Minorities

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

16.92 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.

17.0 Source Documents and Access to Source Data

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documentation refers to original records of observations, clinical findings, and evaluations that are subsequently recorded as data. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

TrialMaster, an electronic database capture system will be created to record the data for this trial. Research coordinators will input clinical trial data into the database. This database is password protected and only the PI, assigned study team members, and CTO staff will have access to the database. DataCore, a core resource of the institution, will provide the primary data collection instrument for the study. All data requested in the system must be reported. All missing data must be explained. The quality assurance specialists will monitor this trial every 4-6 weeks for data entry accuracy.

Source documentation should be consistent with data entered into any electronic medical record or the electronic data capture system. Relevant source documentation to be reviewed by the DSMC throughout the study includes:

1. Baseline measures to assess pre-protocol disease status
2. Treatment records
3. Adverse events

Access to study records will be limited to IRB-approved members of the study team. The investigator will permit study-related monitoring, audits, and inspections by the CTO, IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

18.0 **Ethics/Protection of Human Subjects**

18.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

18.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

18.3 Informed Consent Process

18.31 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study product.

18.32 Consent Procedures and Documentation

The consenting process and documentation will follow Standard Operating Procedures (Obtaining Informed Consent for Clinical Trials) of the NYU Langone Health PCC CTO.

18.33 Informed Consent

A participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the potential participant; also must address any questions/concerns prior to obtaining written informed consent for participation and HIPAA authorization can also obtain consent.

Patients will be given adequate time to read the consent form. They will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, or qualified research study team member all of whom have completed requisite training for human subject research. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

The Investigator will explain to each potential participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, potential compensation and or costs incurred by the patient and any discomfort this trial may entail. This informed consent should be given by means of standard written statement, written in non-technical language. All patients will be required to sign a written informed consent prior to being registered on this study. No patient can enter the study before his/her informed consent has been obtained. Every effort will be made to answer questions raised by patients and their families or advocates regarding the protocol and alternative therapies prior to asking a patient to sign the consent form.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB approval.

If applicable

For non-English speaking patients, institutional translation services will be utilized. All procedures for consenting non-English speaking patients will be in accordance with NYU Langone Health PCC CTO guidelines and policies.

For patients who cannot read. A witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The

investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

18.34 Documentation of Consent

The Principal Investigator or IRB approved sub-investigator will be responsible for documentation in the medical record that consent has been obtained from all participants. A signed copy of the consent form will be given to each participant. Original consent forms will be stored in the subject's medical chart.

18.4 Participant and Data Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at NYU Langone Medical Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems

used by clinical sites and by NYU Langone Medical Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NYU Langone Medical Center.

18.41 Research Use of Stored Human Samples, Specimens, or Data

- Intended Use: Samples and data collected under this protocol may be used to evaluate the clinical efficacy of AZD1775 in combination with AraC in patients with newly diagnosed AML, relapsed/refractory AML, and hypomethylating agent failure MDS by perfroming state of the art molecular biomarker analysis . No hereditary genetic testing will be performed.
- Storage: Access to stored samples will be limited to the study team. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.
- Tracking: Data will be tracked using Trialmaster.
    - Disposition at the completion of the study: All stored samples will be sent to CBRD. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

Future Use of Stored Specimens

Data collected for this study will be analyzed and stored at the NYU Langone Health. After the study is completed, the de-identified, archived data will be transmitted to and stored via an electronic database system, under the supervision of Dr. Raoul Tibes, with the potential for use by other researchers including those outside of the study. Permission of storage of samples, specimens, and data are required to participate in this study and will be included in the informed consent.

With the participant's approval and as approved by local IRs, de-identified biological samples will be stored at the NYU Center for Biospecimen Research & Development. These samples could be used for research into the most appropriate treatment combinations for individuals with MPM and Hodgkin Lymphoma. The stored specimen and data will be coded and de-identified; the linking key will be maintained by the Principal Investigator. The CBRD will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided through the supervision of the principal investigator, Dr. Raoul Tibes, these sample will be stored indefinitely.

19.0 Data Handling and Record Keeping

19.1 Data Collection and Management Responsibilities

NYU's Datacore will be responsible for the development of a relevant database and data transfer mechanisms, along with appropriate validation of data and resolution of queries. Data generated within this clinical study will be handled according to the relevant standard operating procedures of the Clinical Trials Office at NYU.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Trialmaster, a 21 CFR Part 11-compliant data capture system provided by Omnicom. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

20.0 Quality Assurance and Quality Control

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan detailed below. Serious adverse events are evaluated regularly by the principal investigator in conjugation with the research team, the DSMC is notified of serious adverse events via email initially, reviewed offline by the designated medical monitor, and presented at the next DSMC monthly meeting. The Data Safety and Monitoring Committee (DSMC) will review the study at least quarterly. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Data and Safety Monitoring Committee
This investigator-initiated study will be monitored by the Data Safety Monitoring Committee (DSMC) of the New York University (NYU) Perlmutter Cancer Center (PCC). The DSMC operates based on the National Cancer Institute approved Charter. It is an existing and multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses, and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and

compliance in accordance with protocol data monitoring plans for interventional clinical trials conducted in the NYU Langone Health Perlmutter Cancer Center that are not monitored by another institution or agency. The DSMC reports to the Director of the NYU Langone Health PCC.

Per the NYU PCC Institutional Data Safety and Monitoring Plan, this phase II trial will be monitored by DSMC *quarterly* (from the date the first patient is enrolled), at protocol-specified interim time points, and at the completion of the study prior to study closure. This review includes accrual data, subject demographics and adverse events. Principal Investigators are required to attend the review of their studies. Additional reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. The DSMC will review safety data every 3 months.

20.1 Study Monitoring Plan

Overall study monitoring will be conducted through a combination of on-site visit (NYU Langone Health), and remote monitoring (Subsite locations). A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. A quality assurance specialist, will conduct regularly scheduled reviews of the trial, and study data. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the quality assurance specialist in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct, which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform AstraZeneca of any audit requests by health authorities, and will provide AstraZeneca with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research

activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

At the NYU Langone Health Perlmutter Cancer Center, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, IRB review and DSMC review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) DSMC, quarterly

(3) Institutional Review Board (IRB): An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

(4) In addition, the quality assurance unit the quality assurance unit will monitor this trial every 4-6 weeks, this includes real- time review of all eCRFs to ensure completeness and to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines. Additionally, a first subject audit is to be conducted within four weeks of enrollment.

Subsite monitoring

Monitoring visits are done remotely unless otherwise specified, via remote EMR access. If not possible, secure email exchange will be utilized. The quality assurance specialist will confirm an upcoming monitoring visit with a Subsite Investigator and staff. If remote EMR access is not available, then the Subsite Coordinator will ensure that all source documents for subjects are de-identified and labeled only with the subject ID number(s), and emails all requested documents to the quality assurance specialist by the specified visit date. All documents are reviewed and a monitoring report is submitted within 5 business days from the date of the visit. Any outstanding documents will be listed in the report as a high- priority request for the next monitoring visit. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database. Continued non-compliance and failure to submit documentation will result in the suspension of subject enrollment at the site, until the documents have been received.

20.2 Study Records Retention

It is the investigator's responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

20.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

All protocol deviations must be addressed in study source documents, and reported to the Quality Assurance Unit and the DSMC.

Protocol deviations must be reported to the local IRB per guidelines. The site PI/study staff is responsible for knowing and adhering to IRB requirements.

21.0 Ethical Considerations

This study is to be conducted in accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB) or independent Ethics Committee (EC) in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/EC concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of IRB/EC members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB/EC for the study. The formal consent of a subject, using the IRB/EC-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

22.0 Budget Considerations

22.1 Costs charged to subjects: all standard of care tests and procedures such as physical exams, blood CBC and chemistries, bone marrow biopsies, AraC drug and administration costs, etc

22.2 Tests to be research funded: research blood and bone marrow collection and processing, AZD1775 drug dispensing

22.3 Other budget concerns: Drug and PK analysis will be supported by AstraZeneca.

22.4 No subjects will receive payments or stipends for participation in this research study.

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Appendix I

ECOG Performance Status Scale

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

Appendix II: MEDICATION DIARY

Name _____

NYU Clinic No_____

Study Name/Number_____

Patient Instructions

- Please indicate on the calendar below *every* day that you take your study medication by placing a check mark for each day that you take AZD1775.
- Avoid grapefruit, grapefruit juices, grapefruit hybrids, Seville oranges, pummelos, and exotic citrus fruits.
- Please take your medication either 2 hours before or 2 hours after a meal.

Start Date: _____

Medication(s)	Dose
AZD1775	MG

Study Drug	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
AZD1775							

Study Drug	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**
AZD1775							

Study Drug	**Day 15**	**Day 16**	**Day 17**	**Day 18**	**Day 19**	**Day 20**	**Day 21**
AZD1775							

Study Drug	**Day 22**	**Day 23**	**Day 24**	**Day 25**	**Day 26**	**Day 27**	**Day 28**
AZD1775							

Date:_____ Participants Signature:_____

Area Below Only To Be Completed only by Coordinator

Number of pills returned_____ Study Coordinator Initials_____

Date_____ Discrepancy Yes____ No_____

Appendix III

New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Appendix IV: Revised International Prognostic Scoring System (IPSS-R) for MDS

IPSS-R Cytogenetic risk groups*,**

Cytogenetic prognostic subgroups	Cytogenetic abnormalities
Very good	-Y, del(11q)
Good	Normal, del(5q), del(12p), del(20q), double including del(5q)
Intermediate	del(7q), +8, +19, i(17q), any other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), Complex: 3 abnormalities
Very poor	Complex: >3 abnormalities

IPSS-R Prognostic Score Values*

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Intermediate	Poor	Very Poor
BM Blast %	<=2		>2-<5%		5-10%	>10%	
Hemoglobin	=>10		8-<10	<8			
Platelets	=>100	50-<100	<50				
ANC	=>0.8	<0.8					

IPSS-R Prognostic Risk Categories/Scores*

RISK CATEGORY	RISK SCORE
Very Low	<=1.5
Low	>1.5 - 3
Intermediate	>3 - 4.5
High	>4.5 - 6
Very High	>6

*Greenberg, Tuechler, Schanz et al, Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndrome, Blood 120: 2454, 2012.
**Schanz J et al, J Clin Oncology 2012; 30:820

Appendix V:

RISK STATUS BASED ON VALIDATED CYTOGENETICS AND MOLECULAR ABNORMALITIES[1]

RISK STATUS	CYTOGENETICS	MOLECULAR ABNORMALITIES
Better-risk	inv(16)[2,3] or t(16;16)[2] t(8;21)[2] t(15;17)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or isolated biallelic CEBPA mutation
Intermediate-risk	Normal cytogenetics +8 alone t(9;11) Other non-defined	t(8;21), inv(16), t(16;16): with c-KIT[5] mutation
Poor-risk	Complex (≥3 clonal chromosomal abnormalities) Monosomal karyotype -5, 5q-, -7, 7q- 11q23 - non t(9;11) inv(3), t(3;3) t(6;9) t(9;22)[4]	Normal cytogenetics: with FLT3-ITD mutation[6]

[1]The molecular abnormalities included in this table reflect those for which validated assays are available in standardized commercial laboratories. Given the rapidly evolving field, risk stratification should be modified based on continuous evaluation of research data. Other novel genetic mutations have been identified that may have prognostic significance.

[2]Other cytogenetic abnormalities in addition to these findings do not alter better risk status.

[3]Paschka P, Du J, Schlenk RF, et al. Secondary genetic lesions in acute myeloid leukemia with inv(16) or t(16;16): a study of the German-Austrian AML study group (AMLSG). Blood 2013;121:170-177.

[4]For Philadelphia+ AML t(9;22), manage as myeloid blast crisis in CML, with addition of tyrosine kinase inhibitors.

[5]Emerging data indicate that the presence of c-KIT mutations in patients with t(8;21), and to a lesser extent inv(16), confers a higher risk of relapse. These patients should be considered for clinical trials, if available.

[6]FLT3-ITD mutations are considered to confer a significantly poorer outcome in patients with normal karyotype, and these patients should be considered for clinical trials where available. There is controversy as to whether FLT3-TKD mutations carry an equally poor prognosis.

Version 2.2014, 03/28/2014. National Comprehensive Cancer Network, Inc. 2014.

Appendix VI: List of prohibited concomitant medications and concomitant medications requiring caution

DISALLOWED MEDICATIONS AND MEDICATIONS TO BE ADMINISTERED WITH CAUTION

Formal drug-drug interaction studies have not yet been performed with AZD1775, therefore, the potential for drug-drug interaction described in this protocol are based on findings from in vitro studies and clinical experience.

In vitro data has shown that AZD1775 is metabolised predominantly by CYP3A4, with an FMO3 and/or FMO5 component. As a result, there is potential for the exposure of AZD1775 to be effected by drugs which inhibit or induce the metabolism of CYP3A4. In the clinic, coadministration of AZD1775 with the moderate CYP3A4 inhibitor, aprepaitant, resulted in a 40% increase in the plasma levels of AZD1775. Drugs known to be moderate to strong inhibitors/inducers of CYP3A4 are therefore prohibited for use in the current study, including aprepitant.

In vitro data suggests that AZD1775 may be a weak reversible inhibitor of CYP2C19 (IC_{50} 12 uM). Caution should therefore be exercised when AZD1775 is coadministered with agents that are sensitive substrates of CYP2C19, or substrates of this enzyme with a narrow therapeutic range.

Based on in vitro studies, AZD1775 has been show to be a weak reversible inhibitor (IC_{50} 14 μM) and a time-dependent inhibitor of CYP3A4 (K_{inact} 0.061/min, K_i 6.04 μM). The full impact of the time dependent inhibition is currently unknown, however, modelling data has predicted an 8-10 fold increase in the exposure of sensitive CYP3A4 substrates when administered with AZD1775 (250 mg BID for 5 doses). To date, no significant DDI effects have been reported in the clinic that may be related to the TDI finding. However, sensitive CYP3A4 substrates or substrates of CYP3A4 with a narrow therapeutic window are prohibited.

AZD1775 has been shown to be a weak inducer of CYP1A2 in vitro (39% increase in activity of positive control). Given the nature of the AZD1775 dosing schedule, however, the risk of induction in the clinic is considered low. No specific precautions are recommended at this time, except to be initially vigilant when using substrates of CYP1A2 with a narrow therapeutic range.

Transporter studies (in vitro) have shown that AZD1775 is both a substrate and inhibitor (IC_{50} 20 μM) of P-gp. Maximum impact of these finding is likely to occur for drugs administered orally at the same time as AZD1775. Caution should therefore be exercised when agents that are inhibitors or substrates of P-gp are administered concomitantly with AZD1775.

Recent invitro transporter studies have shown AZD1775 to be an inhibitor of BCRP (IC_{50} 5.1 μM). This finding is particularly relevant for drugs administered orally where exposure is normally limited by BCRP-mediated efflux, in particular some statins. Modelling has predicted a substantial increase in the exposure of Atorvastatin when coadministered with AZD1775 and the use of Atoravastatin is therefore prohibited in the current study. Other drugs where the disposition is mediated via BCRP should be administered with caution, dose modification considered or substituted by an alternative drug.

Herbal preparations/medications can be substrates, inhibitors and inducers, similar to any registered medication. Herbal preparations are therefore not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng.

In addition, any other drugs should be avoided at the Investigator's discretion if, in their opinion, the co-administration with AZD1775 may increase the risk of a clinically significant drug interaction.

A list of the main CYP3A4 substrates, inhibitors (strong and moderate) and inducers, CYP2C19 substrates, P-gp substrates and inhibitors and BCRP substrates are shown below. This is not an exhaustive list and further details can be found at Expert Opin. Drug Metab. Toxicol. (2013) 9(6):737-751.

CYP3A4 Inhibitors

Strong

Boceprevir
Clarithromycin
Cobicistat (GS-9350)
Conivaptan
Danoprevir
Elvitegravir
Fosamprenavir
Grapefruit juice
Idelalisib
Indinavir
Itraconazole
Ketoconazole
LCL161
Lopinavir
Mibefradil
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Tipranavir
Troleandomycin
Voriconazole

Moderate

ACT-178882
Amprenavir
Aprepitant
Atazanavir
Casopitant
Ciprofloxacin
Crizotinib
Darunavir
Dronedarone
Diltiazem
Erythromycin
FK1706
Fluconazole*
Fosamprenavir
Imatinib
Ledipasvir
Lomitapide
Netupitant
Schisandra sphenanthera
Tofisopam
Verapamil

*The preferred azole anti-fungal medication is Fluconazole, alternatively Posaconazole may be given. For dose modification see section 9.5.

CYP3A4 Inducers (Strong and Moderate)

Avasimibe
Bosentan
Carbamazepine
Efavirenz
Enzalutamide
Nafcillin
Phenobarbital
Phenytoin
Rifabutin
Rifampin

Etravirine
Genistein
Lersivirine
Lopinavir
Mitotane
Modafinil
Ritonavir
Semagacestat
St John's Wort
Thioridazine
Tipranavir

CYP3A4 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

ABT-384
Alfentanil
Aprepitant
Alfuzosin
Almorexant
Alpha-Dihydroergocryptine
Amiodarone
Aplaviroc
Aprepitant
Astemizole
Atazanavir
Atorvastatin
Avanafil
Bexarotine
BIRL 355
Bortezomib
Bosutinib
Brecanavir
Brotizolam
Budesonide
Buspirone
Capravirine
Carbamazepine
Casopitant
Cisapride,
Conivaptan
Cyclophosphamide
Cyclosporine
Danoprevir
Darifenacin
Darunavir
Dasatinib
Dihydroergotamine
Disopyramide
Dronedarone
Docetaxol
Ranolazine
Ridaforolimus
Romidepsin
Saquinavir
Sildenafil
Simeprevir
Simvastatin
Sirolimus
Tacrolimus
Temsirolimus
Terfenadine
Ticagrelor
Theoophylline
Thioridazine
Thiotepa
Tilidine
Tipranavir
Tolvaptan
Triazolam
Tretinoin
Ulipristal
Vardenafil
Vicriviroc
Voclosporin
Elvitegravir
Eplerenone
Ergotamine
Erlotinib
Etoposide
Everolimus
Felodipine
Fentanyl
Fluticasone
Gefitinib
Halofantrine
Ibrutinib
Ifosfamide
Imatinib
Indinavir
Ironotecan
Ivacaftor
Ixabepilone
L-771,688
Lapatinib
Levomethadyl (LAAm)
Lomitapide
Lopinavir
Lovastatin
Lurasidone
Maraviroc,
Midazolam
Midostaurin
Mosapride
Neratinib
Nilotinib
Nisoldipine
Paclitaxel
Pazopanib
Perospirone
Pimozide

Dofetilide
Doxorubicin
Ebastine
Eletriptan
Propafenone
Propofol
Quetiapine
Quinidine

CYP2C19 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

Diazepam
Gliclazide
Lansoprazole
(R)-Lansoprazole
(S)-Lansoprazole
(S)-Mephenytoin
(R)-Mephobarbital
Omeprazole
(R)-Omeprazole
Pantoprazole
(+)-Pantoprazole
Rabeprazole
Tilidine

CYP1A2 Sensitive Substrates or Substrates with a Narrow Therapeutic Range

Alosetron
Caffeine
Duloxetine
Melatonin
Ramelteon
Tacrine
Theophylline
Tizanidine

P-gp Substrates

^Colchicine
*Digoxin
Fexofenadine
Indinavir
Paclitaxel
Toptecan
Vincristine

*If a patient requires initiation of digoxin during the study, or is already receiving treatment with digoxin, monitoring of digoxin levels is recommended according to local practice (as the levels of digoxin may increase). Monitoring of digoxin levels is also recommended when the patient has completed dosing with study treatment (as the levels of digoxin may then decrease).

^Colchicine may be given during study, with expected less clinical efficacy and patients should be carefully monitored clinically.

P-gp Inhibitors (Strong)

Cyclosporine
Elacridar
Erythromycin
Itraconazole
Ketocoanzole
LY335979Quinidine
Ritonavir
Valspodar
Verapamil

BCRP Substrates

Daunorubicin
Doxorubicin
Rosuvastatin
Sulfasalazine
Topotecan

Appendix VII: Patient Information Sheet

PATIENT INFORMATION SHEET
Patient Completed Quality of Life Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains two sets of questions:
   - EORTC QLQ-C30 (30 questions)
   - MPN-SAF TSS (11 questions)

2. Directions on how to complete each set of questions are written on the top of each set.

3. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

Thank you for taking the time to help us.

Appendix VIII: EORTC QLQ-C30 and Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

EORTC QLQ - C30 (Version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Myeloproliferative Neoplasm Symptom Assessment Form
Total Symptom Score (MPN-SAF TSS)

Symptom	**1 to 10 (0 if absent) ranking** **1 is most favorable and 10 least favorable**
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes, during the past week how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (Early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/ Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Thank you for taking the time to help us.

Appendix IX: Childbearing Potential & Contraception

Female patients are considered to be of childbearing potential unless

- they are post-menopausal (defined as older than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments),
- there is documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy (but not tubal ligation), or
- they are 50 years or younger but have been amenorrhoeic for at least 12 months following the cessation of exogenous hormonal treatments, and have serum follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels in the postmenopausal range for the institution.

Female patients who are of childbearing potential must agree to use adequate contraceptive measures (as defined below) for the duration of study participation, and for 6 months after the final dose of study drug; cessation of birth control after this point should be discussed with a responsible physician. They also may not be breast feeding and must have a negative serum or urine pregnancy test within 72 hours prior to start of study treatment.

Acceptable methods of contraception include true abstinence in line with the preferred and usual lifestyle choice of the subject, tubal ligation, vasectomised partner, and methods listed below**Error! Reference source not found.**. All methods of contraception (with the exception of total abstinence) should be used in combination with the use of a condom by their male sexual partner for intercourse. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.
Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

Effective Methods of Contraception

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
• Cap plus spermicide • Sponge plus spermicide • Diaphragm plus spermicide	• Copper T • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	Any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents) such as • Implants • Hormone shot or injection • Combined pill • Minipill • Patch

a This is also considered a hormonal method.