A Phase 1b/2 Study of TP-0903 in Patients with Acute Myeloid Leukemia and FLT3 mutations

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Synopsis

We propose a phase 1b/2 study of TP-0903 in AML patients with *FLT3* mutations. The study will include non-intensive therapy, using TP-0903 monotherapy for relapsed/refractory patients.

TREATMENT PLAN

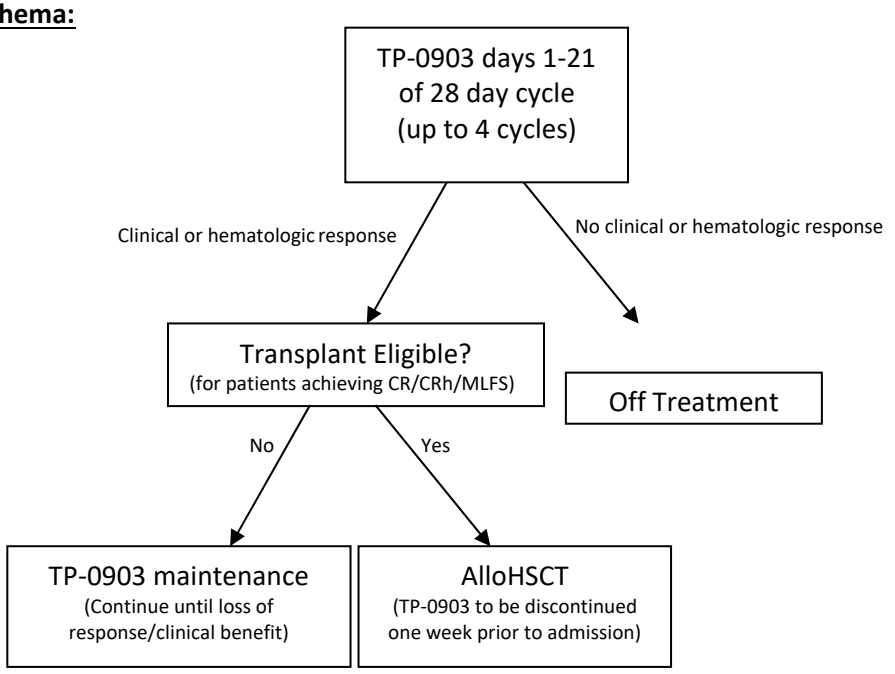
TP-0903 MONOTHERAPY FOR AML PATIENTS WITH FLT3 MUTATIONS AND RELAPSED/REFRACTORY DISEASE

AML patients with FLT3 mutations and relapsed/refractory disease are eligible to receive TP-0903, at a starting dose of 50 mg daily as a single agent for days 1-21 of a 28-day cycle. If the 50 mg dose does not meet the tolerability criteria, a lower dose level of 37 mg daily as a single agent for days 1-21 of a 28-day cycle will be considered.

Dose Level	TP-0903 (D1-21) (mg/day PO)
-1	25
0	37
1	50

Patients may continue treatment indefinitely for as long as clinical benefit is achieved per the investigator's judgment. Bone marrow examinations for disease response assessment will be mandated after the first cycle and at the end of treatment. Subsequent bone marrow examinations may be completed at the discretion of the treating physician.

Schema:



Abbreviations: AlloHSCT, allogeneic hematopoietic stem cell transplant; CR, complete remission; CRh, complete remission with incomplete count recovery; MLFS, morphologic leukemia free state

Study Objectives

Primary Objectives

- **To determine a tolerable dose of TP-0903 monotherapy for relapsed/refractory patients with FLT3 AML.**
- **To determine the complete remission (CR) or complete remission with partial hematologic recovery (CRh) rate following induction therapy with TP-0903 in relapsed/refractory patients with FLT3 AML.**

Secondary Objectives

- **To determine the toxicity profile of TP-0903 monotherapy.**
- **To determine disease-free survival for patients achieving CR/CRh.**
- **To determine overall survival for patients.**
- **To determine the proportion of patients who go to transplant.**

Exploratory Objectives

- **To conduct pharmacokinetic studies of TP-0903 monotherapy.**
- **To examine changes in circulating AXL, Gas6, FLT3 ligand, and other cytokines/chemokines by TP-0903.**
- **To determine the impact of TP-0903 on the inhibition of kinase signaling (AXL, FLT3, STAT5, AURKA), and metabolomics in AML cells.**
- **To determine differentially expressed genes in bone marrow stromal cells and AML cells upon TP-0903 treatment.**
- **To examine sensitivity and resistance patterns associated with TP-0903 by genomic, epigenomic, and transcriptomic profiling.**

Abbreviations

Acronym	Definition
AE	adverse event
AST	aspartate aminotransferase
BM	Bone marrow
BSA	body surface area
BUN	blood urea nitrogen
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
ECG	Electrocardiogram
FLT3	Fms-like tyrosine kinase 3
G-CSF	granulocyte-colony stimulation factor
GI	gastrointestinal
IND	Investigational New Drug [Application]
IV	intravenous
JAK2	Janus kinase 2
kD	kilodalton (molecular weight)
MR	minimal response
MTD	maximum tolerated dose
NS	not specified
ORR	overall response rate
OS	overall survival
p21	cyclin dependent kinase (CDK4) inhibitor protein of 21K molecular weight
P2RD	phase 2 recommended dose
p53	tumor suppressor gene/protein of 53K molecular weight, TP53
PBMCs	peripheral blood mononuclear cells
PD	progressive disease
PDn	pharmacodynamics
PI3K	phosphoinositol triphosphate kinase
PK	pharmacokinetics
PO	per os (oral)
PR	partial response
QOD	every other day dosing
QODx3	every other day dosing for 3 doses (over 5 days)
QT interval	the interval between Q and T waves of the electrocardiogram
QTc interval	corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SD	stable disease
TIW	three times weekly

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1. Background and Rationale

1.1 AML

Acute myeloid leukemia (AML) is a clonal hematopoietic disorder characterized by genetic and epigenetic alterations that lead to a block in granulocyte differentiation and accumulation of leukemic blasts in blood and bone marrow (BM). Nonrandom chromosomal abnormalities (e.g., deletions, translocations) are identified in approximately 55% of all adult primary AML patients and are thought to provide the most significant information regarding prognosis and responsiveness to intensive therapy as well as to direct initial treatment strategies, including allogeneic transplantation in first CR[2]; however, approximately half of AML diagnoses are associated with a normal karyotype and highly variable disease outcomes[2, 3]. Over the past two decades, advances in molecular diagnostics have improved our understanding of AML biology and has contributed remarkably to refining overall prognosis, particularly in patients with cytogenetically normal AML (CN-AML) [4].

With current treatment strategies, approximately 40% of AML patients achieve long-term remission. Of those patients who relapse, only a fraction successfully undergo salvage treatment followed by allogeneic stem cell transplant with curative intent. For older adults (>65 years), the prognosis is even more dismal as patients in this age group often have poor-risk disease that is associated with adverse or complex karyotypes. Furthermore, the presence of comorbid conditions and lack of suitable donors render these patients ineligible for aggressive treatment (i.e., allogeneic stem cell transplant). Even with adaptation of cytogenetically risk-stratified therapies, 20% to 30% of AML patients never achieve CR, and greater than 50% of patients who achieve CR subsequently experience very early disease relapse. The lack of significant advances in the treatment of AML in adults highlights the need for development of novel therapeutic strategies, particularly those directed against molecular targets that are known to be involved in disease pathogenesis.

1.2 FLT3 mutations and targeted therapies in AML

Mutations in the fms-like tyrosine kinase 3 (*FLT3*) gene were one of the first molecular abnormalities to be described in AML. FLT3 is a type 3 receptor tyrosine kinase expressed on normal bone marrow progenitor cells; its expression is normally lost with maturation of these progenitors[5]. Binding of FLT3 ligand to FLT3 activates the FLT3 signal transduction pathway, which works in concert with other signaling pathways (including STAT, MAPK and PI3K) to regulate hematopoietic cell maturation and growth[5, 6]. FLT3 is expressed on AML cells in at least seventy-percent of cases, and approximately one third of AML patients harbor activating mutations of *FLT3*, including internal tandem duplications (ITDs) in 25% and tyrosine kinase domain (TKD) point mutations in 5% [5, 7, 8], resulting in constitutive activation of FLT3 signaling.

The presence of the *FLT3-ITD* mutation has a well-recognized adverse prognostic impact on disease outcomes, with short disease-free survival following standard AML chemotherapy [9-11]. As such, molecularly targeted therapies directed at inhibiting FLT3 signaling are an attractive treatment option to improve disease outcomes in this ill-fated subset of patients.

A number of FLT3 tyrosine kinase inhibitors (TKIs) have been evaluated, initially as single agents, then in

combination with chemotherapy, to assess AML response and impact on outcomes in AML patients who carry *FLT3* mutations. Phase I/II trials of single-agent lestaurtinib (CEP 701), midostaurin (PKC 412) and sorafenib, demonstrated that these agents were generally well tolerated and upward of seventy-percent of patients achieved some degree of hematologic improvement, as evidenced by reduction in blood and/or bone marrow blasts [12-15]. However, with single-agent therapy these responses were incomplete and transient, leading to evaluation of these agents in combination with standard chemotherapy regimens. A phase III trial of midostaurin in combination with chemotherapy for FLT3-ITD+ AML was completed and showed prolonged overall and event-free survival, which led to FDA approval in this disease [16]. These "first-generation" FLT3 inhibitors may not be optimal due to high plasma protein binding, [17] significant toxicities, and lack of potent FLT3 inhibition [18-22]. "Second- generation" FLT3 inhibitors with more selective and potent FLT3 inhibition, including quizartinib, crenolanib and gilteritinib are in phase II and III clinical evaluation alone and in combination with chemotherapy in *FLT3-ITD*+ AML[23].

1.3 Mechanisms of resistance to FLT3 inhibitors

One of the most well described mechanisms of acquired resistance to FLT3 TKIs is the development of secondary *FLT3* TKD mutations, primarily at residues D835 and F691. TKD point mutations alters the conformation of the kinase which deters proper binding of the inhibitors. Docking models suggest that TKIs bind to the ATP-binding pocket and DFG residues in a region of the activation loop in the kinase domains. Substitution of amino acid residues within the activation loop shift the orientation of DFG residues to a "DFG-out" motif. Binding of TKIs with type II properties are perturbed by this substitution mutation, whereas TKIs with type I or type II properties have altered binding to FLT3 mutations at the gatekeeper residue, F691, in the ATP-binding pocket [24]. Currently, sorafenib and quizartinib are type II FLT3 TKIs used clinically in AML that have been shown to be susceptible to resistance conferring TKD mutations [24-26]. While FLT3 D835 mutations have not been shown to emerge during gilteritinib and crenolanib treatment (type I TKIs), clinical studies have shown patients develop F691 gatekeeper mutations that confer drug resistance [27, 28]. Pharmacokinetic studies have revealed that some FLT3 TKIs have suboptimal properties such as high plasma protein binding and/or a short half-life, which can be associated with subtherapeutic plasma concentrations and insufficient cytotoxic effects. For example, the FLT3 TKI crenolanib must be administered three times daily to remediate such shortcomings[29]. The lack of patient medication adherence to strict drug regimens can become an added hurdle to achieve adequate drug response. Nonetheless, *FLT3* inhibition remains an important therapeutic target that is the subject of ongoing studies.

1.4 Co-occurring baseline and acquired somatic mutations with FLT3-ITD during TKI therapy

Recent studies have reported the co-occurrence of mutations with *FLT3-ITD*, such as *NPM1*, *DNMT3A*, *WT1*, *IDH1/2*, and *TET2*, that likely impact prognosis and clinical outcomes.[30, 31] Using a targeted gene panel, WES, and deep amplicon sequencing of *FLT3* TKD1 (exon 17) and TKD1 (exon 20), we determined the mutations that co-occurred with *FLT3-ITD* in patients prior to receiving crenolanib as a single agent, and compared the gene profiles between different crenolanib response groups. Higher frequencies of *IDH1/2* and *TET2* mutations, among others, were present in poor responders versus crenolanib good responders. We did not observe an association of *FLT3* mutation status (ITD, TKD or both) with crenolanib response, although 1 patient harboring a baseline *FLT3* F691L mutation was a poor responder. Paired samples (pre-

TKI/during ≥ 28 days of TKI) from 14 patients were profiled for *FLT3* mutations. *FLT3* F691L mutations arose in 2 patients. Further profiling revealed that *TET2*, *IDH1/2*, and *NRAS* mutations were not cleared during treatment, and new mutations in *IDH1* and *NRAS* emerged in several patients during crenolanib treatment. A recent analysis by next generation sequencing of paired samples (pre-TKI/TKI progression) from 16 patients receiving gilteritinib (type I TKI) treatment revealed the emergence of new mutations including *FLT3* F691L (N=3) and mutations in *IDH2 (*N=1) and *NRAS* (N=4).[32] These data highlight the genomic complexity of FLT3-ITD+ AML and the potential role that baseline and/or acquired co-occurring somatic mutations contribute to FLT3 TKI resistance.

1.5 Axl and Gas6 in AML biology and TKI resistance

The receptor tyrosine kinase Axl was first discovered 20 years ago and subsequently identified to be involved in the pathogenesis of various cancers. Axl, along with Tyro-3 and Mer, are receptor tyrosine kinase that belong to the TAM family of kinases. TAM kinases are involved in a variety of cellular processes including cell proliferation and survival, and cell adhesion and migration. The prognostic implications of Axl in AML was initially illustrated in the 1990s and has been reported to be associated with AML leukemogenesis [33]. Several literature reports have indicated that Gas6 (growth arrest specific 6), an Axl ligand, has prognostic implications. In 270 adults with de novo cytogenetically normal AML, patients expressing Gas6 more often failed to achieve a remission and had shorter overall survival and disease-free survival. Recently, the role of Axl in FLT3-ITD+ AML biology and as a potential therapeutic target has been described [34-36]. Axl and FLT3-ITD interaction was first proposed by Park et al., where phosphorylation of FLT3-ITD was disrupted by Axl-Fc (soluble Axl chimeric protein that binds to Axl ligand abrogating Axl activation) or siRNA targeting of Axl[35]. Axl inhibition by Axl-Fc led to a decrease in proliferation of FLT3-ITD+ AML cells and patient primary blasts due to cell cycle arrest and apoptosis. Further *in vivo* effects of Axl inhibition by Axl-Fc was demonstrated in a primary human FLT3-ITD+ AML xenograft in SCID mice, where there was less human CD45+ cells detected in the Axl-Fc treatment group compared to the control-Fc group.

Another group evaluated Axl in the context of AML in the tumor microenvironment [36]. They demonstrated that AML cells stimulate bone marrow stromal cells to upregulate Gas6. Upregulation of Gas6 fostered AML cell growth and cytarabine drug resistance through Axl signaling, whereas silencing Axl in Gas6-negative AML cells in the absence of stromal cells did not produce significant effects [36].

The same group further determined the effects of Axl inhibition in FLT-ITD+ AML in combination with chemotherapy. Inhibition of Axl by BGB324, an Axl TKI undergoing clinical development, or Axl shRNA with concomitant administration with cytarabine or doxorubicin led to additive *in vitro* anti-leukemic effects. Upon silencing Axl, *FLT3-ITD*+ MV4-11 cells became more sensitive to doxorubicin compared to control group. Conversely, overexpression of Axl led to increased chemo resistance against doxorubicin. When primary AML cells were treated concurrently with BGB324 and cytarabine, the combination exerted additive effects compared to either drug alone. Considering that combination chemotherapy is utilized as the standard of care in managing AML, additive or synergistic effects upon concomitant inhibition of Axl with AML gold standard chemotherapeutic agents provides justification that Axl inhibitors in combination regimens could potentially be used as a therapeutic approach in treating patients with FLT3-ITD.

More specifically, later published work by Park et al identified Axl as a key component of resistance to the

FLT3 TKIs, midostaurin and quizartinib[35]. Axl phosphorylation was increased in FLT3- ITD+ AML cells exposed to midostaurin and quizartinib, and inhibition of Axl by TP-0903, the Axl-Fc chimeric protein or lentiviral encoding shRNA targeting Axl in midostaurin-resistant MOLM13 cells, sensitivity to midostaurin and quizartinib was restored. While phospho-Axl was detected in FLT3-ITD+ primary blast samples with midostaurin resistance *ex vivo*, it was not detected in blasts that were sensitive to midostaurin therapy. Similar findings were observed in *in vivo* in a midostaurin-resistant MOLM13 cell line xenograft model. Mice were treated with either vehicle control, midostaurin alone, TP-0903 alone, or the combination of midostaurin and TP-0903. Combination therapy prolonged survival in mice compared to either TKI alone. As midostaurin received Breakthrough Therapy status from the FDA, identification of resistance mechanisms to midostaurin may have serious therapeutic implications for patients receiving this agent, and therapeutic strategies to circumvent resistance will be needed. Collectively, these findings indicate that upregulation of Axl is involved in resistance to several FLT3 TKIs, and inhibition of Axl is a potential approach to counteract FLT3 TKI resistance.

1.6 FLT3-ITD+ AML cell metabolic adaptations to FLT3 inhibition

Previous studies have demonstrated that FLT3-ITD+ AML cells display increased glycolysis and central carbon metabolism compared to FLT3 wild type cells, supported by analysis of clinical gene expression datasets showing signatures of upregulated glucose metabolism and TCA cycle.[37, 38] Two recent studies have highlighted the role of metabolic adaptations in response to FLT3 TKI treatment. One group showed that FLT3 inhibition with quizartinib impaired glycolysis in MOLM13 and MV411 AML cell lines.[38] By performing cellular uptake studies with glucose and glutamine, metabolic flux analysis using U-$^{13}C_6$-glucose, and gene expression profiling, they showed that quizartinib blocked glucose uptake, but not glutamine, reduced glucose labeling of glycolytic intermediates, and downregulated glycolytic enzyme gene expression. They concluded that FLT3-ITD inhibition impairs glycolysis without affecting glutamine metabolism. Another group demonstrated that quizartinib impairs glutamine metabolism in MOLM13 cells through metabolic flux analysis using ^{13}C,^{15}N-labeled glutamine; quizartinib decreased intracellular labeled glutamine and downstream metabolites (glutamate, α-ketoglutarate)[39]. These studies suggest AML cells undergo metabolic changes during FLT3 inhibitor treatment, which we will evaluate in response to TP-0903 treatment in primary patient AML samples.

1.7 Summary of TP-0903 preclinical studies

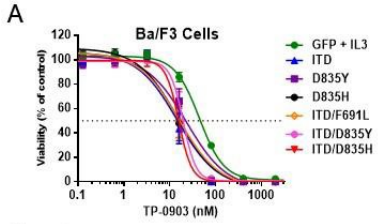
TP-0903 is an orally bioavailable inhibitor of Axl. The chemical name of TP-0903 is 2-{[5-chloro-2- ({4-[{4-methylpiperazin-1-yl)methyl]phenyl}amino)pyrimidin-4-yl]amino}-N,N-dimethylbenzene -1-sulfonamide mono-tartrate salt. Based on previous reports that Axl is an important mechanism of resistance to FLT3 TKIs and AML-directed chemotherapy, we were interested in evaluating TKIs that target Axl as a possible therapy against *de novo* and drug resistant FLT3-ITD+ AML. Previously, in a screen consisting of 40 kinases, TP-0903 (200 nM) was shown to inhibit (>50%) eleven kinases[40]. We evaluated the inhibition of these kinases, as well as Axl, by TP-0903 in a binding assay with the resultant Kd values: Axl (8.2 nM), MER (4.4 nM), TYRO3 (970 nM), AURKA (0.99 nM), CHEK1 (24 nM), JAK2 (0.2 nM), ABL1 (1.2 nM), IGF1R (56 nM), CSF1R (16 nM), PDGFRB (80 nM), and VEGFR2 (110 nM). In a kinase assay, TP-0903 inhibited Axl with an IC50 value of 4.9 nM. It has been reported that other AXL inhibitors in development also target FLT3[41]. Therefore, we profiled the activity of TP-0903 against FLT3 and ITD/TKD mutants. TP-

0903 had potent binding affinities against wild type FLT3 (FLT3-WT) (Kd = 0.93 nM), FLT3-ITD (Kd = 5.6 nM), FLT3 TKD D835 mutants (Kd = 0.79 - 2.1 nM), and the double ITD/TKD F691L gatekeeper mutant (Kd = 1.9 nM) (**Table 1**). For comparison, binding affinities clinical candidate FLT3 inhibitors including gilteritinib, a FLT3/Axl inhibitor, are shown in **Table 1**. In a kinase assay, TP-0903 inhibited FLT3-ITD and the D835Y mutant with IC50s of 3.9 and 0.12 nM, respectively. The observation that TP-0903 has greater potency against FLT3 activation loop D835 mutations suggests that TP-0903 has type I kinase inhibitor properties. These findings provide the rationale for further evaluation of TP-0903 in *de novo* and TKI resistant FLT3-ITD+ AML.

Kd (nM) – Binding Assay						
FLT3	Sorafenib	Quizartinib	Midostaurin	Crenolanib	Gilteritinib	TP-0903
Wild type	7.0	1.5	2.6	0.15	1.9	0.93
ITD	33	8.5	3.2	0.26	0.91	5.6
D835H	17	2.3	1.3	0.16	0.86	1.9
D835V	92	5.6	1.5	3.3	0.15	2.1
D835Y	60	11	1.4	0.14	0.65	1.4
ITD/ D835V	4600	340	2.3	3.6	0.12	0.79
ITD/ F691L	1100	83	2.7	22	0.32	1.9

Table 1. Inhibition of FLT3-ITD and TKD mutants by TP-0903 and other FLT3 TKIs in a binding assay.

We compared the activity of TP-0903 and a series of clinical candidate FLT3 TKIs in Ba/F3 cells expressing FLT-ITD and TKD mutants, which many groups including our lab have used to understand the impact of different FLT3 mutations on TKI sensitivity [25, 42-44]. While sorafenib and quizartinib, were resistant to TKD mutations, TP-0903 showed activity against all FLT3 TKD mutations. The latter included the gatekeeper F691L mutation, which gilteritinib, crenolanib, and midostaurin showed reduced sensitivity by 36-, 32-, and 4.8-fold, respectively, compared to cells expressing FLT3-ITD (**Figure 1A and 1C**). In Ba/F3 cells expressing FLT3-ITD and TKD single and double mutations, TP-0903 inhibited the phosphorylation of FLT3 and downstream STAT5 in a dose-dependent manner starting at 10nM, as assessed by western blot (**Figure 1B**). Development of TKD mutations are major obstacles to FLT3 TKI therapy presented in real clinical settings [24, 25, 42, 45, 46]. Here, *in vitro* sensitivity testing suggests that TP-0903 could overcome drug resistance from acquired TKD mutations. Additionally, TP-0903 has the most potent activity against the gatekeeper F691L mutation, which current FLT3 inhibitors succumb to. TP-0903 was originally designed on an Axl scaffold that does not clash with the Axl gatekeeper residue, Leu620. Given its initial drug design, TP-0903 may bind to F691 substitution mutation to leucine in similar manner as it does to L620 in Axl. Based on these data, TP-0903 can be used as a strategy to overcome clinically relevant *FLT3* TKD mutations reported to date.



C

Ba/F3 Cells IC50 (nM)						
FLT3	Sorafenib	Quizartinib	Midostaurin	Crenolanib	Gilteritinib	TP-0903
GFP+ IL3	3848	>10,000	328	773	972	47
ITD	1.4	0.15	4.2	1.8	5.4	15
D835H	76	2.2	1.2	0.27	0.5	16
D835Y	233	11.7	1.5	0.068	22	22
ITD/D835H	463	28	28	38	20	16
ITD/D835Y	3337	199	33	35	55	20
ITD/F691L	1339	232	20	58	193	16

Figure 1. Effect of TP-0903 and other TKIs in Ba/F3 cells transfected with FLT3 mutants. (**A**) Cell viability curve. (**B**) FLT3 signaling assessed by western blot after 4h of treatment with designated concentrations. (**C**) FLT3 TKI IC50 values (MTT assay, 72h, N=18).

We further evaluated the *in vitro* potency of TP-0903 in the FLT-ITD+ AML cell lines MOLM13, MOLM13-Res, and MV4-11 in a cell viability assay. MOLM13-Res cells are a FLT3 TKI resistant progeny of MOLM13 cells that harbor a dual ITD/D835Y mutation, that were generated in our lab [43]. TP-0903 had potent anti-leukemic activity in all AML cell lines (**Figure 2**). For comparison, IC50 values for other FLT3 TKIs are shown in **Figure 2B**. Collectively, our preliminary data indicate that TP-0903 has therapeutic potential in both *de novo* and TKI resistant FLT3-ITD+ AML, by targeting FLT3-ITD, FLT3 TKD mutations, Axl and potentially other kinase targets.

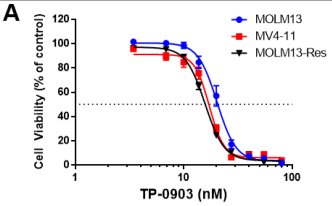


Figure 2. Effect of TP-0903 and other FLT3 TKIs on cell viability in FLT3-ITD+ AML cell lines. (**A**) Cell viability curve (data are mean ± SEM). (**B**) FLT3 TKI IC50 values (MTT assay; 72h; N=18)

B

Cell lines	IC50 (nM)					
	Sorafenib	**Quizartinib**	**Midostaurin**	**Crenolanib**	**Gilteritinib**	**TP-0903**
MOLM13	26	2.5	39	7.4	17	21
MOLM13-Res	1790	400	41	11	11	16
MV4-11	8	1.7	51	6.6	8	17

To determine if TP-0903 induces cytotoxicity in FLT3-ITD+ AML cell lines, we performed apoptosis and cell cycle assays by annexin-V/DAPI staining and flow cytometry. TP-0903 20nM induced significant apoptosis at 24 and 48h of treatment (**Figure 3A and 3B**), and a G2-M cell cycle arrest at 6h and 12 h (**Figure 3 C**). Consistent with cells undergoing apoptosis, an increase in a sub-G1 peak was observe at 24 h (**Figure 3D**). The observed G2-M arrest is likely related to AURKA inhibition, which is a unique feature of TP-0903 relative to other clinical candidate FLT3 TKIs.

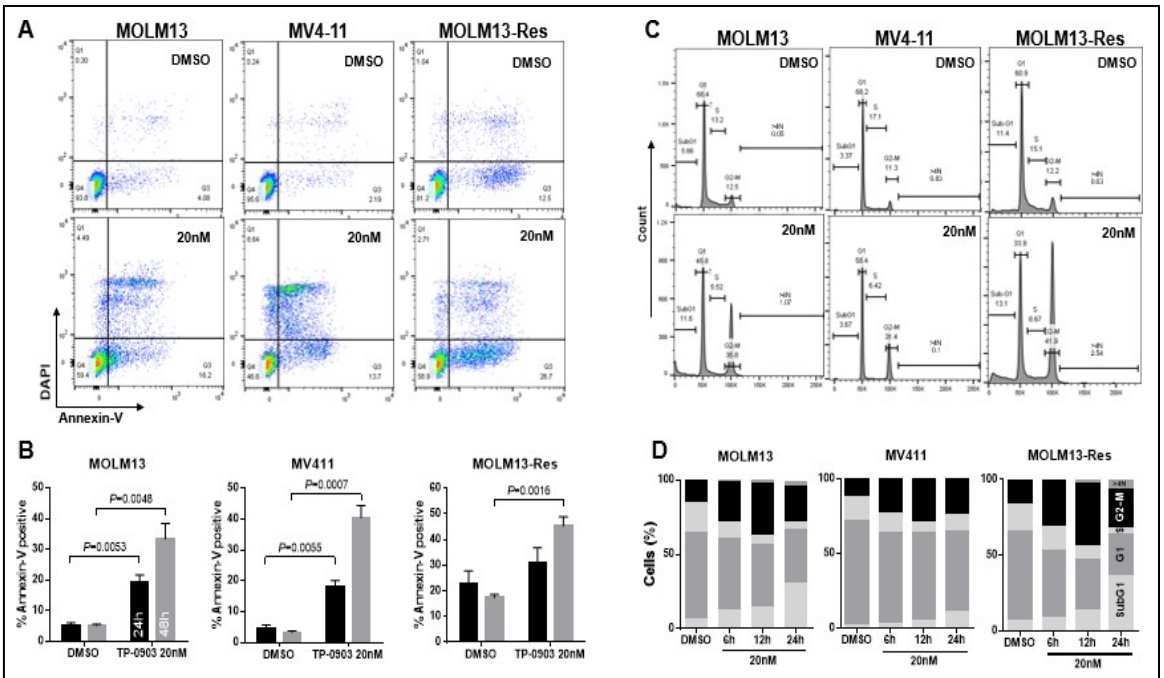


Figure 3. TP-0903 induces apoptosis and a G2-M cell cycle arrest in AML cell lines. (**A**) Representative flow cytometry measurement of apoptosis using annexin-V and DAPI staining at 48h of treatment. (**B**) Quantification of annexin-V positive cells at designated treatment times (N=3). **(C**) Representative cell histograms after 12h of treatment. (**D**) Quantification of each cell cycle phase is shown at designated treatment time (N=3).

There are literature reports in FLT3-ITD+ patients where FLT3 TKIs induced terminal myeloid

differentiation in leukemic blasts. Patients with minimal change in ITD allelic ratios post-quizartinib treatment displayed predominantly mature neutrophils with very little wild-type FLT3 allele [47]. This was also observed in sorafenib treated patients where blast-free bone marrow with normocellular or hypercellular marrows had readily detectable FLT3-ITD. This was further confirmed by in vivo transplantation in which sorafenib differentiated FLT3-ITD+ myeloblasts [45]. With induction of differentiation in blasts as another potential mechanism of action in FLT3 TKIs, we also examined if TP-0903 differentiates FLT3-ITD+ AML cells to mature myeloid cells. We first measured CD11b expression in AML cell lines via flow cytometry. TP-0903 increased CD11b expression to 3- to 30-fold at 48-72h compared to DMSO control (**Figure 4A**). In parallel, we measured expression of different genes that are expressed in more mature myeloid cells including the granulocyte colony stimulation factor receptor (GCSFR) and lysozyme gene using TaqMan Real-Time PCR (RT-PCR). In all FLT3-ITD+ AML cell lines, GCSFR and lysozyme gene expression was increased by up to 20-fold with TP-0903 treatment compared to DMSO control (**Figure 4B**). *Ex vivo* treatment of two FLT3-ITD+ primary patient blast samples with TP-0903 in a CFU assay, cells showed morphologic differentiation with multilobulated nuclei compared to DMSO control (**Figure 4C**). These data indicate that TP-0903 induces differentiation of FLT3-ITD+ leukemic blasts.

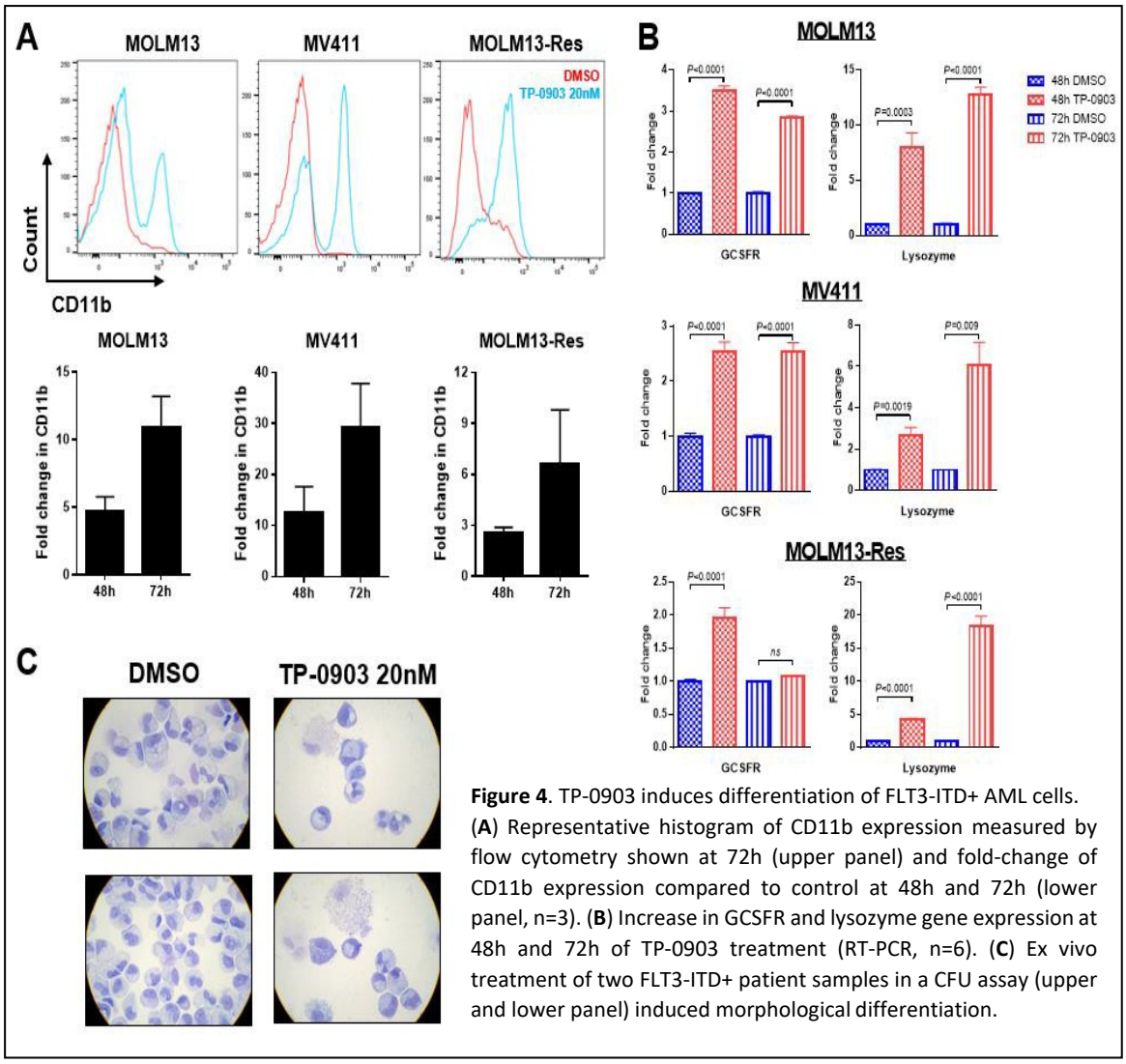
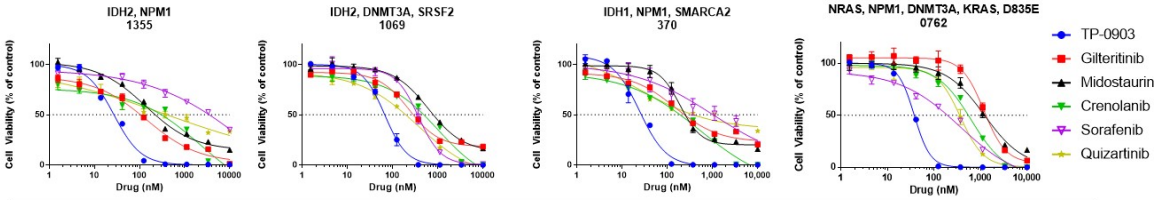


Figure 4. TP-0903 induces differentiation of FLT3-ITD+ AML cells. (**A**) Representative histogram of CD11b expression measured by flow cytometry shown at 72h (upper panel) and fold-change of CD11b expression compared to control at 48h and 72h (lower panel, n=3). (**B**) Increase in GCSFR and lysozyme gene expression at 48h and 72h of TP-0903 treatment (RT-PCR, n=6). (**C**) Ex vivo treatment of two FLT3-ITD+ patient samples in a CFU assay (upper and lower panel) induced morphological differentiation.

We assessed the *ex vivo* activity of TP-0903 in human primary FLT3-ITD+ AML samples with co-occurring mutations including *NRAS*, *IDH1/2*, *SMARCA2*, *NPM1*, and among others. TP-0903 inhibited the viability of patient samples with IC50 values ranging from 26.6-67 nM; in comparison, gilteritinib was 3.5- to 35-fold less potent than TP-0903 with IC50 values ranging from 1.5 105 to 1300 nM (**Figures 5A and 5B**). Other FLT3 TKIs showed much less potent activity in these samples compared to TP-0903. Although preliminary, these data suggest that TP-0903 may have activity against clinically relevant TKI-resistance conferring co-occurring mutations as described above.

A



B

Ex vivo primary human FLT3-ITD+ samples (co-occurring mutations)	IC50 (nM)					
	TP-0903	Gilteritinib	Midostaurin	Sorafenib	Quizartinib	Crenolanib
1355 (IDH2, NPM1)	26.8	105	222	3534	400	305
1069 (IDH2, DNMT3A, SRSF2)	67	286	794	357	195	488
370 (IDH1, NPM1, SMARCA2)	26.6	239	249	1031	375	192
0762 (NRAS, NPM1, DNMT3A, KRAS, D835E)	38	1307	1220	195	357	547

Figure 5. Effect of TP-0903 and other FLT3 TKIs on the viability of primary human FLT3-ITD+ AML samples with co-occurring mutations *ex vivo*. Cell viability curves in (**A**) patient blast samples and (**B**) TKI IC50 values (CellTIter-Glo assay, 72 h, N=3-6).

With positive *in vitro* and *ex vivo* data demonstrating antileukemic activity in FLT3-ITD+ cells, we evaluated the *in vivo* therapeutic potential of TP-0903 in MOLM13-YFP/Luciferase (MOLM13-Luc+) and MOLM13-RES-Luc+ mouse xenograft models. We performed tolerability studies of TP-0903 in tumor-bearing 8- to 12-week old female NSG mice (1 million cells administered by tail vein injection) at doses ranging from 40-80 mg/kg administered once daily or daily x 5/week for 3 weeks and determined that 60 mg/kg was the MTD on these schedules. PK studies performed in mice at TP-0903 60 mg/kg show that plasma exposure achieved is in the range observed in patients in the ongoing phase I clinical trial in solid tumors (data on file at Sumitomo Dainippon Pharma Oncology, Inc. (SDPO)). For efficacy studies, treatment was started on days 7 or

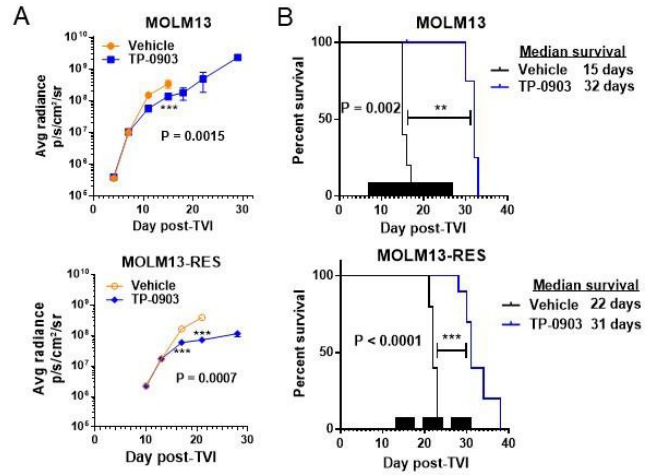


Figure 6. *In vivo* activity of TP-0903 in MOLM13-Luc+ and MOLM13-RES-Luc+ xenograft mouse models. (**A**) Bioluminescence imaging reported as average radiance. (**B**) Survival by Kaplan-meier analysis. Black bars depict treatment duration.

13 in the MOLM13-Luc+ and MOLM13-RES-Luc+ xenografts, respectively, after a similar level of bone marrow engraftment was documented by bioluminescence imaging (**Figure 6A**). In both xenograft models, TP-0903 delayed the outgrowth of leukemia cells (P=0.0015 and 0.0007, respectively) (**Figure 6A**) and prolonged survival by 17 and 9 days (P<0.0001 and P=0.002, respectively) compared to vehicle-treated mice (**Figure 6B**).

In the MOLM13-Res-Luc+ xenograft efficacy study, we collected bone marrow and blood samples when mice succumbed to leukemia. Bone marrow samples were enriched for MOLM13-RES cells by CD45 selection, RNA was extracted and AXL gene expression was measured by RT-PCR. Plasma Gas6 was measured by ELISA. TP-0903 significantly decreased AXL gene expression in leukemic cells (P=0.0009) (**Figure 7A**). High levels of circulating Gas6 was observed in vehicle-treated mice, which was significantly reduced in mice treated with TP-0903 (P=0.017) (**Figure 7B**). These preliminary data demonstrate that TP-0903 modulates AXL expression in leukemia cells and reduces circulating levels of its ligand Gas6 in the in vivo setting. These

studies will be incorporated in the clinical pharmacodynamic studies outlined in Aim 2. Combined, our preclinical studies demonstrate that TP-0903 has activity in *de novo* and TKI-resistant FLT3-ITD+AML and provide the scientific premise to conduct a phase 1b/2 trial of TP-0903 in patients with FLT3-ITD+ AML. It is anticipated that TP-0903 will have immediate clinical impact to circumvent and treat currently identified clinically relevant FLT3 TKI resistance mechanisms.

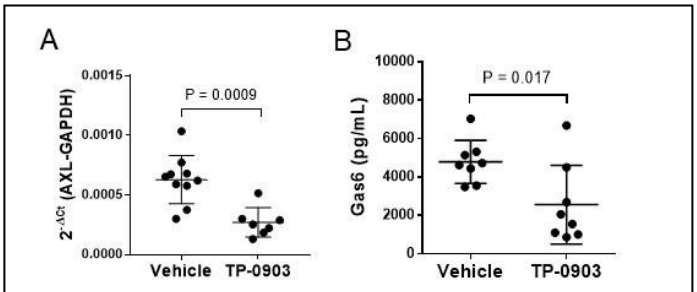


Figure 7. Effect of TP-0903 treatment on (**A**) AXL gene expression in bone marrow AML cells (by RT-PCR) and (**B**) circulating plasma Gas6 (by ELISA) in a MOLM13-RES-Luc+ xenograft mouse model.

Given the recent interest in the discovery and development of agents to target cancer metabolism, [48] these studies suggest the metabolic changes that occur during FLT3 TKI treatment can be exploited therapeutically. However, the exact mechanisms leading to metabolic reprogramming are not well described and it is unknown if different FLT3 TKIs induce distinct metabolic responses. To begin to address this, we performed gene expression analysis (RNASeq) of bone marrow MOLM13-RES AML cells obtained from mice treated with TP-0903 or vehicle (**Figure 6**) and determined the changes of genes involved in glutamine and glucose cellular transport and metabolism. TP-0903 significantly downregulated genes involved in glutamine transport and metabolism (**Figure 8A**). Five of 7 top downregulated genes in these pathways were: **1**) three cell membrane glutamine transporters, SLC38A1 (SNAT1), SLC1A5 (ASCT2), and SLC7A5 (LAT1); **2**) glutamic-pyruvic transaminase 2 (GPT2), a mitochondrial transaminase that converts glutamate→α-ketoglutarate; and **3**) asparagine synthetase (ASNS), an enzyme that converts aspartate → asparagine coupled to the metabolism of glutamine → glutamate. Expression changes in these genes were validated by RT-PCR (**Figure 8B**). Expression changes in these genes were validated by RT-PCR (**Fig 8B**). We confirmed that TP-0903 inhibited the uptake of glutamine, which was not observed with gilteritinib (**Fig 8C**).

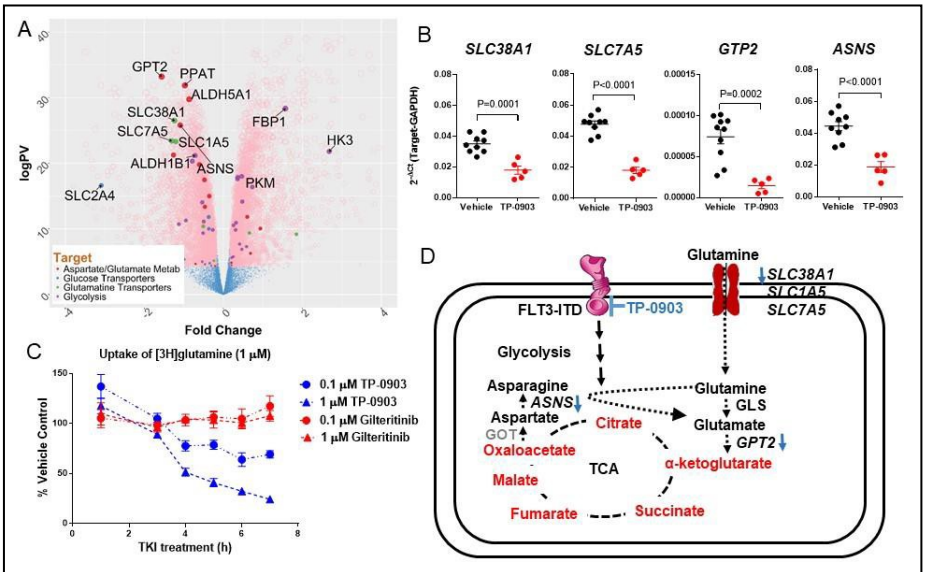


Figure 8. TP-0903 impairs glutamine transport/metabolism in a MOLM13-RES-Luc+ xenograft model. (**A**) Volcano plot for gene expression changes by RNASeq in cells from mice treated with TP-0903 (N=5) or vehicle (N=10). (**B**) Validation of gene expression changes by RT-PCR. P values are from unpaired t-tests, two-sided. (**C**) TP-0903, but not gilteritinib, inhibits glutamine uptake in HeLa cells. (**C**) Model depicting pathways involved in impaired glutamine transport/metabolism by TP-0903.

Fig 8D illustrates a working model depicting the pathways involved in the inhibition of glutamine transport and metabolism by TP-0903. These data provide the scientific rationale to perform metabolomics and carbon flux studies in primary patient AML samples in response to TP-0903 treatment.

1.8 Summary of clinical studies

The first-in-human phase 1a/1b study with TP-0903, TP-0903-101 (Clinicaltrials.gov identifier: NCT02729298) is ongoing in patients with refractory solid tumors. The Phase 1a study is designed to identify the maximum tolerated dose (MTD) and to identify the safety profile and recommended phase 2 dose of TP-0903. Once the MTD has been established, 5 additional cohorts of up to 20 patients each with specific tumor type will be enrolled at the MTD in the phase 1b study. TP-0903 is administered once daily for 21 days followed by a 7-day drug-free period for one cycle. Patients are allowed to continue on TP-0903 if it shows benefit and is reasonably well tolerated. As of August 2018, adverse events observed in patients treated at the first 7 dose levels are shown in Table 2. Patients are consistently presenting with nausea/vomiting, diarrhea, and anorexia and no DLTs have been observed. Thus far, TP-0903 has been well tolerated with no patients coming off study due to drug-related toxicity. As of March 2019, a flat dose of 50 mg daily on days 1-21 of a 28 day cycle is the dose that will be used for future phase 1b expansion cohorts.

Table 2. Treatment-emergent adverse events by body system and preferred term by dosing cohort (safety population and overall).

	BSA-based Dose (mg/m²)									Flat Dose (mg)
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7	Cohort 8	Cohort 9	Cohort 10
MedDRA System Organ Class [a]	1.5	3.0	6.0	9.0	12	16	21	28	37	50
MedDRA Preferred Term	(n=3)	(n=3)	(n=3)	(n=3)	(n=3)	(n=5 [b])	(n=3)	(n=6)	(n=6 [c])	(n=3)
Metabolism and nutrition disorders (cont)										
Hypokalaemia	0	0	0	1 (33.3%)	1 (33.3%)	1 (20.0%)	0	0	1 (16.7%)	0
Hyperglycaemia	0	1 (33.3%)	0	0	0	0	0	2 (33.3%)	0	0
Hypocalcaemia	0	1 (33.3%)	1 (33.3%)	0	0	0	0	0	1 (16.7%)	0
Hyponatraemia	0	0	0	1 (33.3%)	0	1 (20.0%)	0	0	0	0
Musculoskeletal and connective tissue disorders										
Back pain	0	3 (100%)	0	0	0	2 (40.0%)	0	1 (16.7%)	2 (33.3%)	0
Musculoskeletal pain	0	0	1 (33.3%)	0	1 (33.3%)	0	1 (33.3%)	1 (16.7%)	0	0
Musculoskeletal chest pain	0	0	0	0	0	1 (20.0%)	1 (33.3%)	1 (16.7%)	0	0
Myalgia	1 (33.3%)	1 (33.3%)	0	0	0	0	0	1 (16.7%)	0	0
Nervous system disorders										
Dizziness	1 (33.3%)	0	0	0	0	3 (60.0%)	0	2 (33.3%)	0	0
Dysgeusia	0	0	1 (33.3%)	0	2 (66.7%)	1 (20.0%)	0	1 (16.7%)	0	0
Headache	0	0	0	1 (33.3%)	1 (33.3%)	0	0	1 (16.7%)	1 (16.7%)	0
Psychiatric disorders										
Insomnia	1 (33.3%)	0	0	0	1 (33.3%)	1 (20.0%)	0	0	1 (16.7%)	0
Respiratory, thoracic and mediastinal disorders										
Dyspnoea	0	1 (33.3%)	0	0	0	1 (20.0%)	0	2 (33.3%)	0	0
Cough	0	0	1 (33.3%)	0	0	0	0	2 (33.3%)	0	0
Oropharyngeal pain	0	0	0	0	0	1 (20.0%)	0	1 (16.7%)	0	1 (33.3%)
Skin and subcutaneous tissue disorders										
Dry skin	1 (33.3%)	0	0	0	1 (33.3%)	0	0	0	0	1 (33.3%)

	BSA-based Dose (mg/m²)									Flat Dose (mg)
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	Cohort 7	Cohort 8	Cohort 9	Cohort 10
MedDRA System Organ Class [a]	1.5	3.0	6.0	9.0	12	16	21	28	37	50
MedDRA Preferred Term	(n=3)	(n=3)	(n=3)	(n=3)	(n=3)	(n=5)	(n=3)	(n=6)	(n=6)	(n=3)
Blood and lymphatic system disorders										
Anaemia	0	0	1 (33.3%)	0	0	2 (40.0%)	1 (33.3%)	1 (16.7%)	2 (33.3%)	1 (33.3%)
Thrombocytopenia	0	0	0	1 (33.3%)	1 (33.3%)	0	0	2 (33.3%)	2 (33.3%)	0
Leukopenia	0	0	1 (33.3%)	0	0	0	0	1 (16.7%)	0	0
Cardiac disorders										
Tachycardia	1 (33.3%)	0	0	0	0	1 (20.0%)	0	1 (16.7%)	0	0
Gastrointestinal disorders										
Vomiting	2 (66.7%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	2 (66.7%)	3 (60.0%)	2 (66.7%)	5 (83.3%)	6 (100%)	3 (100%)
Nausea	1 (33.3%)	1 (33.3%)	1 (33.3%)	0	2 (66.7%)	4 (80.0%)	3 (100%)	5 (83.3%)	4 (66.7%)	3 (100%)
Diarrhoea	0	0	0	1 (33.3%)	0	3 (60.0%)	1 (33.3%)	5 (83.3%)	3 (50.0%)	2 (66.7%)
Constipation	1 (33.3%)	1 (33.3%)	0	0	0	2 (40.0%)	1 (33.3%)	0	3 (50.0%)	2 (66.7%)
Abdominal pain	0	0	0	0	0	2 (40.0%)	0	4 (66.7%)	1 (16.7%)	0
Abdominal pain upper	0	0	0	0	1 (33.3%)	0	1 (33.3%)	0	1 (16.7%)	0
General disorders and administration site conditions										
Fatigue	0	1 (33.3%)	0	1 (33.3%)	2 (66.7%)	1 (20.0%)	1 (33.3%)	3 (50.0%)	3 (50.0%)	0
Oedema peripheral	0	1 (33.3%)	0	1 (33.3%)	0	2 (40.0%)	2 (66.7%)	0	0	0
Asthenia	0	0	0	0	0	1 (20.0%)	1 (33.3%)	1 (16.7%)	1 (16.7%)	0
Disease progression	1 (33.3%)	1 (33.3%)	0	0	0	1 (20.0%)	0	1 (16.7%)	0	0
Pyrexia	1 (33.3%)	0	0	0	0	0	1 (33.3%)	1 (16.7%)	1 (16.7%)	0
Infections and infestations										
Urinary tract infection	0	0	1 (33.3%)	1 (33.3%)	0	1 (20.0%)	1 (33.3%)	1 (16.7%)	1 (16.7%)	0
Investigations										
Weight decreased	2 (66.7%)	0	0	0	1 (33.3%)	2 (40.0%)	0	0	0	0
Metabolism and nutrition disorders										
Decreased appetite	2 (66.7%)	1 (33.3%)	1 (33.3%)	0	2 (66.7%)	1 (20.0%)	0	2 (33.3%)	1 (16.7%)	0
Dehydration	0	0	0	0	2 (66.7%)	2 (40.0%)	1 (33.3%)	1 (16.7%)	1 (16.7%)	0
Hypoalbuminaemia	0	1 (33.3%)	1 (33.3%)	0	0	1 (20.0%)	2 (66.7%)	1 (16.7%)	1 (16.7%)	0
Hypomagnesaemia	1 (33.3%)	0	1 (33.3%)	2 (66.7%)	0	0	0	1 (16.7%)	1 (16.7%)	0

1.9. Rationale and Hypothesis

In biochemical and cellular assays, we showed that TP-0903 can overcome drug resistance from acquired

FLT3 TKD mutations, including the gatekeeper F691L mutation, which current clinical candidate FLT3 inhibitors are susceptible to. In *ex vivo* testing of primary FLT3-ITD+ leukemia samples, including those harboring a TKI-resistance conferring *FLT3*-ITD/*IDH2* mutation, TP-0903 was more potent than other FLT3 TKIs. *In vivo*, TP-0903 delayed the outgrowth of leukemia and prolonged survival in xenograft models of FLT3-ITD+ AML. **Collectively, our preclinical data demonstrate that TP-0903 has activity in *de novo* and TKI-resistant FLT3-ITD+ AML with the potential to be a best-in-class FLT3 TKI, and provide strong scientific premise to conduct a phase 1b/2 trial of TP-0903 in patients with FLT3-ITD+ AML**. Previous studies have shown that responses with single-agent FLT3 TKI therapy are generally short-lived, which has led to the evaluation of several TKIs in combination with chemotherapy in phase II/III trials [15, 18, 21, 49, 50]. Therefore, we propose to evaluate TP-0903 as monotherapy for *FLT3*-ITD+ AML patients with relapsed or refractory disease. **We hypothesize that TP-0903 will have immediate clinical impact in *FLT3*-ITD+ AML**.

2. Patient Selection

2.1. Eligibility Criteria

2.1.1. Patients age ≥18 with relapsed/refractory AML and the presence of *FLT3*-ITD mutation.

2.1.2. Patients with secondary AML or therapy related disease (t-AML) are eligible.

2.1.3. If the patient has co-morbid medical illness, life expectancy attributed to this must be greater than 6 months.

2.1.4. ECOG performance status ≤2

2.1.5. Patients must have adequate organ function as defined below:

- Total bilirubin <2.0mg/dL unless due to Gilbert's disease
- AST (SGOT)/ALT (SGPT) <2.5 X institutional upper limit of normal
- Cr clearance >50mL/min by Cockcroft-Gault calculation
- NYHA CHF Class II or better
- Cardiac ejection fraction ≥40%

2.1.6. Female patients of child-bearing potential must agree to use dual methods of contraception and have a negative serum pregnancy test at screening, and male patients must use an effective barrier method of contraception if sexually active with a female of child-bearing potential. Acceptable methods of contraception are condoms with contraceptive foam, oral, implantable or injectable contraceptives, contraceptive patch, intrauterine device, diaphragm with spermicidal gel, or a sexual partner who is surgically sterilized or post-menopausal. For both male and female patients, effective methods of contraception must be used throughout the study and for three months following the last dose.

2.1.7. Ability to understand and willingness to sign the written informed consent document.

2.1.8. HIV infection without history of AIDS and sufficiently high CD4 cells (>400/mm3) and low

HIV viral loads (<30,000 copies/ml plasma) not requiring anti-HIV therapy are eligible.

2.2. Exclusion Criteria

2.2.1. Patients with acute promyelocytic leukemia.

2.2.2. Patients who have had chemotherapy or radiotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study. Treatment with hydoxyurea is permitted during cycle 1 to maintain WBC< 40,000/uL.

2.2.3. Patients receiving any other investigational agents or patients that have received other investigational agents within 14 days of enrollment.

2.2.4. Patients with *active* CNS malignancy.

2.2.5. Major surgery within 2 weeks before Day 1.

2.2.6. Uncontrolled active infection. Patients with infection requiring parenteral antibiotics are eligible if the infection is controlled.

2.2.7. Patients with significantly diseased or obstructed gastrointestinal tract.

2.2.8. Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure (New York Heart Association (NYHA) Class III or IV), unstable angina pectoris, myocardial infarction within 6 months prior to enrollment, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening has to be documented by the investigator as not medically relevant.

2.2.9. Patients with serious medical or psychiatric illness likely to interfere with participation in this clinical study.

2.2.10. Pregnant women or women who are breastfeeding are excluded from this study. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.

2.2.11. Patients with advanced malignant solid tumors.

2.2.12. Patients who are not able to swallow capsules or tablets.

2.3. Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

3. Treatment Plan

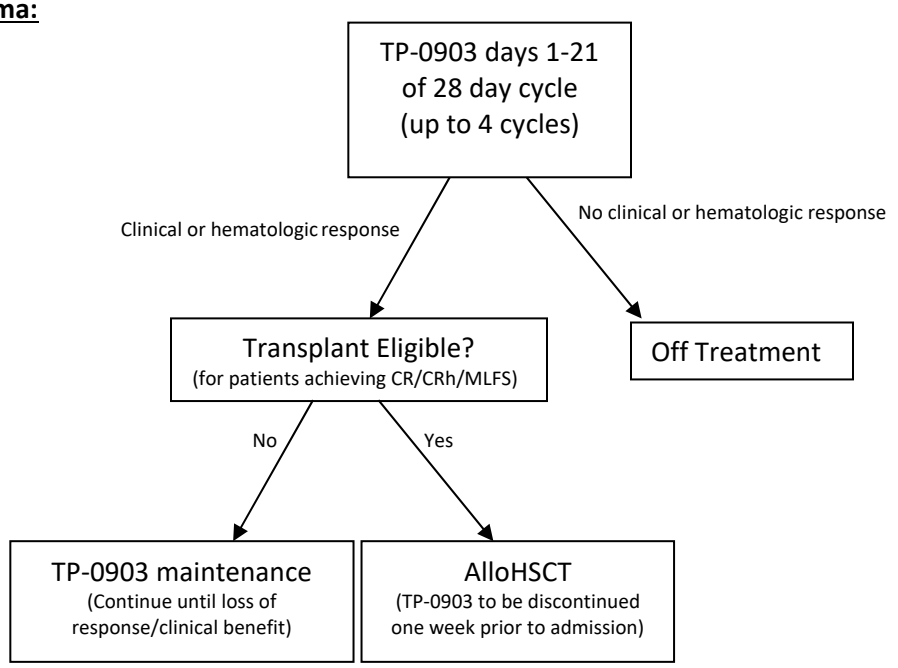
TP-0903 MONOTHERAPY FOR AML PATIENTS WITH FLT3 MUTATIONS AND RELAPSED/REFRACTORY DISEASE

AML patients with FLT3 mutations and relapsed/refractory disease are eligible to receive TP-0903, at a starting dose of 50 mg daily as a single agent for days 1-21 of a 28-day cycle. If the 50 mg dose does not meet the tolerability criteria, a lower dose level of 37 mg daily as a single agent for days 1-21 of a 28-day cycle will be considered.

Dose Level	TP-0903 (D1-21) (mg/day PO)
-1	25
0	37
1	50

Patients may continue treatment indefinitely for as long as clinical benefit is achieved per the investigator's judgment. Bone marrow examinations for disease response assessment will be mandated after the first cycle and at the end of treatment. Subsequent bone marrow examinations may be completed at the discretion of the treating physician.

Schema:



Abbreviations: AlloHSCT, allogeneic hematopoietic stem cell transplant; CR, complete remission; CRh, complete remission with incomplete count recovery; MLFS, morphologic leukemia free state

3.1. Duration of Follow-up

Patients will be followed monthly for treatment failure until the time of transplant or maintenance therapy, at which time they will go to clinical follow-up, followed every 3 months for up to 2 years from registration and then every 6 months for up to 5 years from registration until relapse or death. Patients who end treatment for reasons other than relapse or a subsequent AML treatment (excluding transplant) will follow the same clinical follow-up schedule. Patients who relapse or receive a subsequent AML therapy (excluding transplant) will go to survival follow-up, followed every 6 months for 5 years from registration until death or the completion of the study. A survival follow-up visit can be conducted by phone or electronic contact with the patient or authorized representative. Please see the study calendar in Section 9 for details.

3.2. Recommended supportive care treatment and special considerations

3.2.1. Nausea

Patients experiencing Grade ≤ 2 nausea or vomiting on any dose level should be instructed to take prochlorperazine by mouth 10 mg every 6 hours as needed. Patients experiencing Grade 3 nausea on any dose level should be instructed to take 10 mg of prochlorperazine by mouth 30 minutes before their scheduled dose of TP-0903. Additional doses of prochlorperazine may be given on an as needed basis (10 mg every 6 hours). If this is ineffective, patients may receive ondansetron 4 mg as an alternative, but will need an EKG checked prior to starting given the risk for increasing QTc interval.

3.2.2 Diarrhea

Patients experiencing Grade ≤ 3 diarrhea should be instructed to take loperamide following each loose bowel movement (4 mg initial dose, followed by 2 mg after every loose bowel movement; maximum dose is 16 mg daily).

4. Definition of Dose Limiting Toxicity (DLT)/Dosing Delays and Treatment Modifications

4.1. Definition of Dose Limiting Toxicity (DLT)

Drug-related toxicity in this population may be difficult to ascertain, given the aggressive nature of the underlying hematologic disease. Investigators will attempt to assign attribution of toxicities to each drug if possible. Toxicity attributed to any of the agents will be considered dose limiting. DLT will be assigned only to adverse events occurring with cycle 1 of therapy.

Patients who experience dose limiting toxicity may continue on trial provided that the toxicity has resolved to at least Grade 2. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (http://ctep.cancer.gov) will be used to characterize toxicities. However, any adverse reaction that leads to dose reduction or withdrawal will be considered a DLT.

Non Hematologic:

Any ≥ Grade 4 non-hematologic toxicity will be considered a DLT.

Any non-Hy's law ≥ Grade 3 liver abnormality is a DLT unless it resolves within 72 hours.

Any ≥ Grade 3 infection lasting more than 7 days in the absence of active AML is considered a DLT.

Any ≥ Grade 3 bleeding with thrombocytopenia in the absence of active AML is considered a DLT.

Any ≥ grade 3 non-hematologic toxicity not resulting directly from active leukemia is a DLT, with the exceptions of:

- Alopecia
- Line associated venous thrombosis
- Grade 3 fatigue, anorexia, constipation
- Grade 3 or 4 electrolyte disturbance that resolves within 24 hours with electrolyte correction and is not clinically significant,
- Grade 3 nausea or vomiting that does not require hospitalization or support with total parenteral nutrition and resolves to < grade 2 within 72 hours

The DLT observation period is defined as cycle 1 day 1 until completion of cycle 1 and will require that in the absence of DLT, patients receive at least 14 of the 21 planned doses of TP-0903 during cycle 1 to be considered evaluable for the tolerability check of the phase 1b. In other words, a patient will be considered unevaluable for the tolerability check and phase 1b component if a patient does not complete the DLT observation period due to reasons other than toxicity (e.g. progression). These patients will still be considered evaluable and included in the denominator when analyzing efficacy endpoints.

Hematologic toxicity:

Any ≥ Grade 4 neutropenia lasting more than 14 days past the end of the cycle (by day 42) in the absence of active AML should be considered DLT. For patients with > 5% blasts, myelodysplastic changes, or evidence of disease by flow cytometry/cytogenetics, failure to recover normal neutrophil count will not be considered DLT as this could be the result of persistent disease. Any patients who stop treatment prior to completing evaluation for the DLT observation period due to disease progression or refusal for further participation for reasons other than toxicity will be replaced for the purposes of dose- finding and safety evaluations.

Other events may occur which do not meet the definition of a DLT but are concerning to the investigators and sponsor and may be then considered to be DLTs. Any other toxicities occurring during subsequent cycles after cycle 1 will lead to dose modifications as specified below. The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (http://ctep.cancer.gov) will be used to characterize toxicities.

4.2. Dosing Delays/Dose Modifications

4.2.1 Dosing Delays/Dose Modifications for DLTs:

4.2.1.1 Non-hematologic DLT:

Study treatment will be held for any patients experiencing a DLT.

Patients experiencing Grade ≥ 3 non-hematologic toxicity will have study treatment held until the toxicity resolves to NCI CTCAE ≤ grade 1 or to the patient's baseline values. Patients may restart TP-0903 at the next lower dose level when the adverse event recovers to CTCAE ≤ grade 1. If study treatment is restarted and another non-hematologic DLT (Grade ≥ 3) is encountered at the lower dose, the patient must be removed from the study. If the non- hematologic toxicity does not recur on re-challenge, the dose level may be re-escalated at the initiation of next cycle at the discretion of the investigator. Study treatment will be discontinued permanently for any grade 4 non-hematologic DLT.

4.2.1.2 Hematologic DLT:

After the 42 day period and confirmed hematologic DLT: If peripheral blasts are absent AND bone marrow blasts are less than 5%, then the patient may restart study treatment on cycle 2 at the next lower dose level.

After achieving CR, the dose level may be re-escalated at the initiation of next cycle at the discretion of the investigator.

4.2.2 Dose Delays/Dose Modifications for Non-DLTs

4.2.2.1 Induction

Patients experiencing non-DLT toxicities during induction related believed to be due to TP-0903 therapy that present a challenge to medical management (i.e. grade 2 chronic nausea, myalgia, or fatigue) should have their dose held until it falls to a level of grade 1 or < and then re-start at a -1 dose reduction in therapy. If this recurs at the lower dose, the patient will discontinue TP-0903 and be followed on the treatment regimen.

4.2.2.2 Maintenance

Non-hematologic toxicities

Dose modifications due to TP-0903: Patients experiencing grade 3 non-hematologic toxicities believed to be related to TP-0903 therapy (excluding correctable electrolyte abnormalities), select grade 2 toxicities (neurologic), or chronic grade 2 toxicity that presents a challenge to medical management (i.e. grade 2 chronic nausea, myalgia, or fatigue) should have their TP-0903 dose held until this resolves to grade 1 or < and then it may be initiated at a dose level below the treating dose. If this recurs at the lower dose, the patient will discontinue TP-0903 and be followed on the treatment regimen. Patients experiencing any grade 4 non-hematologic toxicities will have treatment discontinued permanently.

Hematologic toxicities

TP0903 dose reductions in subsequent cycles after CR/CRi is achieved (i.e., Subsequent cycles after being in CR/CRi for at least 1 cycle) will depend on the counts prior to starting the preceding cycle.

a) If prior to the previous cycle (for e.g., patient is starting C5, check the counts prior to starting C4) if the counts were: WBC ≥ 3.0 $x10^9$/L, ANC ≥ 1.5 $x10^9$/L, and platelets ≥ 75.0 $x10^9$/L (all three must apply), adjust the dose as follows, based on nadir counts of the prior cycle (per the e.g. above the prior cycle will be C4):

Nadir Counts		% Dose TP- 0903 in the Next Course
ANC ($x10^9$/L)*	Platelets ($x10^9$/L)*	50%
<0.5	<25.0	

* Dose reductions applies when either ANC OR Platelets are at these values

4.3 General Administration Guidelines

4.3.1 Missed or Vomited Doses

Missed or vomited doses will not be made up. The patient will follow regular schedule starting the next study dosing day. All missed doses should be documented in the patient diary. If a dose is vomited within one hour of ingestion, it will be considered a missed dose and recorded as such on the patient diary. If vomiting occurs more than 1 hour after dosing, it will still be considered a complete dose.

5. Safety and Reporting Requirements

5.1. Assessment of Safety

Safety assessments will consist of monitoring and recording adverse events (and serious adverse events); measurements of protocol-specified hematology, clinical chemistry, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug and should be consistent with institutional standards and Good Clinical Practice.

5.2. Definitions

5.2.1. Adverse Events (AE)

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution. For the purposes of this clinical study, adverse events include only treatment-emergent events which are either new or represent detectable exacerbations of pre-existing conditions.

This includes the following:

• Subjective or objective symptoms spontaneously offered by the subject and/or observed by the investigator or study staff including laboratory abnormalities of clinical significance.

• Any adverse events experienced by the subject through the completion of final study procedures.

• AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with MCL that were not present before the AE reporting

period

• Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies)

The following are NOT considered an adverse event:

• **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.

• **Preplanned hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration but not performed before enrollment in the study will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Hospitalizations for social reasons or due to long travel distances are also not SAEs.

• **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as adverse events or serious adverse events, but rather the cause for the test or procedure should be reported.

5.2.2. Serious Adverse Event

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations to applicable regulatory authorities.

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

• It results in death (i.e., the AE actually causes or leads to death).

• It is life-threatening (with regards to determining if an AE is serious, "life-threatening" is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.).

• It requires or prolongs in-patient hospitalization.

• It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).

• It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.

• It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent 1 of the outcomes listed

above).

5.2.3. Severity

Definitions found in the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) will be used for grading the severity (intensity) of AEs. The CTCAE v5.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a patient experience any AE not listed in the CTCAE v5.0, the following grading system should be used to assess severity:

• Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the patient's daily activities

• Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the patient, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

• Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the patient's usual daily activity, and require systemic drug therapy or other treatment

• Grade 4 (Life-threatening or disabling AE) – experiences which cause the patient to be in imminent danger of death

• Grade 5 (Death related to AE) – experiences which result in patient death

5.2.4. Suspected Adverse Reaction

• A Suspected Adverse Reaction is any adverse event for which there is a "reasonable possibility" that the drug caused the adverse event.

• "Reasonable Possibility", for the purposes of safety reporting, means there is evidence to suggest a causal relationship between the drug and the adverse event. Examples of evidence that would suggest a causal relationship between the drug and the adverse event are:

• A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, and Stevens-Johnson Syndrome).

• One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., include tendon rupture or heart valve lesions in young adults, or intussusception in healthy infants). If the event occurs in association with other factors strongly suggesting causation (e.g., strong temporal association, event recurs on rechallenge), a single case may be sufficiently persuasive; but often, more than one occurrence (from one or multiple studies) would be needed before the sponsor could make a determination of whether the drug caused the event.

• An aggregate analysis of specific events that can be anticipated to occur in the study population independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (e.g., symptoms or disease progression), or events unlikely to be related to the underlying disease or condition under investigation, but commonly occur in the study population

independent of drug therapy (e.g., cardiovascular events in an elderly population). An aggregate analysis (across studies) will identify those events that occur more frequently in the drug treatment group than in a concurrent or historical control group.

5.2.5. Unexpected

An “unexpected” AE is an AE that is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be “unexpected” (by virtue of greater severity) if the Investigator Brochure referred only to elevated hepatic enzymes or hepatitis. "Unexpected" also refers to AEs that are mentioned in the Investigator Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

5.3. Documenting and Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs)

The Sponsor-investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the case report form (CRF). All SAEs also must be reported according to the OSU IRB guidelines.

5.3.1. Adverse Event Reporting Period

The AE reporting period for this study begins after first dose of study drug administration until 30 days after discontinuation of the study drug. All AEs and SAEs that are encountered during the protocol specified AE reporting period should be followed to resolution or until the investigator assesses the patient as stable, a new anti-cancer therapy is initiated, or the patient is lost to follow up or withdrawals consent Resolution/stable means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

5.3.2. Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation time points during the study. All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, clinically significant laboratory test, or other means will be recorded in the patient’s medical record and on the AE CRF and, when applicable, on an SAE/Event reporting form.

Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the investigational product (see following guidance), and any actions taken.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported.

An SAE will qualify for expedited reporting to regulatory authorities if the SAE is considered a Suspected Adverse Reaction and is not listed in the current Investigator’s Brochure (i.e., an unexpected event). To ensure consistency of AE and SAE causality assessments, investigators should apply the followinggeneral guideline:

Fatal	Adverse event resulted in death.

Unrelated	Another cause of the adverse event is more plausible; a temporal sequence cannot be established with the onset of the adverse event and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Possibly Related	There is a clinically plausible time sequence between onset of the adverse event and administration of the investigational product, but the adverse event could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible adverse event causes.
Definitely Related	The adverse event is clearly related to use of the investigational product.

5.4. Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy (See Section 4.2.4). Report any pregnancy that occurs in a patient or patient's partner from the time of consent to 30 days after the last dose of study drug. Record any occurrence of pregnancy in the patient's medical records and notify the treating physician within 24 hours of learning of the event. Abortion, whether therapeutic, elective or spontaneous, will be reported as an SAE.

A patient must immediately inform the investigator if the patient or patient's partner becomes pregnant from the time of consent to 30 days after the last dose of study drug. Any female patients receiving TP-0903 PO who become pregnant must immediately discontinue the drug. The investigator should counsel the patient, discussing any risks of continuing the pregnancy and any possible effects on the fetus. Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Report any pregnancy that occurs in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug. Record any occurrence of pregnancy on appropriate case report form and send it to Sumitomo Dainippon Pharma Oncology, Inc. (SDPO), or designee, within 24 hours of learning of the event. The pregnant female will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as an SAE.

5.5. Expedited Reporting Requirements for Serious Adverse Events

Institution/IND-Sponsor (OSU) of studies conducted under an IND must comply with the following safety reporting requirements. The Institution/IND-Sponsor (OSU) must submit each IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review and archive. A copy of this IND safety report must also be sent to Sumitomo Dainippon Pharma Oncology, Inc. (SDPO) within 24 hours. The Institution/IND-Sponsor (OSU) must notify FDA and Sumitomo Dainippon Pharma Oncology, Inc. (SDPO) of any serious, unexpected, suspected adverse reaction observed during the conduct of the study as soon as possible but in no case later than 15 calendar days after becoming aware of the occurrence. The Institution/IND- Sponsor (OSU) must notify FDA and Sumitomo Dainippon

Pharma Oncology, Inc. (SDPO) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but no later than 7 calendar days after the Institution/IND- Sponsor's (OSU) receipt of the information. Upon request from the FDA or Sumitomo Dainippon Pharma Oncology, Inc. (SDPO) additional data or information that the agency or Sumitomo Dainippon Pharma Oncology, Inc. (SDPO) deems necessary, must be reported as soon as possible but no later than 15 calendar days.

All SAEs (initial and follow-up information) will be reportedon an Event Reporting form and submitted to the OSU IRB within 24 hours of the discovery of the event or information. All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. If study drug is discontinued because of an SAE, this information must be included in the SAE report.

As noted above, in addition to reporting to the FDA, OSU will forward completed SAE and pregnancy forms to representatives of Sumitomo Dainippon Pharma Oncology, Inc. (SDPO).

Address and phone number of person/sponsor responsible for SAE management at Sumitomo Dainippon Pharma Oncology, Inc. (SDPO).

- SDPO Pharmacovigilance: BBISafety@bostonbiomedical.com

5.6. Routine Adverse Event Reporting

Adverse events which do not meet the definition of an SAE also require timely reporting dependent upon the grade of adverse event using CTCAE criteria, as defined by the protocol, attribution, and whether the event is expected or unexpected. All expedited adverse event reports must be reported to the CTO and OSU IRB, in accordance with the IRB reporting guidelines. These reports must be included in the in routine study data submission for the data safety monitoring report.

5.7. Type and Duration of Follow-up of Patients after Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the patient as stable, a new anticancer therapy is initiated, or the patient is lost to follow-up or withdraws consent.

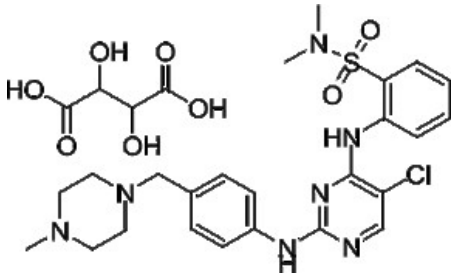
5.8. Data Safety Monitoring Plan (DSMP)

The data and safety monitoring plan for this phase 2 trial will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data completeness and patient safety at the AML program meetings (twice monthly) and at the Phase 1/ 2 weekly meeting of phase I investigators and staff. This review of the trials includes discussion of 'milestone' events including encounters of DLT or SAEs. All discussions will be documented in the minutes. The PI of the trial will review toxicities and responses of the trial, where applicable, at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with the sponsors, to determine if the trial should be terminated before completion. Serious adverse events will also be reviewed monthly and overall summary reports submitted by the PI to the OSU-CCC Data and Safety Monitoring Committee (DSMC) quarterly.

6. Pharmaceutical Information

6.1 Drug information

6.1.1 Drug substance and description

Generic name	TP-0903
Chemical name	2-{[5-chloro-2-({4-[{4-methylpiperazin-1-yl)methyl]phenyl}amino) pyrimidin-4-yl]amino}-N,Ndimethylbenzene-1-sulfonamide mono-tartrate salt
Other names	TP-0903, TP-0903 tartrate, HCL-2084, CCS-1589/STG-08
Chemical formula	$C_{28}H_{36}ClN_7O_8S$
Molecular weight	666.15 Daltons
Structure	

The drug substance is a white crystalline solid with a melting point around 296°C. The tartrate salt is soluble in water in a pH dependent manner; solubility increases with decreasing pH. In simulated gastric fluid (SGF) the solubility is 3.64 mg/mL. In pH 6.5 USP buffer solubility was poor, at 0.013 mg/mL. The drug is also soluble in various commonly used and pharmaceutically acceptable organic solvents.

TP-0903 forms a stable polymorph that can be consistently prepared. The compound is hygroscopic, and will pick up as much as 12% of its weight in water, with about 3% observed in the drug substance at the 6-month retest. Adding and subsequently removing water does not alter the polymorph form or have an impact on compound stability.

Drug is supplied in 4 mg, 25 mg, and 100 mg dosage strengths in hard gelatin capsules (size #3).

6.1.2 Preclinical absorption, distribution, metabolism, and excretion

6.1.2.1 Drug transporter effects

TP-0903 was tested in a bidirectional cell permeability assay using confluent monolayer of Caco- 2 cells in a 96-well based format. Fenoterol, propranolol and digoxin were used as controls. The efflux ratio (mean Papp A to B / mean Papp B to A) for TP-0903 was determined to be 1.49. Although mass recovery was low, this data suggests that TP-0903 is not a substrate for P-glycoprotein and is a compound of moderate permeability.

6.1.2.2 CYP450 effects

TP-0903 was evaluated for the inhibition of human cytochrome P450 isozymes using human liver microsomes in the presence of NADPH. At 10 µM, TP-0903 inhibited the activity of only isoform 2C19 by more than 50% out of the isozymes selected for testing. The IC50 values were determined against all the CYP isozymes used in the panel and, consistent with the percent inhibition data, only 2C19 was inhibited at a concentration lower than 10 µM (IC50 4.4 µM).

6.1.2.3 Liver microsome stability

The stability of TP-0903 in the presence of isolated microsomes from three species (human, rat and dog) were determined. The concentration of TP-0903 was measured by liquid chromatography- tandem mass spectrometry (LC-MS/MS) with reference to a standard curve. The half-life of TP-0903 ranged from 4.3 minutes in humans to 7.2 minutes in dogs.

6.1.2.4 Serum albumin binding

The serum albumin binding levels for TP-0903 were determined using human plasma in a dialysis plate-based assay. The free fraction of TP-0903 was measured by LC-MS/MS, by reference to a standard curve, and warfarin was used as a control. Data showed that TP-0903 has moderate human serum albumin binding (7% unbound). Recovery of protein bound drug (80.3 %) indicated the binding was reversible.

6.1.2.5 pKa of TP0903

The pKa values for TP-0903 were determined by titration using ultraviolet metric detection. The pKa was determined in aqueous buffer and separately in the presence of two co-solvents (80% MeOH and 60% DMSO). The final pKa values were calculated as an average of the three values obtained under different solvent conditions with the exception of pKa 3, for which the pKa value determined in DMSO was excluded. The final pKa values for pKa1, pKa2, and pKa3 were 3.02, 3.96, and 7.81, respectively.

6.1.2.6 pH-dependent solubility of TP0903

The equilibrium solubility of TP-0903 tartrate was determined in the following media: pH 3.5, 4.5, 5.5, 6.5 USP buffers, 0.1N HCl, simulated gastric fluid (SGF), fasted state simulated intestinal fluid, and fed state simulated intestinal fluid. As expected, based on the pKa determination, TP-0903 showed greatest solubility in acidic media.

6.2 Potential drug-drug interactions and concomitant medications

Clinicians should be aware of the possibility of drug interactions when TP-0903 is co-administered with drugs that are inhibitors or inducers of CYP2C19. Clinicians should refer to the products label and to the drug interaction website (***http://medicine.iupui.edu/clinpharm/ddis/main-table***). The website listing Cytochrome P450 inhibitors and inducers is updated on an ongoing basis and can be found at Appendix A.

6.3 Prohibited therapies

CYP2C19 substrates: Patients receiving CYP2C19 substrates prior to study treatment should be monitored closely. If possible, the investigator should cease patient's treatment with a CYP2C19 substrate prior to first dose, or at a minimum, switch to an alternative, but equivalent treatment that is not a CYP2C19 substrate. If a patient must remain on a CYP2C19 substrate, treatment with TP-0903 should proceed cautiously and the patient observed closely throughout the duration of the study. (See Appendix A)

Patients must not be taking H2-receptor antagonists such as cimetidine, ranitidine, and famotidine, or any proton pump inhibitors such as omeprazole, lansoprazole, esomeprazole and pantoprazole. Patients must stop these medications within 7 days prior to starting treatment. Antacids such as calcium carbonate, aluminum hydroxide, sodium bicarbonate should be avoided just prior to administration of TP-0903.

6.4. Study Drug Management

6.4.1. TP-0903 Drug Product

The study drug, oral TP-0903, is supplied by Sumitomo Dainippon Pharma Oncology, Inc. (SDPO) as a powder in hard gelatin capsules (size #3) and is manufactured under current Good Manufacturing Practices (cGMP) for investigational use.

TP-0903 capsules are formulated in 4-mg, 25-mg and 100-mg strengths. Further information is available in the 2019 DSUR, Regional Appendix 5, (page 64).

6.4.2 Study Drug Dispensing and Accountability

TP-0903 will be provided by the Sponsor to study centers as an investigational drug. The label and package for the drug product will be prepared in accordance with current regulatory requirements. The Investigator or designee will inventory and acknowledge receipt of all shipments of study drugs. The study drugs must be kept in a locked area with access restricted to designated study personnel.

An accurate and current accounting of the dispensing of the study drugs for each patient will be maintained on an ongoing basis by a member of the study site staff in a drug accountability log or equivalent document and will be verified by the sponsor's study monitor. All drug supplies, including unused study drug, must be accounted for. A final inventory of the total amount of drug received at each study site against the amount used and returned must be recorded in the study drug accountability log or an equivalent document. Inventory and dispense records must be readily available for inspection by the study monitor and/or auditor, and open to government inspection at any time. Study drug destruction will be handled by the sites of open/used vials. Unopened study drug vials should be returned to the Sponsor or CRO at the end of the study **after full drug accountability has been completed by the study monitor**.

6.4.3. Storage at Study Center

Study drug should be stored at room temperature. Protection from light is not necessary.

6.4.4. Accountability and Destruction of Investigational Medicinal Product

The Principal Investigator (or an authorized designee) at each participating institution must maintain a careful record of the inventory of the Investigational medicinal product received using the Drug Accountability Form. The study drug will be destroyed as per site's destruction policies and documentation of study drug destruction will be provided to the sponsor. Both used and unused study drug may be returned to Sumitomo Dainippon Pharma Oncology, Inc. (SDPO) if requested.

6.4.5. Drug Administration

TP-0903 will be provided by Sumitomo Dainippon Pharma Oncology, Inc. (SDPO). OSU must request study drug by submitting an order form directly to the drug depot in order for the study drug to be shipped to the site pharmacy. The Investigator (or designee) will verify and acknowledge receipt of all study drug shipments by signing and returning all required forms.

Study drug accountability records will be maintained at the site pharmacy and will be available for review by the study monitor during each monitoring visit and at the close out visit.

All medication must be stored in a secure area under the proper storage requirements with access restricted to the site staff pharmacist or designee(s).

The Investigational medicinal product should not be used for any purpose outside the scope of this protocol, nor can Investigational medicinal product be transferred or licensed to any party not participating in the clinical study. Sumitomo Dainippon Pharma Oncology, Inc.'s (SDPO) data for Investigational medicinal product are confidential and proprietary and shall be maintained as such by the Investigators.

7. Measurement of Effect

7.1. Response Criteria

Assessment of clinical response will be made according to 2017 ELN AML Recommendation [1]. The major criteria for judging response will include physical examination and examination of blood and bone marrow. All laboratory studies that are abnormal prior to study will be repeated to document the degree of maximal response.

Complete Remission without minimal residual disease (CRMRD-)

- If studied pre-treatment, CR with negativity for a genetic marker by realtime quantitative polymerase chain reaction (RT-qPCR), or CR with negativity by multi-color flow cytometry [Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)

Complete Remission (CR)*

CR requires all of the following:

- Bone marrow blasts <5%
- Absence of circulating blasts and blasts with Auer rods.
- Absence of extramedullary disease
- Absolute neutrophil count ≥1.0 x 10^9/L (1,000/µL).
- Platelet count ≥100 x 10^9/L (100,000/µL).

**MRD positive or unknown

Complete Remission with hematologic improvement (CRh)**

CRh meets all Criteria for CR except for residual thrombocytopenia and/or neutropenia defined as:

- Bone marrow blasts <5%
- Absence of circulating blasts on differential from peripheral blood (as determined by flow cytometry or blasts with morphologic Auer rods)
- Absence of extramedullary disease (disease outside of bone marrow not including findings on CT scan or other organ sites that have not been biopsied to confirm leukemia)
- Absolute neutrophil count > 0.5 x 10^9/L (500/µL)
- Platelet count > 50 x 10^9/L (50,000/µL)

Complete Remission with incomplete blood count recovery (CRi)**

CRi meets all CR criteria except for Residual neutropenia or thrombocytopenia:

- Bone marrow blasts <5%
- Absence of circulating blasts and blasts with Auer rods.
- Absence of extramedullary disease
- Residual neutropenia <1.0 x 10^9/L (1,000/µL) or
- Residual Thrombocytopenia <100 x 10^9/L (100,000/µL)

****If patients meet criteria for both CRh and CRi, they should be classified as CRh**

Morphologic leukemia free state (MLFS)***

- Bone marrow blasts <5%
- Absence of blasts with Auer rods.
- Absence of extramedullary disease
- No hematologic recovery required

*** Marrow should not merely be “aplastic”; at least 200 cells should be enumerated or cellularity should

be at least 10%

Partial Remission (PR)

PR meets all hematologic criteria of CR:

- Absolute neutrophil count ≥1.0 x 10^9/L (1,000/µL).
- Platelet count ≥100 x 10^9/L (100,000/µL).

And

- Decrease of bone marrow blast percentage to 5% to 25%
- Decrease of pretreatment bone marrow blast percentage by at least 50%

Stable Disease:

- Absence of CRMRD-, CR, CRh, CRi, PR, MLFS; and criteria for PD not met.

Progressive Disease (PD):

Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:

- >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or
- Persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in absolute neutrophil count (ANC) to an absolute level [>0.5 x 10^9/L (500/µL), and/or platelet count to >50 x 10^9/L (50,000/µL) non-transfused]; or
- >50% increase in peripheral blasts (WBC x % blasts) to >25 x 10^9/L (>25,000/µl) (in the absence of differentiation syndrome)****; or
- New extramedullary disease

**** Certain targeted therapies, for example, those inhibiting mutant IDH proteins, other kinases or other targets may cause a differentiation syndrome, i.e., a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate progressive disease. When this happens, it will be discussed with Beat AML Chief Medical Officer (CMO) on a case by case bases.

Treatment Failure

Treatment failure will be classified as one of the following:

- Primary refractory disease: No CRMRD-, CR, CRh, CRi and MLFS after defined period of time; excluding patients with death in aplasia or death due to indeterminate cause
- Death in aplasia: Deaths occurring ≥7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia
- Death from indeterminate cause: Deaths occurring before completion of therapy, or <7

days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available.

Recurrence

Recurrence on this study is defined below.

Recurrence for patients with prior morphological CRMRD-, CR, CRh, CRi or MLFS which is defined as:

- Evidence of morphologic relapse with the reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause. In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5-20% blasts, a bone marrow biopsy should be repeated within 1 week to distinguish relapse from bone marrow regeneration.
- The reappearance of cytologically proven extramedullary disease also indicates relapse.
- New CNS disease or other new sites of extramedullary involvement.

It should be noted that reappearance of a cytogenetic or molecular abnormality would be considered a cytogenetic or molecular relapse. In the absence of morphologic relapse, this would not be considered a relapse.

8. Correlative Studies

8.1. Collection of specimens.

See section 9 for time points for blood and/or marrow sampling for pharmacokinetic (PK) and pharmacodynamics (PD studies). At each time point, peripheral blood and bone marrow aspirate for PD studies will be collected. The samples will be processed at The OSUCCC Clinical Trials Processing Lab (CTPL) or the Leukemia Tissue Bank (LTB) Shared Resources.

8.2. Pharmacokinetic and pharmacodynamic studies in blood and marrow.

For standard techniques, only a brief summary is provided. For non-standard methods, additional information is provided on the technique to be utilized unless the method has been published. Blood samples for plasma PK will be transferred to the Pharmacoanalytical Shared Resource for bioanalytical analysis and estimation of pharmacokinetic parameters by Dr. Mitch Phelps and Dr. Sharyn Baker. Plasma, peripheral blood or bone marrow specimens for correlative PD studies will be transferred to Dr. Sharyn Baker's lab for processing of cells for single cell RNA-seq analysis of AML cells and bone marrow stromal cell in the Genomics Shared Resource (GSR), and multicolor flow cytometry and Fluorescence Activated Cell Sorting of AML cells b in the Analytical Cytometry Shared Resource (ACSR).

8.2.2 Sampling for Plasma Pharmacokinetic and Pharmacodynamic studies

All samples will be collected in green top (heparin) tubes. An intensive PK sampling scheme will be performed during course 1 in the patients enrolled during the phase I dose escalation phase. A limited sampling strategy will then be developed by Dr. Mitch Phelps for subsequent patients enrolled to the phase 2 portion of the trial.

Sampling for TP-0903 plasma pharmacokinetic assessments will occur at the following times (cycle 1 only):

Day 1 and 5: just before dosing and at 0.5, 1, 2, 4, 8, and 24 hours after drug administration. The 24-hour post-dose blood sample must be collected prior to the patient receiving TP-0903 on Day 2.

Day 12: just before dosing and at 0.5, 1, 2, 4, 8, and 24 hours after drug administration (prior to the next dose).

Plasma samples will be quantitated by a validated LC-MS/MS assay and pharmacokinetic parameters will be estimated using the software program Phoenix WinNonlin.

Sampling for TP-0903 plasma pharmacodynamics assessments for Axl, Gas6, FLT3 ligand and other cytokines/chemokines will occur at the following times:

Day 1: Pre-dose then 2 and 24 hours after drug administration (prior to the next dose)

Day 5 and 12: Pre-dose

On the first day (pre-dose) prior to each subsequent dose

Axl, Gas6, and FLT3 ligand will be determine by ELISA and other cytokines/chemokines will be determined using a multiplexed Luminex assay.

8.2.3. Sampling for Blood and Bone Marrow Pharmacodynamic Studies

All patients will have serial peripheral blood sampling where cells are isolated at screening, day 5, at count recovery, at day 28 of each subsequent cycle (when available) and at time of relapse (in responding patients). Samples will be collected in green top (heparin tubes).

Patients will also have serial bone marrow sampling at screening, day 5, the time of remission marrow, and at time of relapse.

In these samples we will assess the following*:

- In baseline samples and paired baseline/relapse samples, patterns of sensitivity and resistance patterns will be assessed by genomic, epigenomic, and transcriptomic profiling.

- In paired baseline and day 5 samples, differentially expressed genes in bone marrow stromal cells and AML cells will be assessed by single-cell RNA-eq.

- In paired baseline and day 5 samples, changes in pAXL, pFLT3, pSTAT5, pAURKA, cell cycle distribution, apoptosis will be assessed by multicolor flow cytometry.

- In paired baseline and day 5 samples, changes in metabolites and the flux of carbon derived from either isotopically labeled glutamine (13C,15N-Gln), glucose (13C6-Glc) or other substrates (e.g. palmitate, pyruvate, aspartate), will be determined using UPLC-MS/MS analysis

* Correlatives studies will be prioritized as above, depending on the amount of sample that is available for analysis.

** If a significant potential somatic, acquired mutation is identified patients will not be returned these results. However, if in the future it is decided that a germline analysis should be done, we will amend the protocol as appropriate and patients will be given the option to have these germline mutation results returned and undergo CLIA-certified germline testing for the potential pathogenic mutation.

9. Study Calendars

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Labs must be done prior to treatment on day 1 and maybe used for screening purposes as well. Scans and X-rays must be done <4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

TP-0903 monotherapy, (Cycle 1 only)

	Screening*	**Induction**																			**End-of Treatment[10]**	**Follow-up[11]**
		D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**D14**	**D15**	**D16**	**D18**	**D21**	**D28**		
Medical History	x																				x	
Complete Physical exam and ECOG PS	x																				x	x
Weight and BSA	x	x				x													x	x	x	
Symptom directed physical evaluation		x				x							x						x		x	
Vitals signs[1]	x	x				x							x							x	x	x
12-Lead Electrocardiogram (ECG)[2]	x	x																			x	
Serum pregnancy test[3]	x																				x **if fertile female only	
CBC[4]	x	x				x							x							x	x	x
Complete Serum chemistry[5]	x	x				x							x							x	x	x
Coagulation tests (PT and PTT)	x	x				x							x								x	
TP-0903 dosing in Clinic/Home/Inpatient[6]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Bone Marrow (BM) aspiration and biopsy[7]	x					x														x		

Adverse event and Toxicity evaluation[8]	x					x							x						x	x	x	
Correlative Studies[9]	x	x				x							x							x		

* *Treatment may begin on the same day as screening.

[1] Vital signs including blood pressure [BP], heart rate [HR], respiratory rate [RR], temperature [T] pulse oximetry (POX) and weight will be assessed prior to administration of TP-0903.

[2] ECGs: to be performed in the supine position at screening and day 1 of the first cycle.

[3] Applies to women of childbearing potential (WOCP) only. WOCP must have a negative pregnancy test within 2 weeks prior to the initiation of therapy.

[4] Complete Blood count with differential will be performed about twice weekly during induction and then as clinically indicated.

[5] Complete serum chemistries includes: Sodium, Potassium, Chloride, Bicarbonate, Creatinine, BUN, Glucose, Phosphorus, Albumin, Total bilirubin, SGOT (AST), SGPT (ALT), Alkaline phosphatase and LDH Women of childbearing potential must have a negative pregnancy test within 2 weeks prior to the initiation of therapy.

[6] TP-0903 will be administered per section 3.

[7] Bone marrow (BM) core biopsy and aspiration which will include cytogenetics, flow cytometry, targeted mutational analyses and morphologic assessment. Aspirate (10ml) only is required on day 5 of cycle 1 for correlative studies. Cycle 1, day 28 BM examination will require 10 ml aspirate to be collected for correlative studies. All the specimens for correlative studies will be processed at the OSU Leukemia Tissue Bank. Aspiration only may be acceptable for patients with BM biopsy that falls out of the window, provided AML diagnosis is unequivocal.

[8]Logistical issues that preclude patient visit on days noted will be allowed under special circumstances but must be discussed with the PI. Should such occasions arise, evaluations should be done as soon as feasible, preferably within 24-48hours

[9] Correlatives studies to be performed per section 8.2 (+/- 1 day). All patients will have serial peripheral blood sampling where cells are isolated at screening, day 5, day 12, at count recovery, at day 28 of each subsequent cycle (when available) and at time of relapse (in responding patients). Samples will be collected in green top (heparin tubes).

[10] End of Treatment visit, if applicable, is to be performed 30+7 days following patient last drug administration.

[11]Patients will be followed monthly for treatment failure until the time of transplant or maintenance therapy, at which time they will go to clinical follow-up, followed every 3 months for up to 2 years from registration and then every 6 months for up to 5 years from registration until relapse or death. Patients who end treatment for reasons other than relapse or a subsequent AML treatment (excluding transplant) will follow the same clinical follow-up schedule. Patients who relapse or receive a subsequent AML therapy (excluding transplant) will go to survival follow-up, followed every 6 months for 5 years from registration until death or the completion of the study. A survival follow-up visit can be conducted by phone or electronic contact with the patient or authorized representative.

TP-0903 monotherapy (Cycles 2-4 and maintenance)

	Cycles 2-4 and maintenance																		**End of Treatment[6]**	**Follow-up[7]**
	D1	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**D14**	**D15**	**D16**	**D18**	**D21**	**D28**	
Weight and BSA	x																		x	x	x
Physical examination	x					x														x	
Vitals signs	x					x						x							x	x	x
12-Lead Electrocardiogram (ECG)[1]	x																			x	
CBC	x					x						x							x	x	x
Complete Serum chemistry	x					x						x							x	x	x
Coagulation tests (PT and PTT)	x											x								x	
TP-0903 dosing in Clinic/Home/Inpatient[2]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x			
Bone Marrow (BM) aspiration and biopsy[3]																			x		
Adverse event and Toxicity evaluation[4]	x											x							x	x	
Correlative Studies[5]																			x		

[1] ECGs to be completed on day 1 of cycles 2, 3 and 4 only. Subsequent ECGs for cycle 5 and later may be completed based on clinical judgment.
[2] TP-0903 will be administered per section 3.
[3] Bone marrow (BM) core biopsy and aspiration which will include cytogenetics, flow cytometry, targeted mutational analyses and morphologic assessment is required **only on Cycle 4, day 28**. BM examination on cycle 4, day 28 will require 10 ml aspirate to be collected for correlative studies. However, if the patient has persistent cytopenias or if there is concern for relapse, BM examination can be completed sooner based on clinical judgment. All the specimens for correlative studies will be processed at the OSU Leukemia Tissue Bank. Aspiration only may be acceptable for patients with BM biopsy that falls out of the window, provided AML diagnosis is unequivocal.
[4]Logistical issues that preclude patient visit on days noted will be allowed under special circumstances but must be discussed with the PI. Should

such occasions arise, evaluations should be done as soon as feasible, preferably within 24-48hours. Toxicity assessments on day 12 are only required for cycles 2-4. Cycles 5 and beyond require toxicity assessment only on days 1 and 2.

[5] If applicable, peripheral blood will be collected for correlative studies at day 28 of each subsequent cycle (when available) and at time of relapse (in responding patients). Samples will be collected in green top (heparin tubes).

[6] End of Treatment visit, if applicable, is to be performed 30+7 days following patient last drug administration.

[7]Patients will be followed monthly for treatment failure until the time of transplant or maintenance therapy, at which time they will go to clinical follow-up, followed every 3 months for up to 2 years from registration and then every 6 months for up to 5 years from registration until relapse or death. Patients who end treatment for reasons other than relapse or a subsequent AML treatment (excluding transplant) will follow the same clinical follow-up schedule. Patients who relapse or receive a subsequent AML therapy (excluding transplant) will go to survival follow-up, followed every 6 months for 5 years from registration until death or the completion of the study. A survival follow-up visit can be conducted by phone or electronic contact with the patient or authorized representative.

10. Statistical Considerations

Overview

This phase 1b/2 study will be conducted in adult relapsed/refractory AML patients with FLT3 mutations treated with TP-0903 monotherapy.

The study will open to accrual initially to confirm tolerability of TP-0903 monotherapy using 50 mg daily. If in the first 6 patients treated, tolerability is not confirmed, then an additional 6 patients will be treated using 37 mg daily. Once a tolerable dose level of TP-0903 monotherapy is confirmed, full accrual to the phase 2 portion of the trial will continue. Design details described below assume that TP- 0903 monotherapy of 50 mg daily will be found tolerable.

Confirmation of Tolerability

TP-0903 monotherapy has been evaluated in solid tumors and found to be safe at a dose level of 50 mg daily. Although we do not anticipate any safety challenges in patients with AML at this dose level, an early tolerability assessment will be included for the first 6 patients enrolled based on a standard Rolling 6 design. If at most one in 6 patients has a DLT (See Section 4), then TP-0903 monotherapy at 50 mg daily will be considered safe and we will proceed with full accrual of the phase 2 study. If however TP-0903 monotherapy at 50 mg daily does not have acceptable toxicity in the first 6 patients, then an additional 6 patients will be treated at a lower dose level of TP-0903 at 37 mg daily, and the same rule will be used to confirm tolerability. Once a tolerable dose level is confirmed, enrollment can continue to the phase 2 component at that dose level.

Phase 2

At the confirmed tolerable dose level, TP-0903 monotherapy will be assessed for efficacy in a phase 2 component. Efficacy data from patients treated at the confirmed tolerable dose level during the tolerability check will be utilized in the phase 2 portion of the trial. Efficacy will be assessed using Simon's optimal two-stage phase 2 clinical trial design constraining type I and II errors to 10%.

The primary endpoint is the composite CR rate (CR/CRh), defined according to the 2017 ELN AML Recommendation. All eligible patients who start therapy will be considered evaluable for the primary endpoint and included in the denominator when calculating the composite CR rate. In relapsed/refractory adult patients with AML and FLT3 mutations, the ADMIRAL phase 3 study reported a composite CR rate of 34% with the FLT3 inhibitor gilteritinib, which led to improved overall survival (REF). We will therefore test the null hypothesis that the composite CR rate with TP-0903 is 30% versus the alternative hypothesis that it is 55%. By design, if 13 or more of 31 evaluable patients achieve CR/CRh, then there will be sufficient evidence to warrant further study of TP-0903 in this patient population. An interim analysis will occur after 13 patients have response determined. If 4 or fewer of 13 evaluable patients achieve CR/CRh, then the study will be terminated early. If 5 or more of 13 evaluable patients achieve CR/CRh then enrollment will continue as planned for all 31 evaluable patients. The probability of early termination under the null hypothesis is 0.65.

Toxicity will continue to be monitored throughout the phase 2 component, and a rule for excessive toxicity will be continuously applied. The monitoring rule will be evaluated during the first cycle of

therapy and will be based on the number of patients with a DLT out of the total number of patients treated (See Table Below). The number of patients with a DLT that would warrant accrual suspension corresponds to a high posterior probability that the true DLT probability is greater than an acceptable level (i.e., $Pr(p_i > 0.25 \mid data) > 0.95$), where the posterior probability is determined from a *Beta-Binomial* distribution with *Beta* (1, 1) as the prior on p_i. For example, if 9 patients have been treated in the phase 2 study, and 5 or more patients have a DLT, then this is sufficient evidence of excessive toxicity and accrual will be suspended while data are reviewed more closely, and a decision will be made to modify or close the study.

Table: Excessive Toxicity Rule, following the Confirmation of Tolerability in the First 6 Patients

Number of Patients	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Number with DLT	4	4	5	5	6	6	6	7	7	7
Number of Patients	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**
Number with DLT	8	8	8	9	9	9	10	10	10	11
Number of Patients	**27**	**28**	**29**	**30**	**31**					
Number with DLT	11	11	12	12	12					

Accrual

In the phase 1b component, we expect 6 patients and a maximum of 12 patients. In the phase 2 component, we will over-accrue by roughly 10% and target an accrual of 34 patients. Overall, we plan to accrue 40-46 patients. Based on past accrual of FLT3-mutated AML patients at OSU, we would anticipate accruing 1-2 patients per month, with accrual completed in 2-3 years.

Analysis of Secondary Endpoints

The degree of response will be summarized. Among eligible patients who achieve CR/CRh, disease-free survival (DFS) will be calculated. DFS is defined from the date of first CR/CRh until the first date of relapse/progression or death from any cause. Any patient without progression or death will be censored at the last date of clinical assessment. Further, patients who go to transplant prior to a progression will be censored at that time. The number and proportion of patients going to transplant prior to progression will be provided. Overall survival (OS) will be calculated for all eligible patients who start therapy. OS will be defined from the treatment start date until the date of death from any cause or date last known alive. Both time-to-event endpoints will be summarized by the Kaplan-Meier method. Associations between baseline variables and clinical outcome will be descriptive in nature due to the small sample sizes, primarily using

graphical displays to identify patterns and trends.

The maximum grade of each type of adverse event will be recorded for each patient and summarized. Treatment-related adverse events, defined as possibly, probably or definitely related to study treatment per NCI CTCAE v5.0 will be summarized separately. In addition, reasons for treatment discontinuation and number of TP-0903 cycles received will be summarized and used to assess tolerability. All patients who have received at least one dose of study drug will be evaluable for safety and tolerability assessments.

Initial analysis of plasma PK data will include standard compartmental and non-compartmental methods using Phoenix WinNonlin version 6.3 to generate estimates for relevant parameters (CL/F, V/F, Cmax, t1/2, AUC, etc.). Descriptive statistics will include means, standard deviations, and frequencies will be computed for all variables. Relationships between continuous variables will be performed using standard linear correlation and linear regression. Relationships between PK parameters such as Cmax and AUC with response will be performed using standard t-tests or Wilcoxon rank sum tests and illustrated using boxplots or other graphical displays. Differences in cytokines/chemokines, kinase signaling, and gene expression between days 1 and 5 will be evaluated using paired t-tests or Wilcoxon signed rank tests. Values will be log transformed as appropriate to reflect biologic plausibility. Patterns of sensitivity and resistance will be purely descriptive.

11. Ethics and Regulatory Requirements

11.1. Patient Protection

This study will be conducted according to the principles outlined by the Declaration of Helsinki and all applicable amendments; the International Conference of Harmonization 29 Version 05/21/2013 (ICH) Guidelines for Good Clinical Practice; the U.S. Food and Drug Administration (FDA) regulations regarding the conduct of clinical trials and the protection of human subjects; the Institutional Review Board (IRB), any applicable local health authority, and the Ethics Committee requirements.

11.2. Patient Information

Before entry into the trial all eligible patients will receive written patient information describing the aim of the study, as well as probable and possible side effects and risks. Oral information from one of the investigators or a delegated person at the institution will also be given, and the patient must have the opportunity to ask questions, and to consider participation together with his/her family members if applicable. It will be emphasized that the participation is voluntary and that it is the right of the patient to refuse further participation in the study whenever he/she wants and that this will not influence his/her subsequent care.

11.3. Informed Consent

Patient / Legally acceptable representative (LAR) (as applicable) written consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements and must conform to the ICH guidelines for Good Clinical Practice, prior to any study-specific screening procedures and trial entry. The written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative. A copy of the signed informed consent will be given to the patient or patient's legally authorized representative. The original signed consent must be maintained by the investigator at OSU available for inspection by the sponsor, or regulatory authority

at any time. The IRB will review the consent form for approval.

11.4. Ethics Board Approval

This study must obtain the approval of the protocol, the informed consent document and any other material used to inform the patient about the nature of the trial by a properly constituted IRB. The trial should not start until a copy of this written approval has been received by the Investigator. The Investigator will supply with a copy of the IRB approval letter stating that the study protocol and any subsequent amendments and informed consent have been reviewed and approved. The investigator or designee will be responsible for obtaining annual IRB re-approval throughout the duration of the study including at completion or termination.

Any changes to this protocol made by the Investigator must be in the form of a written amendment and the amendment will be appended to the protocol. Approval of amendments by the IRB is required prior to their implementation, unless there are overriding safety reasons.

Upon completion of the trial, the Investigator must provide the IRB and sponsor with a summary of the trial's outcome.

Annual Report: The PI will submit annual reports to the sponsor and FDA.

12. Documentation, Record Access and Maintenance of Study Records

12.1. Documentation of Patient's Participation

A statement acknowledging the participation of a patient in this clinical trial must be documented in the patient's medical records along with the signed ICF.

12.2. Source Documentation

Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the Case Report Forms (CRFs).

12.3. Regulatory Requirements

Before the investigational drug is shipped to the Investigator, the Investigator will provide to the sponsor with a copy of the IRB approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

12.4. Patient Confidentiality and Access to Source Data/Documents

12.4.1. Patient Identification

A sequential unique identification number will be attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. A patient will not be identified by name, only by his/her initials. The patient's name or any identifying information will not appear in any reports published as a result of this study. In order to avoid identification errors, patient's initials and date of birth (as permitted by the ethics board) will also be reported on the study forms. Any

research information obtained about the patient in this study will be kept confidential. However, information obtained from individual patient's participation in the study may be disclosed with his/her consent to the health care providers for the purpose of obtaining appropriate medical care. The patient's medical records/charts, tests will be made available to the sponsor Sumitomo Dainippon Pharma Oncology, Inc. (SDPO), the US FDA, and the IRB and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A patient's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A patient may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the patient will not be able to remain in the study. No new information that identifies the patient will be gathered after that date. However, the information about the patient that has already been gathered and transferred may still be used and given to others as described above in order to preserve the scientific integrity and quality of the study.

12.5. Confidentiality of the Study

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the IRB. The Investigator shall permit sponsor, authorized agents of the sponsor, and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all source documents. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of sponsor.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

12.6. Registration of Clinical Trial

Prior to the first patient being registered/enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered appropriately to remain eligible for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE).

12.7. Maintenance of Study Records

To enable evaluations and/or audits from Regulatory Authorities, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition.

According to 21 CFR 312.62(c), the Investigators shall retain records required to be maintained under this part for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the Investigator shall retain these records until two years after the

investigation is discontinued and the FDA is notified. The Investigator must retain protocols, amendments, IRB approvals, copies of the Form FDA 1572, signed and dated consent forms, medical records, case report forms, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

If the investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records.

13. Administrative Procedures

13.1. Protocol Deviations and Violations

All violations or deviations are to be reported to the site's IRB (as per the ethics board's guidelines). All IRB correspondence is to be forwarded to the sponsor. The site must notify the sponsor immediately of any protocol violations.

13.2. Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the trial for any reason but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigators must contact all participating patients immediately after notification. Standard therapy and follow-up for patients will be assured and, where required by the applicable regulatory requirement(s), the relevant regulatory authority(ies) will be informed.

The IRB will be informed promptly and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all CRFs completed to the greatest extent possible in the case of a premature discontinuation of study.

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Appendix A. Cytochrome P450 Drug Interaction Table

Physicians should be aware of the possibility of drug interactions when TP-0903 is co-administered with drugs that are inhibitors or inducers of CYP2C19. Physicians should refer to the products label and to the drug interaction website provided below. The website listing Cytochrome P450 inhibitors and inducers is updated on an ongoing basis and can be found at ***http://medicine.iupui.edu/clinpharm/ddis/main-table***. Below is a snapshot of the website as of August 2018. **Attention should be focused on the 2C19 column**. Please note that the website also lists substrates of CYP2C19.

Cytochrome P450 Drug Interaction Table

Substrates							
1A2	**2B6**	**2C8**	**2C9**	**2C19**	**2D6**	**2E1**	**3A 4,5,6**
amitriptyline caffeine2 clomipramine clozapine cyclobenzaprine duloxetine estradiol fluvoxamine haloperidol imipramine N-DeMe mexiletine nabumetone naproxen olanzapine ondansetron phenacetin1→ acetaminophen → NAPQI propranolol riluzole ropivacaine tacrine2	artemisinin bupropion1 cyclophosphamide efavirenz1 ifosphamide ketamine meperidine methadone nevirapine propafol selegiline sorafenib	amodiaquine cerivastatin paclitaxel repaglinide sorafenib torsemide	NSAIDs: diclofenac ibuprofen lornoxicam meloxicam S- naproxen→ Norpiroxicam suprofen Oral Hypoglycemic Agents: tolbutamide glipizide Angiotensin II Blockers: losartan irbesartan Sulfonylureas:	PPIs: esomeprazole lansoprazole omeprazole2 pantoprazole Anti-epileptics: diazepam→ Nor phenytoin(O) S-mephenytoin1 phenobarbitone amitriptyline carisoprodol citalopram chloramphenicol clomipramine clopidogrel cyclophosphamide hexobarbital	tamoxifen Beta Blockers: carvedilol S-metoprolol propafenone timolol Antidepressants: amitriptyline clomipramine desipramine fluoxetine imipramine paroxetine venlafaxine Antipsychotics: haloperidol perphenazine risperidone→9-OH	Anesthetics: enflurane halothane isoflurane methoxyflurane sevoflurane acetaminophen→ NAPQI aniline2 benzene chlorzoxazone1 ethanol N,N- dimethylformamide theophylline→8- OH	Macrolide clarithromycin erythromycin2 (not NOT telithromycin Anti-arrhythmics: quinidine→3-OH Benzodiazepines: alprazolam diazepam→3OH midazolam1 triazolam2 Immune: cyclosporine tacrolimus (FK506) HIV indinavir

theophylline2 tizanidine triamterene verapamil (R)warfarin zileuton zolmitriptan			glyburide glibenclamide glipizide glimepiride tolbutamide amitriptyline celecoxib fluoxetine fluvastatin glyburide nateglinide phenytoin-4-OH2 rosiglitazone tamoxifen torsemide valproic acid S-warfarin zakirlukast	imipramine N-DeME indomethacin labetalol R- mephobarbital moclobemide nelfinavir nilutamide primidone progesterone proguanil propranolol teniposide R-warfarin→8-OH voriconazole	thioridazinezuclopenthixol alprenolol amphetamine aripiprazole atomoxetine bufuralol1 chlorpheniramine chlorpromazine clonidine codeine (→O-desMe) debrisoquine2 dexfenfluramine dextromethorphan1 donepezil duloxetine encainide flecainide fluvoxamine lidocaine metoclopramide methoxyamphetamine mexiletine minaprine nebivolol nortriptyline ondansetron oxycodone perhexiline phenacetin phenformin promethazine propafenone propranolol risperidone sparteine		nelfinavir ritonavir saquinavir Prokinetic: cisapride Antihistamines: astemizole chlorpheniramine terfenadine2 Calcium amlodipine diltiazem felodipine lercanidipine nifedipine2 nisoldipine nitrendipine verapamil HMG: atorvastatin cerivastatin lovastatin NOT NOT simvastatin Steroid estradiol hydrocortisone progesterone testosterone1

					tramadol		Miscellaneous: alfentanil aprepitant aripiprazole boceprevir buspirone carbamazepine cafergot caffeine→TMU cilostazol cocaine codeine-N-demethylation dapsone dexamethasone dextromethorphan 2 docetaxel domperidone eplerenone fentanyl finasteride gleevec haloperidol irinotecan LAAM lidocaine methadone nateglinide nevirapine ondansetron pimozide propranolol quetiapine quinine

							risperidone romidepsin salmeterol sildenafil sirolimus sorafenib sunitinib tamoxifen taxol telaprevir terfenadine torisel trazodone vemurafenib vincristine zaleplon ziprasidone zolpidem
Inhibitors							
1A2	**2B6**	**2C8**	**2C9**	**2C19**	**2D6**	**2E1**	**3A 4, 5, 6**
fluvoxamine ciprofloxacin cimetidine amiodarone efavirenz fluoroquinolones fluvoxamine furafylline1 interferon methoxsalen mibefradil ticlopidine	clopidogrel thiotepa ticlopidine voriconazole	gemfibrozil2 trimethoprim 2 glitazones montelukast1 quercetin1	fluconazole2 amiodarone efavirenz fenofibrate fluconazole fluvastatin fluvoxamine2 isoniazid lovastatin metronidazole paroxetine phenylbutazone probenicid sertraline	PPIs: esomeprazole lansoprazole omeprazole2 pantoprazole Other: chloramphenicol cimetidine felbamate fluoxetine fluvoxamine indomethacin isoniazid ketoconazole	bupropion cinacalcet fluoxetine paroxetine quinidine1 duloxetine sertraline terbinafine amiodarone cimetidine celecoxib chlorpheniramine chlorpromazine citalopram clemastine	diethyl-dithiocarbamate2 disulfiram	HIV Antivirals: indinavir nelfinavir ritonavir clarithromycin itraconazole1 ketoconazole nefazodone saquinavir suboxone telithromycin aprepitant erythromycin fluconazole grapefruit juice

			sulfamethoxazole sulfaphenazole1 teniposide voriconazole zafirlukast	modafinil Oral contraceptives: oxcarbazepine probenicid ticlopidine2 topiramate voriconazole	clomipramine cocaine diphenhydramine doxepin doxorubicin escitalopram halofantrine haloperidol histamine H1 receptor antagonists hydroxyzine levomepromazine methadone metoclopramide mibefradil midodrine moclobemide perphenazine promethazine ranitidine reduced-haloperidol ritonavir ticlopidine tripelennamine		verapamil2 diltiazem cimetidine amiodarone chloramphenicol boceprevir ciprofloxacin delaviridine diethyl-dithiocarbamate fluvoxamine gestodene imatinib mibefradil mifepristone norfloxacin norfluoxetine starfruit telaprevir voriconazole
Inducers							
1A2	**2B6**	**2C8**	**2C9**	**2C19**	**2D6**	**2E1**	**3A 4, 5, 6**
broccoli brussel sprouts carbamazepine char-grilled meat insulin methylcholanthrene 1 modafinil	artemisinin carbamazepine efavirenz nevirapine phenobarbital phenytoin rifampin	rifampin	carbamazepine enzalutamide nevirapine phenobarbital rifampin secobarbital St. John's Wort	carbamazepine efavirenz enzalutamide norethindrone NOT pentobarbital prednisone rifampicin	dexamethasone rifampin	Ethanol isoniazid	HIV Antivirals: efavirenz nevirapine barbiturates carbamazepine enzalutamide glucocorticoids modafinil

nafcillin beta-naphthoflavone1 omeprazole1 rifampin tobacco				ritonavir St. John's Wort			oxcarbazepine phenobarbital2 phenytoin2 pioglitazone rifabutin rifampin St. John's Wort troglitazone