OSU Protocol # 14078:

TITLE: Phase II study of ponatinib for advanced cancers with genomic alterations in fibroblastic growth factor receptor (FGFR) and other genomic targets (KIT, PDGFRα, RET FLT3, ABL1)

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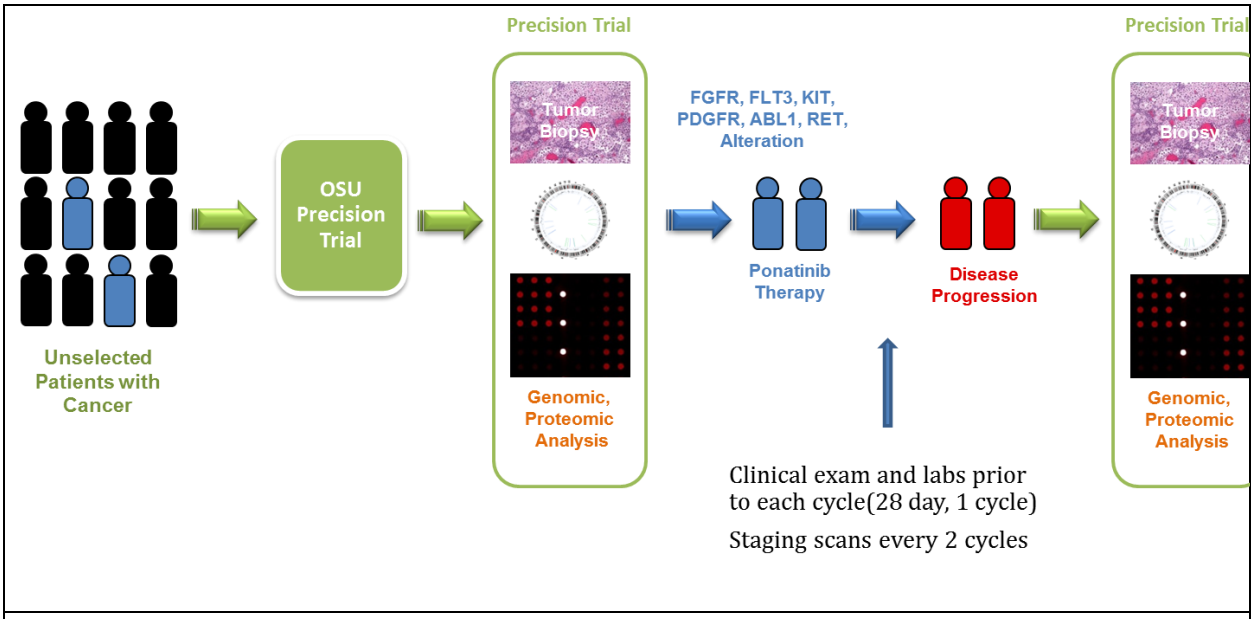

Figure 1: Trial outline is shown

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1. OBJECTIVES

1.1 Primary Objectives

To evaluate the response of ponatinib in solid tumor patients with *FGFR* alterations.

1.2 Secondary Objectives

- To assess the safety and tolerability of ponatinib in advanced solid tumors with genomic *FGFR* alterations
- To assess progression free survival (PFS) and overall survival (OS) with ponatinib
- To determine candidate genomic and proteomic biomarkers of sensitivity and resistance to ponatinib using unbiased high throughput approaches (exome, transcriptome, RPPA)
- To assess response of ponatinib in advanced cancers with subsets of genomic *FGFR* alterations (fusions vs. amplifications vs. mutations)
- To assess response of ponatinib by tumor type

2. BACKGROUND

2.1 Study Disease(s)

Fibroblast growth factors (FGF) and their receptors (FGFRs) play essential roles in mediating cell proliferation, migration, angiogenesis, and survival.[1] FGFR belongs to the receptor tyrosine kinase (RTK) receptor family of proteins that also includes epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) family. FGFR family has 5 members (FGFR1-4 and FGFRL1) and 18 known ligands. The ligand-receptor interaction is stabilized by the formation of a ternary complex involving heparan sulfate proteoglycans (HSPG) or Klotho proteins.[2] Specificity in signaling is afforded based on tissue specific expression as well as interaction of FGFs, FGFRs, HSPGs, and Klotho proteins. FGFR activation leads to phosphorylation of FGFR substrate 2 (FRS2) and recruitment of growth factor-receptor bound 2 (GRB2) resulting in the activation of downstream mitogen activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/ Akt pathway. Additionally, activation of PKC is carried out independent of FRS2, through phospholipase C-γ (PLC-γ) mediated activation of phosphatidylinositol 3,4,5-triphosphate (PIP3) and diacylglycerol (DAG).

Deregulation of FGF-FGFR signaling has been recognized in multiple solid tumors including breast, prostate, bladder, stomach, endometrial and lung cancers.[1] Cancer genomic analyses have identified alterations in *FGFR* including point mutations, amplifications, and gene fusions. A list of common *FGFR* alterations in cancers is shown in Table-1. Mutations in *FGFR2* have been observed in about 10-15% of endometrial cancers and these have also shown sensitivity to FGFR inhibitors.[1] *FGFR3* mutations are reported in approximately 70% of low grade urothelial carcinomas.[3] Mutations in *FGFR4* are identified in 7 to 8% of rhabdomyosarcomas.[4] Approximately, 10% of the patients with breast cancer harbor the 8p11-12 amplicon leading to overexpression of *FGFR1*[5] in the highly proliferative luminal B breast cancers and has been shown to correlate with resistance to hormonal therapy leading to worse outcomes.[6, 7] Amplification of *FGFR2* has also been implicated in 4% of triple-negative breast cancers (TNBC)[8], particularly in BRCA2 associated tumors.[9] *FGFR1* amplification has also been

reported in 22% of squamous lung carcinomas.[10] Gene fusions involving *FGFR1* have been reported in alveolar rhabdomyosarcomas, 8p11 myeloproliferative syndrome and glioblastomas.[11, 12] *FGFR3-MMSET* fusion resulting from t(4:14) translocation, is seen in 15 to 20% of patients with multiple myeloma and is associated with a worse prognosis.[13] Recently, the Chinnaiyan Lab (Co-Investigator) at University at Michigan identified novel *FGFR2 and FGFR3* fusions in diverse solid tumors including biliary, breast, and prostate cancers. They further demonstrated that the *FGFR* fusions result in constitutive activation of FGFR signaling, substantiating that *FGFR* fusions could potentially be a clinically important target.[14] The widespread prevalence of *FGFR* activating alterations across multiple cancer subtypes provides an excellent opportunity to assess if FGFR inhibitors would lead to meaningful clinical responses among patients with activating alterations in *FGFR*.[15-18]

FGFR Alteration	Cancer	Prevalence
Amplifications		
FGFR1	Squamous Lung Cancer[18]	22%
	Breast Cancer (Estrogen Receptor-Positive)[19]	10%
FGFR2	Gastric Cancer[20]	9%
	Breast Cancer (Triple Negative)[8]	4%
Mutations		
FGFR2	Endometrial Cancer[16]	10%
	Melanoma[11]	10%
FGFR3	Bladder Cancer (Invasive)[3]	15%
	Multiple Myeloma[21]	1%
FGFR4	Rhabdomyosarcoma[4]	8%
Fusions/ Translocations		
FGFR1	8p11 Myeloproliferative Syndrome[22]	>90%
	Alveolar Rhabdomyosarcoma[23]	80%
	Glioblastoma Multiforme[12]	3%
FGFR2	Cholangiocarcinoma[14]	Rare (<1%)
	Breast Cancer[14]	Rare (<1%)
	Prostate Cancer[14]	Rare (<1%)
	Thyroid cancer[14]	Rare (<1%)
FGFR3	Multiple Myeloma[13]	12%
	Peripheral T Cell Lymphoma[24]	Rare (<1%)
	Glioblastoma Multiforme[12]	3%
	Bladder Cancer[14]	Rare (<1%)
Table 1: Distribution and prevalence of FGFR genomic alterations		

2.2 Investigational New Drug

2.2.1 *Ponatinib (AP24534)*

Ponatinib (Takeda Pharmaceutical Company; Iclusig) is a FDA-approved oral drug for the treatment of adult patients with T315I-positive chronic myeloid leukemia (CML) (chronic phase, accelerated phase, or blast phase) or T315I-Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL). It is also indicated in the treatment of adult patients with chronic phase, accelerated phase, or blast phase CML or Ph+ ALL for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated.[25] In addition to BCR-ABL, it has activity against FGFR, KIT, platelet-derived growth factor receptor (PDGFR), RET and FLT3 kinases.[17, 26]

The following information is summarized from the Ponatinib Investigator's Brochure (4.2014) and USPI (12.2013).

Mechanism of Action

AP24534 (international non-proprietary name [INN]: ponatinib) is a novel, orally-available TKI. In addition to BCR-ABL, ponatinib is also a potent inhibitor of members of the FGFR family, which are implicated in a variety of solid tumors. Ponatinib also inhibits other kinases, including KIT, RET, VEGFR, PDGFRα, FMS-like tyrosine kinase 3 (FLT3) receptor tyrosine kinase expressed on vascular endothelium (TIE2), and tyrosine kinase homologous to the Rous sarcoma virus oncogene protein PP60 (SRC). Taken together, the kinase inhibition profile of ponatinib suggests the potential for clinical activity in other hematologic and non-hematologic malignancies in addition to CML.

Preclinical data:

FGFR

Ponatinib potently inhibited the *in vitro* kinase activity of all 4 FGFRs (IC50: 2 to 18 nM). In Ba/F3 cells dependent on activated variants of native FGFR1-4 (via fusion to a TEL dimerization domain), ponatinib inhibited viability with IC50s of 14-47 nM. In Ba/F3 cells engineered to express activated FGFR1-4, ponatinib potently inhibited FGFR mediated signaling and viability with IC50s <40 nM, with substantial selectivity over parental Ba/F3 cells. Similar potency was observed in human embryonic kidney (HEK-293) cells transiently transfected to overexpress full-length FGFR1-3, as measured by inhibition of FGFR phosphorylation (IC50s 15-35 nM). In a panel of 14 cell lines representing multiple tumor types (endometrial, bladder, gastric, breast, lung, and colon), and containing FGFRs dysregulated by a variety of mechanisms, ponatinib inhibited FGFR mediated signaling with IC50s <40 nM and inhibited viability with IC50 values of 7 to 181 nM.[17] Ponatinib had substantially reduced activity (IC50s>300nM) against cells that did not contain a deregulated FGFR. Daily oral dosing of ponatinib (10 to 30 mg/kg) to mice reduced tumor growth and inhibited signaling in all 3 FGFR-driven models examined. These results demonstrate that ponatinib is a potent inhibitor of all 4 FGFR family members with activity in multiple FGFR-driven cancer types.

The HEK cell system was used to further assess ponatinib's ability to inhibit FGFR mutations. Of 12 FGFR2 mutants tested, ponatinib inhibited the activity of 10 with high potency and 2 with moderate potency. The 10 mutants inhibited most potently (IC50 < 45 nM) included the 2 that together account for over half of those observed in endometrial cancer (S252W and N550K). Also included were the mutants located in all 4 functional domains: the LB domain (S252W and P253R), the EC domain (Y376C and W290C), the TM domain (C383R), and the KD domain (I548V, N550K, G584W, K660N and R738K). The 2 FGFR2 mutants inhibited with moderate potency (IC50: 113 nM to 152 nM) were N550H and K660E. Ponatinib had moderate potency against the FGFR3-S249C EC domain mutant (IC50: 128 nM) commonly found in bladder cancer, and did not inhibit the less common K652E KD mutant. Ponatinib potently inhibited the FGFR1-N546K KD mutant found in glioblastoma multiforme (IC50: 18 nM).

RET

RET kinase is deregulated by activating mutations or fusion gene formation in multiple cancers. RET point mutations are found in 50-95% of medullary thyroid cancers (MTC) and translocations involving RET occur in papillary thyroid cancer.[27] Recently, a novel translocation that results in formation of a KIF5B-RET fusion oncogene has been identified in 1-2% of non-small cell lung cancers (NSCLC).[28] Ponatinib inhibits the in vitro kinase activity of RET with an IC50 of 0.16 nM. In Ba/F3 cells dependent on activated RET (activated via fusion to the TEL dimerization domain) ponatinib potently inhibited viability with an IC50 of 8 nM. In Ba/F3 cells dependent on expression of the most common, naturally-occurring activated variants of RET found in MTC and NSCLC, ponatinib potently inhibits viability of RET C634R, RET M918T, and KIF5B-RET cells with IC50s of 2, 3, and 11 nM, respectively. Consistent with these effects being due to inhibition of RET, ponatinib inhibited RET phosphorylation with similar potency in each respective cell line (IC50s of 4, 2, and 9 nM).

PDGFR and KIT

In *in vitro* assays, ponatinib has been shown to inhibit the kinase activity of PDGFRα (1.1 nM IC50), as well as PDGFRβ. In Ba/F3 cells dependent on activated PDGFRα, ponatinib inhibited viability and PDGFRα phosphorylation with IC50s of 1 and 5 nM, respectively and in a cell line containing an activated PDGFRα (FIP1L1- PDGFRα fusion), ponatinib inhibited viability and PDGFRα phosphorylation with IC50s of 0.5 and 0.6 nM, respectively. Ponatinib also potently inhibited viability of Ba/F3 cells expressing activated PDGFRα containing the gatekeeper T674I mutation with an IC50 of 2 nM.[29]

Ponatinib has been shown to inhibit the kinase activity of KIT (12.5 nM IC50). In cellular assays, ponatinib also inhibited activated variants of KIT and variants with secondary mutations that confer clinical resistance to other KIT inhibitors approved for the treatment of gastrointestinal stromal tumors (GIST), imatinib and sunitinib. Ponatinib potently inhibited viability of Ba/F3 cells expressing activated KIT (exon 11 Δ557-8), activated KIT with a secondary T670I gatekeeper mutation, and activated KIT with the secondary activation loop (A-loop) mutations D816H, D820A, N822K, and A829P (IC50s <15 nM for all mutants).[29] Ponatinib potency is slightly reduced versus the KIT exon 9 primary mutant (IC50 = 56 nM), or when V654A is present as a secondary mutation (IC50 = 59 nM).Takeda is supporting a separate

clinical trial investigating the benefit of ponatinib for the treatment of advanced gastrointestinal tumor (GIST) with KIT mutations refractory to two different tyrosine kinase inhibitors.

FLT3

Ponatinib inhibits the *in vitro* kinase activity of FLT3 with an IC50 of 12.6 nM. Studies conducted to examine the activity of ponatinib in models of FLT3-driven AML.[30] Ponatinib potently inhibited phosphorylation of FLT3-ITD and viability of MV4-11 cells with IC50s ≤2 nM. In contrast, ponatinib inhibited viability of RS4-11 cells, which express native FLT3, with an IC50 >100 nM. MV4-11 cells were used to test the antitumor activity of ponatinib in vivo. In a xenograft model, significant inhibition of tumor growth occurred with daily oral dosing of ponatinib at doses of 2.5 mg/kg and greater. After administration of a single dose of ponatinib, a dose-dependent inhibition of FLT3-ITD phosphorylation in the tumor was observed that was associated with the degree of antitumor activity. In an in vitro kinase assay, ponatinib did not potently inhibit FLT3 containing a D835Y activating mutation (IC50: 948 nM).

Pharmacodynamics

In a cell-based assay, ponatinib concentrations of 20 nM (10.65 ng/mL) were sufficient to suppress most BCR-ABL mutant clones. However, ponatinib concentrations of 40 nM (21.3 ng/mL) were required to suppress T315I gatekeeper mutants. The median and range of steady-state Cmax and trough (Cmin) concentrations of ponatinib following 29 days of once-daily dosing of 15 mg, 30 mg and 45 mg are listed below.

Median, Maximum, and Minimum Ponatinib Exposure at Steady-State by Dose

Dose	Median Cmax (Range) (nM)	Median Cmin (Range) (nM)
15 mg QD (n = 8)	49 (23 – 105)	28 (11 – 68)
30 mg QD (n = 9)	125 (67 – 178)	54 (41 – 89)
45 mg QD (n = 21)	161 (64 – 336)	67 (22 – 137)

Pharmacokinetics

Absorption

The AP24534-07-101 Phase 1 study, evaluated the safety, tolerability, maximum tolerated dose (MTD) and biologic properties of ponatinib, using a sequential, dose escalation, 3+3 design with expansion of some cohorts to provide additional safety data at each dose level (2, 4, 8, 15, 30, 45, or 60 mg/day).[25] Dose escalation began at 2 mg and extended up to 60 mg once-daily oral dosing. The pharmacokinetic profiles of parent ponatinib and AP24567 (a CYP3A4/5-mediated desmethyl-ponatinib metabolite) were characterized on the first day of study treatment, Cycle 1 Day 1 (C1D1), and on Day 1 of Cycle 2 (C2D1). All patients in the 2, 4, 8, 15, and 30 mg cohorts were given the capsule formulation. However, a total of 24 of 50 patients in the combined 45 and 60 mg cohorts received a tablet formulation instead of the capsule. In the 45 mg and 60 mg cohorts, there was no evidence of statistically important differences between the tablet and capsule formulations based on either C_{max} (p=0.53) or AUC0-τ (p=0.64). Therefore, the capsule and tablet pharmacokinetic data were pooled together in summaries by dose in this analysis. As of 06 January 2014, 24 (29.6%) of the 81 enrolled

patients remained on therapy. Median patient age was 55 years; median time elapsed from original diagnosis to enrollment was 5.5 years. Prior therapies in CML and Ph+ ALL patients included imatinib (97%), dasatinib (89%), nilotinib (55%), and other standard and investigational therapies; 94% of patients experienced a failure of 2 or more prior TKIs, while 62% had experienced a failure of 3 or more TKIs.

Ponatinib plasma level data indicated that C_{max} occurred 4 to 6 hours after dosing, and steady-state t1/2 was between 20 and 29 hours for doses ≥15 mg. The median t_{max} in the 15 through 60 mg cohorts was 4 hours. At 45 mg (the recommended therapeutic dose), steady-state geometric mean (GeoMean) C_{max} and minimum plasma concentration (C_{min}) (both ng/mL), AUC from time 0 to the end of the dosing period (eg, 24 hours; AUC0-τ; h.ng/mL), and t1/2 (hours) were 77.41 (145.3 nM; percent coefficient of variance [%CV] 49.9), 34.22 (64.3 nM; %CV 45.4), 1296 (%CV 48.1), and 22 (%CV 55.5), respectively. The mean steady-state C_{max} and AUC appeared to increase in a manner approximately proportional with increasing dose, particularly in the 15- to 60-mg dose range. C_{max} of 25.82 ng/mL (48.48 nM) at the 15 mg dose, and steady-state trough concentrations (C_{trough}) of 29.85 ng/mL (56.05 nM) at the 30 mg dose exceeded the 40 nM exceeded the concentration (40nM) required for suppression of BCR-ABL. Following ingestion of either a high-fat or low-fat meal by 22 healthy volunteers, plasma ponatinib exposures (AUC and C_{max}) were not different when compared to fasting conditions. The aqueous solubility of ponatinib is pH dependent, with higher pH resulting in lower solubility. Drugs that elevate the gastric pH may reduce ponatinib bioavailability.

Distribution

Ponatinib was very highly bound to plasma protein of mouse, rat, monkey and human (≥99.8%). The blood to plasma partition ratios for ponatinib was 1.20, 1.13, 1.11, and 0.96 respectively, in mouse, rat, monkey, and human blood. The percent distribution into RBCs was 49.2%, 48.8%, 48.5%, and 46.8%, respectively in mouse, rat, monkey, and human blood. These results show ponatinib is equally distributed into RBCs and plasma. The geometric mean (CV%) apparent steady state volume of distribution is 1223 liters (102%) following oral administration of ponatinib 45 mg once daily for 28 days in patients with cancer. Ponatinib is a weak substrate for both P-gp and BCRP *in vitro*. Ponatinib is not a substrate for organic anion transporting polypeptides (OATP1B1, OATP1B3) and organic cation transporter 1 (OCT1) *in vitro*. In vitro, ponatinib bound to human plasma proteins (at 145 nM) was not displaced from the binding sites by other highly protein-bound drugs: ibuprofen, salicylic acid, propranolol, nifedipine, or warfarin.

Metabolism

Ponatinib was not extensively metabolized in rat and human microsomes, but was metabolized to a moderate extent in monkey liver microsomes. The rate of metabolism (pmol/min/mg of protein) was 38.7, 83.5, and 36.2, respectively, in rat, monkey, and human liver microsomes. Major biotransformation pathways in liver microsomes were the formation of N-desmethyl ponatinib (AP24567), and ponatinib N-oxide (AP24734). Metabolite AP24600 was not observed in these in vitro systems. Ponatinib was not metabolized by rhCYPs (recombinant human CYPs) 1A2, 2C9, and 2E1.rhCYPs 3A5 and 2C19 metabolized ponatinib to AP24567 and AP24734, but only to a very low extent of 3% to 5%. At least 64% of a ponatinib dose undergoes phase I and phase II metabolism. Ponatinib was mainly metabolized by CYP3A4 (52%), to a

moderate extent by CYP2C8 (30.4%), and to lesser extent by CYP2D6 (14.4%). Results from the CYP-inhibition studies, using isoform-specific chemical inhibitors and inhibitory monoclonal antibodies, show that ponatinib was mostly metabolized by CYP3A4, and to a lesser extent by CYP2D6, CYP2C8, and CYP3A5.Since ponatinib is mostly metabolized by CYP3A4/5, it is likely to have drug-drug interactions with co-administered CYP3A4/5 inhibitors. Ponatinib is an inhibitor of P-glycoprotein, BCRP, and bile salt export pump (BSEP).

Elimination

The excretion of [14C] ponatinib in humans was investigated following a single target oral dose of 45 mg/100 μCi. [14C] Ponatinib (drug powder in capsules) was administered orally to each of 6 subjects (age 19 to 45 years) as three 15-mg capsules (each containing ~36.7μCi) with 240 mL of non-carbonated water in the fasted state. Whole plasma, urine, feces, and toilet tissue wipes were collected up to the time of discharge (10 to 14 days post dose, different for each subject). The mean percentage radioactive dose recovered was 5.38 ± 0.93% and 86.63 ± 2.37%, in urine and feces respectively. In human plasma following an oral dose of [14C] ponatinib, ponatinib and metabolite AP24600 were the 2 major radioactive components. The levels of AP24600 were 58.4% of ponatinib levels. Urinary metabolites were mostly AP24600 and its glucuronides. In human feces, all of the metabolites were biotransformation products of intact ponatinib. Ponatinib accounted for 23.7% of the radioactivity in feces and there was extensive metabolism of ponatinib in feces. Other metabolites identified in feces were hydroxy ponatinib, N-desmethyl ponatinib, and several minor metabolites. The geometric mean (range) terminal elimination half-life of ponatinib was approximately 24 (12 to 66) hours following ponatinib 45 mg oral administration once daily for 28 days in patients with cancer.

Drug Interactions

Ponatinib is a reversible inhibitor of CYPs, with IC50 in the range of 5.2 to 13.6 μM. Ponatinib is unlikely to inhibit CYP-mediated metabolism of concomitant drugs at plasma concentrations of ≤ 260 nM. Ponatinib is not a metabolism- or time-dependent inhibitor. The major human plasma metabolite, AP24600, was not an inhibitor of CYPs. Ponatinib did not induce expression of CYP1A2, CYP2B6 or CYP3A4 in the primary human hepatocytes up to a concentration of 5 μM.

Based on *in vitro* studies ponatinib is a substrate of CYP3A4/5 and to a lesser extent CYP2C8 and CYP2D6. Ponatinib also inhibits the P-glycoprotein (P-gp), ATP-binding cassette G2 (ABCG2) [also known as BCRP], and BSEP transporter systems *in vitro.* In a drug interaction study in healthy volunteers, co-administration of ponatinib with ketoconazole increased plasma ponatinib $AUC_{0\text{-}inf}$ and C_{max} by 78% and 47%, respectively, while exposure to AP24567 decreased by approximately 70%. When administering ponatinib with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole), the recommended starting dose *should be reduced to 30 mg once daily.* Patients taking concomitant strong inhibitors may be at increased risk for adverse reactions.

The phase 1 rifampin study (AP24534-12-107) was conducted in healthy subjects to

evaluate the effect of multiple oral doses of 600 mg rifampin on the PK of a single oral 45-mg dose of ponatinib and its CYP3A4-mediated human metabolite of ponatinib, AP24567. Overall, the rifampin study demonstrated a statistically and clinically relevant effect of rifampin coadministration on relative ponatinib and AP24567 bioavailability. Estimated mean ratios of C_{max}, AUC0-t , and AUC0-∞, indicated decreased exposure to ponatinib by approximately 42%, 59%, and 62%, respectively. Time to achieve maximal plasma ponatinib and AP24567 concentrations was not altered. Estimated mean ratios of C_{max}, AUC0-t , and AUC0-∞, indicated increased exposure to AP24567 by 222%, 114%, and 93%, respectively. Mean t½ was lower for both ponatinib and AP24567.

Co-administration of strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, and St. John's Wort) with ponatinib should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. Monitor patients for signs of reduced efficacy.

Ponatinib displays pH-dependent aqueous solubility *in vitro*; as pH increases, ponatinib solubility decreases. These in vitro data suggest that concomitant administration of agents that alter gastric pH, including H2 antagonists and proton pump inhibitors, could affect ponatinib absorption and should be avoided unless the benefit outweighs the possible risk of ponatinib underexposure. AP 24534-12-108 is a phase-1 study designed to evaluate the effects of concomitant multiple doses of lansoprazole on the PK profile of single dose ponatinib in healthy subjects.This study demonstrated a statistically significant effect of lansoprazole coadministration on ponatinib C_{max} and T_{max}. However, these changes in absorption-related parameters did not result in corresponding changes in overall plasma exposure to ponatinib across the 2 treatments or the elimination half-life. Similar observations were observed for the main metabolite, AP24600. Estimated mean ratios of ponatinib and AP24600 C_{max} decreased by 25%, and the 90% CIs did not fall within the 80% to 125% required for bioequivalence, suggesting the presence of a statistically significant DDI. Time to achieve maximal plasma ponatinib and AP24600 concentrations was slightly delayed by 1 and 2 hours, respectively; this is not thought to represent a clinically relevant difference. Plasma exposures of ponatinib and AP24600 in terms of AUC0-t and AUC0-∞ were equivalent after ponatinib dosing either alone or with lansoprazole (eg, within the bioequivalence criteria). Mean t½ was not altered for either ponatinib or AP24600. These minor reductions in plasma ponatinib C_{max}, without corresponding decreases in overall plasma exposure, are not believed to be important clinical safety or efficacy findings. Ponatinib therefore may be administered concurrently with drugs that raise gastric pH, without the need for a ponatinib dose adjustment or separation of administration.

In vitro studies demonstrate that ponatinib inhibits the P-gp and ABCG2 [BCRP] transporter systems. The effect of co-administration of ponatinib with sensitive substrates of the P-gp (e.g., aliskiren, colchicine, dabigatran, digoxin, everolimus, fexofenadine, lapatinib, maraviroc, posaconazole, ranolazine, sirolimus, sitagliptin, tolvaptan, topotecan) and ABCG2 (e.g., methotrexate, mitoxantrone, irinotecan, lapatinib, rosuvastatin, sulfasalazine, topotecan) transporter systems on exposure of these substrates has not been evaluated in clinical studies.

Safety Profile

As of 06 January 2014, 753 patients have received ponatinib therapy through clinical studies, and 1312 through global expanded access programs. Following approval of ponatinib in the US and in Europe, more than 900 patients have been treated with ponatinib commercially. Ponatinib has a FDA safety label for arterial thrombosis, heart failure and hepatotoxicity. It is likely that some of the adverse effects are specific to myeloproliferative disorders (e.g. thrombosis, neutropenia). A dose intensity safety analysis showed a significant increase in grade 3 or higher adverse reactions (i.e., hypertension, thrombocytopenia, neutropenia, rash, ALT elevation, AST elevation, pancreatitis, and lipase elevation) with an increase in dose intensity.

Phase -1 (AP24534-07-101) study

In the AP24534-07-101 phase-1 study, all the 81% experienced at least 1 adverse event (AE) during the study. Patients in the phase 1 study received a median dose intensity of 30 mg of ponatinib daily. The median dosing period was 308 days (3 to 1799 days).

By System Organ Class (SOC), 50 or more patients experienced events in the following categories:

- Gastrointestinal disorders (70 patients, 86.4%)
- General disorders and administration site conditions (68, 84.0%)
- Investigations (65, 80.2%)
- Infections and infestations (64, 79.0%)
- Nervous system disorders and Skin and subcutaneous tissue disorders (58, 71.6% each)
- Metabolism and nutrition disorders and Musculoskeletal and connective tissue disorders
- (57, 70.4% each)
- Respiratory, thoracic, and mediastinal disorders (50, 61.7%)

Treatment-emergent adverse events (TEAEs) reported in more than 25% of patients included:

- rash (48.1% of patients)
- nausea (45.7%)
- abdominal pain and fatigue (44.4% each)
- headache (42.0%)
- constipation and arthralgia (39.5% each)
- vomiting (38.3%)
- hypertension (37.0%)
- peripheral edema, pyrexia, and platelet count decreased (35.8% each)
- diarrhea (29.6%)
- dry skin (27.2%)
- pain in extremity (25.9%)

Sixty-nine (85.2%) patients had events considered by the investigator to be related to ponatinib. Treatment-related AEs (TRAEs) of any grade, by preferred term, that occurred in more than 10% of patients included:

- rash (33.3% of patients)

- platelet count decreased (29.6%)
- lipase increased (19.8%)
- arthralgia, dry skin, and fatigue (17.3% each)
- pancreatitis (14.8%)
- nausea, dermatitis acneiform, and headache (13.6% each)
- abdominal pain, neutrophil count decreased, myalgia, and hypertriglyceridemia (12.3%
- each)
- hypertension (11.1%)

Serious AEs (SAEs) were reported for 63 patients. The most commonly reported (≥ 10% of patients) SAEs were:

- febrile neutropenia (14.8% of patients)
- pneumonia (13.6%)
- pyrexia (12.3%)
- pancreatitis (11.1%)

Twenty-one patients had SAEs that were considered by the investigator to be related to treatment, including the following:

- pancreatitis (9 patients, 11.1%)
- myocardial infarction (MI) and peripheral arterial occlusive disease (2 patients each,
- 2.5%)
- abdominal pain, accidental overdose, cardiac failure congestive, cardiomyopathy, cerebral infarction, cholecystitis acute, coronary artery disease, dehydration, ejection fraction decreased, electrocardiogram (ECG) QT prolonged, hypertension, interstitial lung disease, intestinal ischemia, LVD, peripheral ischemia, platelet count decreased, troponin increased, and visceral arterial ischemia (1 patient each, 1.2%)

Twenty patients died within 30 days of their last ponatinib dose. Time on study for these patients ranged from 11 to 1496 days (4.1 years). One patient in the 8-mg cohort died 2 days after receiving the last ponatinib dose, from a possibly related case of acute ischemic bowel. The investigator considered the SAE of acute ischemia bowel to be fatal (Grade 5) in intensity (previously reported as life threatening) and possibly related to study drug.
Since cardiac events have been reported following use of approved TKIs, patients were monitored for signs of QT prolongation. Non-corrected QT decreased in both the 30 mg and 60 mg dose groups between baseline and end-of-study; patients in the 45 mg dose group experienced a mean increase of 3.3 milliseconds in non-corrected QT in the same period.
Twenty-eight patients in the phase 1 study experienced 1 or more events with preferred terms that have been classified as vascular occlusive. Among these 28 patients, 7 experienced 14 vascular occlusive events that were considered by the investigator to be possibly or probably related to ponatinib therapy.

Phase -2 (AP24534-10-201) study

In the Phase 2 Study (AP24534-10-201), for patients who had refractory CML (any phase) or Ph+ ALL, and either were resistant to or intolerant of therapy with either dasatinib or nilotinib; or had developed the T315I mutation of BCR-ABL, as of 06 January 2014, 172 (38.3%) patients remained on treatment, while 277 (61.7%) had discontinued. Median duration of exposure was 508 days (ranging from 1 to 1202 days), with an overall median dose intensity of 36.2 mg QD (ranging from 3 to 52 mg QD). The majority (291, 64.8%) of phase 2 patients had their dose reduced at some point during the study, and 310 (69.0%) had a dose interruption of at least 3 days while on study. Eighty-nine (30.6%) of the patients with dose reductions had their doses later re-escalated, and all (100.0%) of the patients with dose interruptions of 3 or more days resumed ponatinib therapy . All but 1 patient (448, 99.8%) experienced at least 1 TEAE, 419 (93.3%) experienced at least 1 TRAE, 277 (61.7%) experienced at least 1 SAE, and 137 (30.5%) experienced at least 1 treatment-related SAE.

Treatment-emergent AEs of any grade that occurred in ≥10% of patients overall included:

- thrombocytopenia, anemia, neutropenia
- constipation, abdominal pain (including abdominal pain upper), nausea, diarrhea,
- vomiting
- headache
- dry skin, rash
- fatigue
- pyrexia
- arthralgia, myalgia, pain (including pain in extremity, back pain, bone pain, muscle
- spasms)
- hypertension
- lipase increased
- peripheral edema
- alanine aminotransferase (ALT) and aspartate aminotransferase (AST) increased
- cough, dyspnea, upper respiratory tract infection, nasopharyngitis
- asthenia
- decreased appetite
- dizziness
- insomnia

TRAEs were reported for 419 (93.3%) patients. The most commonly reported TRAEs of any grade (≥ 20% of patients) included:

- platelet count decreased (37.6%)
- rash (35.4%)
- dry skin (32.3%)
- abdominal pain (23.4%)

The most common SAEs, by preferred term, that were considered related to ponatinib include: abdominal pain, cardiac failure, cardiac failure congestive, diarrhea, dyspnea, lipase increased, neutrophil count decreased, pancreatitis, pancytopenia, pericardial effusion, peripheral arterial

occlusive disease, platelet count decreased, and pleural effusion.

Serious Treatment-Emergent and Treatment-Related Adverse Events by Preferred Term and Maximum Severity, or of Any Grade in ≥ 1% of Patients (N = 449)

	Serious Treatment-Emergent		Serious Treatment-Related	
Preferred Term	**Any grade n (%)**	**Grade 3 and 4 n (%)**	**Any Grade n (%)**	**Grade 3 and 4 n (%)**
Neoplasm progression	38 (8.5)	5 (1.1)	0	0
Pneumonia	29 (6.5)	23 (5.1)	4 (0.9)	2 (0.4)
Pancreatitis	25 (5.6)	24 (5.3)	24 (5.3)	23 (5.1)
Pyrexia	19 (4.2)	4 (0.9)	6 (1.3)	0
Abdominal pain	18 (4.0)	11 (2.4)	9 (2.0)	6 (1.3)
Myocardial infarction[a]	16 (3.6)	13 (2.9)	7 (1.6)	6 (1.3)
Atrial fibrillation	15 (3.3)	9 (2.0)	5 (1.1)	3 (0.7)
Anaemia	15 (3.3)	11 (2.4)	6 (1.3)	5 (1.1)
Platelet count decreased	14 (3.1)	14 (3.1)	8 (1.8)	8 (1.8)
Febrile neutropenia	13 (2.9)	13 (2.9)	5 (1.1)	5 (1.1)
Coronary artery disease	9 (2.0)	9 (2.0)	4 (0.9)	4 (0.9)
Sepsis	8 (1.8)	5 (1.1)	2 (0.4)	2 (0.4)
Angina pectoris	6 (1.3)	4 (0.9)	2 (0.4)	2 (0.4)
Cardiac failure	8 (1.8)	7 (1.6)	6 (1.3)	6 (1.3)
Cardiac failure congestive	8 (1.8)	6 (1.3)	4 (0.9)	3 (0.7)
Cerebrovascular accident	9 (2.0)	1 (0.2)	4 (0.9)	1 (0.2)
Hypertension	9 (2.0)	8 (1.8)	4 (0.9)	3 (0.7)
Lipase increased	8 (1.8)	6 (1.3)	8 (1.8)	6 (1.3)
Cellulitis	6 (1.3)	5 (1.1)	1 (0.2)	0
Diarrhoea	7 (1.6)	5 (1.1)	5 (1.1)	3 (0.7)
Peripheral arterial occlusive disease	7 (1.6)	6 (1.3)	4 (0.9)	3 (0.7)
Dyspnoea	7 (1.6)	6 (1.3)	5 (1.1)	4 (0.9)
Dehydration	7 (1.6)	5 (1.1)	2 (0.4)	2 (0.4)
Pericardial effusion	6 (1.3)	4 (0.9)	5 (1.1)	3 (0.7)
Pancytopenia	6 (1.3)	6 (1.3)	5 (1.1)	5 (1.1)
Neutrophil count decreased	6 (1.3)	6 (1.3)	5 (1.1)	5 (1.1)
Pleural effusion	6 (1.3)	3 (0.7)	4 (0.9)	1 (0.2)
Clostridium difficile colitis	5 (1.1)	3 (0.7)	0	0
Urinary tract infection	6 (1.3)	4 (0.9)	1 (0.2)	0
Deep vein thrombosis	5 (1.1)	3 (0.7)	1 (0.2)	0
Pulmonary embolism	5 (1.1)	4 (0.9)	2 (0.4)	2 (0.4)
Renal failure acute	6 (1.3)	2 (0.4)	1 (0.2)	0

Data cutoff: 06 January 2014

Sixty-eight patients (46 CP-CML; 9 AP-CML; 11 BP-CML; 2 Ph+ ALL) discontinued participation in the phase 2 study due to a TEAE. Platelet count decreased was the most common TEAE leading to discontinuation (17 patients, 3.8%), and was also the most common TRAE leading to discontinuation (18 patients, 4.0%). Coronary artery disease, myelodysplastic syndrome, and sepsis led to discontinuation of 2 patients each. All other events leading to patients withdrawing from the study occurred in 1 patient each, and can generally be grouped into vascular occlusive events, other cardiac events, laboratory abnormalities, and general conditions (eg, asthenia, pain, headache).

Fifty-two of 449 phase 2 patients (11.6%) have died within 30 days of their last ponatinib dose or due to a treatment-related SAE. As of 06 January 2014, 5 of these deaths, described below, were considered treatment-related due to SAEs of pneumonia, acute myocardial infarction (AMI)/MI, pneumonia fungal, gastritis hemorrhagic, and cardiac arrest, respectively.

Phase-2 study of ponatinib in GIST (AP24534-12-202).

This study was intended to evaluate ponatinib therapy in patients with metastatic and/or unresectable GIST, following failure of prior treatment with 1 or more TKIs. In this study, median dose intensity was 45.0 mg QD, ranging from 23.4 to 45.0 mg QD. Twenty-six percent of patients required either a dose reduction or an interruption of treatment of 3 days or more.

Rash was the most frequently reported TEAE (19 patients, 54.3% of patients overall), followed by:

- myalgia and fatigue (16 patients each, 45.7%)
- dry skin and headache (14, 40.0% each)
- abdominal pain and constipation (12, 34.3% each)
- blood alkaline phosphatase increased and hypertension (10 each, 28.6%)
- peripheral edema (9, 25.7%)
- decreased appetite (8, 22.9%)
- nausea, pyrexia, AST increased, and cough (6, 17.1% each)
- vomiting and ALT increased (5, 14.3% each)
- dyspepsia, lipase increased, dysphonia, dyspnea, and insomnia (4, 11.4% each)

TRAEs affecting 10 or more patients overall included:

- rash (19, 54.3%)
- myalgia (16, 45.7%)
- dry skin and fatigue (14, 40.0% each)
- headache (13, 37.1%)
- constipation (11, 31.4%)
-

All other TEAEs occurred in fewer than 10% of patients, and no events of pancreatitis were reported. There were no grade 4 events. One grade 5 event was reported (preferred term: pneumonia, reported as related to ponatinib treatment). Grade 3 TEAEs in more than 1 patient included: abdominal pain and lipase increased (3 each) and anemia, nausea, vomiting, fatigue, and hypertension (2 each).

Ten patients had at least 1 SAE. Gastrointestinal disorders (5 patients), and Cardiac disorders, General disorders and administration site conditions, and Infections and infestations (2 patients each) contributed the majority of SAEs. By preferred term, the most common SAEs were:

- abdominal pain (4, 11.4%)
- fatigue, nausea, and vomiting (2, 5.7% each)
- intestinal abscess, duodenal stenosis, hypercalcemia, hypoxia, MI, pneumonia, and right ventricular dysfunction (each in single patients, 2.9% each)

Seven patients discontinued the GIST study due to development of AEs. Most patients had been receiving ponatinib for less than 2 weeks at the time of event onset; most events were considered at least possibly related to treatment.

A Comprehensive Adverse Events and Potential Risks (CAEPR) list using NCI Common Terminology Criteria for Adverse Events (CTCAE) terms is included in **Section 7.1** of the protocol.

Vascular Occlusion

Arterial and venous thrombosis and occlusions, including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures have occurred
in at least 27% of ponatinib-treated patients from the phase 1 and phase 2 trials. Ponatinib can cause fatal and life-threatening vascular occlusion within 2 weeks of starting treatment. Ponatinib can also cause recurrent or multi-site vascular occlusion. The median time to onset of the first vascular occlusion event was 5 months. Ponatinib can cause fatal and life threatening vascular occlusion in patients treated at dose levels as low as 15 mg per day. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Vascular occlusion adverse events were more frequent with increasing age and in patients with prior history of ischemia, hypertension, diabetes, or hyperlipidemia

Vascular Occlusion Incidence in Ponatinib-Treated Patients in Phase 2 Trial According to Risk Categories

	Prior history of ischemia, hypertension,diabetes, or hyperlipidemia	No history of ischemia, hypertension, diabetes, or hyperlipidemia
Age: 49 or younger	18% (6/33)	12% (13/112)
Age: 50 to 74 years	33% (50/152)	18% (20/114)
Age: 75 and older	56% (14/25)	46% (6/13)
All age groups	33% (70/210)	16% (39/239)
Total	24% (109/449)	

- **Arterial Thrombosis**

Cardiovascular, cerebrovascular, and peripheral vascular thrombosis, including fatal MI and stroke have been observed in ponatinib-treated patients. *Patients with cardiovascular risk factors are at increased risk for arterial thrombosis with ponatinib; therefore, these patients are excluded for this protocol.* Monitor patients for arterial thrombotic events, and consider interrupting or stopping ponatinib if these events are suspected.

In AP24534-10-201 (phase-2 trial of ponatinib in refractory CML and ALL), 91/449 patients (20%) experienced at least 1 treatment-emergent ischemic vascular event: 55 (12%) had cardiovascular events, 27 (6%) had cerebrovascular events and 36 (8%) had peripheral vascular events.

Overall, 53 patients (12%) experienced ischemic vascular SAEs: 28 (6%) had cardiovascular SAEs, 18 (4%) had cerebrovascular SAEs, and 16 (4%) had peripheral vascular SAEs. The most commonly reported SAEs were MI/AMI (14/449: 3%), CAD (10/449: 2%), and CVA (9/449: 2%). Four fatalities were reported due to events in this MedDRA preferred-term search: AMI (considered by the investigator to be possibly related to ponatinib), CAD, cerebral ischemia, and hemorrhagic cerebral infarction. Of 22 patients with SAEs of MI/AMI or CAD, 14 developed CHF concurrent or subsequent to the myocardial ischemic event. Ten of the 18 patients with SAEs of cerebrovascular ischemic events developed stenosis of large arterial vessels of the brain (eg, carotid, vertebral, middle cerebral artery). Ponatinib was withdrawn for 7 patients due to AEs in this group of preferred terms: CAD, hemorrhagic cerebral infarction, cerebral infarction, cerebral infarction with cerebral artery stenosis, CAD and myocardial ischemia with peripheral arterial occlusive disease (PAOD), CVA, and peripheral ischemia. The hemorrhagic cerebral infarction (considered by the investigator not related) was fatal, and peripheral ischemia and CAD/PAOD (considered by the investigator possibly/probably related) were reported as not resolved. All other events were reported as resolved. Most other patients' SAEs in this list of preferred terms also resolved, either with dose adjustments or no change to the dose. Almost all patients with ischemic vascular SAEs had at least 1 risk factor, and most had more than 1.

Peripheral arterial occlusive events, including fatal mesenteric artery occlusion and life-threatening peripheral arterial disease, have occurred in ponatinib-treated patients. Patients have developed digital or distal extremity necrosis and have required amputations. Peripheral vascular SAEs were also reported in the AP24534-07-101 trial. Angina pectoris and MI were reported as treatment-related SAEs. One case of cerebral infarction in the expanded access program was considered by the investigator possibly related to ponatinib.

- **Venous Thromboembolism**

In AP24534-10-201, venous thromboembolic events were observed in 5% (23/449) of ponatinib-treated patients, including deep venous thrombosis/venous embolism/venous thrombosis (11 patients), pulmonary embolism (6 patients), superficial thrombophlebitis (3 patients), retinal vein thrombosis (2 patients) and 1 case each of portal vein thrombosis, and veno-occlusive liver disease. Consider dose interruption of ponatinib in patients who develop serious venous thromboembolism.

Neuropathy

Similar to vascular occlusion, a prospectively defined, MedDRA-based search strategy, containing nearly 300 preferred terms, was employed in the summarization of neuropathy events. Events were further classified as peripheral or cranial neuropathy.

Peripheral and cranial neuropathy has occurred in ponatinib-treated patients. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness. Consider interrupting ponatinib and evaluate if

suspected.

In AP24534-10-201, neuropathy events were observed in 14% (65/449) of patients (cranial in 1% (6/449) and peripheral in 13% (59/449). The most common events were peripheral neuropathy (4%), paresthesia (4%), hypoesthesia (2%), and hyperesthesia (1%). Of the patients who developed neuropathy, 31% (20/65) developed neuropathy during the first month of treatment. One patient discontinued therapy because of neuropathy events (IVth nerve paralysis).

Hepatotoxicity
Liver function test abnormalities are seen with ponatinib, and hepatic failure has been reported. Hepatotoxicity, most commonly manifested by reversible transaminase and alkaline phosphatase elevation and hyperbilirubinemia, has been observed in patients taking ponatinib. Fulminant hepatic failure leading to death occurred in a patient within one week of starting ponatinib. Two additional fatal cases of acute liver failure also occurred. The fatal cases occurred in patients with blast phase CML or Ph+ ALL. Severe hepatotoxicity occurred in all disease cohorts.

Monitor liver function tests at baseline, then at least monthly or as clinically indicated. Interrupt, reduce or discontinue ponatinib as clinically indicated.

The incidence of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation was 56% (all grades) and 8% (grade 3 or 4). Ponatinib treatment may result in elevation in ALT, AST, or both. ALT or AST elevation was not reversed by the date of last follow-up in 5% of patients. Eight percent of patients had grade 3 or 4 elevation in ALT, 4% had grade 3 or 4 elevation in AST and 2% had grade 3 or 4 elevation in alkaline phosphatase. Two patients whose laboratory values met Hy's Law criteria for drug induced liver injury had other etiology to explain the laboratory results: one patient had liver failure due to disease progression and died due to progressive CML, and the second patient had underlying possible Gilbert's syndrome. Acute hepatic failure leading to death was reported in 1 Ph+ ALL patient with decreased cardiac function (an ejection fraction decreased to 28% from 54% within the 5 months prior to first dose) within one week of starting ponatinib (Japan phase 1/2 trial: AP24534-11-106). One additional case of acute liver failure from the expanded access program was reported. The patient, with Ph+ ALL, had liver failure in conjunction with disease progression.

Congestive Heart Failure (CHF)
Severe congestive heart failure (CHF) and left ventricular (LV) dysfunction have been reported in patients taking ponatinib. Patients with cardiac disease or risk factors for cardiac disease should be monitored carefully and any patient with signs or symptoms consistent with cardiac failure should be evaluated and treated. Consider discontinuation of ponatinib in patients who develop serious CHF.

As of 6 January 2014, 37 (8.2%) patients had events of cardiac failure; 23 (5.1%) of these were serious, with SAEs in 14 patients (3%) considered related to therapy, with 4 fatalities (cardiac failure congestive in 2, and cardiac failure and cardiopulmonary failure in 1 patient each. None of the deaths was considered related to ponatinib). Most patients had advanced CML, and almost all had at least 1 cardiac risk factor, with multiple cardiac risk factors in more than half the patients. Twenty-four patients with cardiac failure events discontinued therapy: 6 did so due to

AEs, 7 because of progressive disease/lack of efficacy, 6 by either patient or investigator withdrawal or for other reasons, and 5 due to fatal events (4 were cardiac events, discussed above; 1 was due to pneumonia, which was considered not related to ponatinib). The majority of patients treated with ponatinib who have experienced cardiac failure AEs have also experienced vaso-occlusive AEs, either with a direct temporal relationship or, less frequently, with timing that makes a relationship less clear. Almost all patients who experienced cardiac failure events in the absence of vascular occlusive events had a strong history of heart failure, ischemic disease, or structural heart disease.

Hypertension

Patients receiving ponatinib have experienced hypertension and blood pressure should be monitored at each visit. In addition, a home blood pressure assessment will be performed twice per week for patients starting ponatinib, using blood pressure cuff supplied by the study sponsor, Takeda. Patients will be instructed to contact their study doctor and/or study coordinator in the event an at-home blood pressure reading reaches ≥ 160/90. Any hypertensive measurement will be confirmed by the study team in clinic. For patients who develop HTN or worsening HTN during study treatment, antihypertensive medication should be initiated or optimized to achieve target blood pressure before interruption or dose reduction of the study treatment at the discretion of the investigator. If hypertension is persistent despite adequate anti-HTN therapy including titration of anti-HTN medication or introduction of additional anti-HTN medications, or if grade 4 HTN develops, dose interruption, reduction or discontinuation is recommended. A measurement of ≥ 160/100 requires dose interruption.

Treatment-emergent hypertension occurred in 67% of patients (300/449) treated with ponatinib. In AP24534-10-201, 9 (2%) patients treated with ponatinib experienced treatment-emergent hypertension as a serious adverse reaction and one patient (<1%) experienced treatment emergent hypertensive crisis as a serious adverse reaction, and required clinical intervention for hypertension associated with confusion, headache, chest pain, or shortness of breath.
In patients with baseline systolic BP<140 mm Hg and baseline diastolic BP<90mm Hg, 78% (220/282) experienced treatment-emergent hypertension; 49% (139/282) developed Stage 1 hypertension (defined as systolic BP≥140 mm Hg or diastolic BP≥90 mm Hg) while 29% developed Stage 2 hypertension (defined as systolic BP≥160 mm Hg or diastolic BP≥100 mm Hg). In 164 patients with Stage 1 hypertension at baseline, 64% (66/164) developed Stage 2 hypertension. No patients discontinued due to AEs of hypertension, although 6 (2.2%) patients had dose reductions or interruptions due to the event. None of the hypertension events were fatal.

Ocular Toxicity

Ocular toxicities have occurred in clinical trials of ponatinib. Serious ocular toxicities leading to blindness or blurred vision have occurred in ponatinib-treated patients. Conduct comprehensive eye exams at baseline and periodically during treatment.

Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage have occurred in ponatinib-treated patients (3%). In AP24534-10-201, adverse events in the more-general eye disorders SOC included dry eyes (7%), blurred vision (4%), conjunctivitis (3%), eye pain (3%), periorbital edema (2%), blepharitis (2%), and cataract (2%). Other ocular toxicities

were cataracts, glaucoma, iritis, iridocyclitis, and ulcerative keratitis.

Pancreatitis
Pancreatitis (symptomatic abdominal pain associated with pancreatic enzyme elevation) and/or elevations in lipase and amylase are known AEs associated with ponatinib. Most cases of pancreatitis or elevated pancreatic enzymes occur within the first 2 months of treatment with ponatinib. The events are generally uncomplicated and reversible and can be managed with a brief interruption of treatment and standard medical management. Almost all patients are able to continue with ponatinib treatment at the same or a reduced dose once the event has improved to grade 1 or resolved.

Patients with low-grade (1 or 2) elevation in amylase can be continued without dose reduction but should be monitored closely with serial enzyme level determinations.

Check serum lipase every 2 weeks for the first 2 months and then monthly thereafter or as clinically indicated. Consider additional serum lipase monitoring in patients with a history of pancreatitis or alcohol use. In patients with pancreatitis, do not consider restarting ponatinib until patients have complete resolution of symptoms and lipase levels are less than 1.5 × ULN.
In AP24534-10-201, treatment-emergent pancreatitis occurred in 7% (30/449) of patients (25; 5.6% Grade 3). Pancreatitis resulted in treatment interruption or dose reduction in 6% of patients (26/449). One patient discontinued ponatinib permanently due to pancreatitis. Twenty-three of 29 patients with pancreatitis had resolution of the events within 2 weeks with dose interruption or reduction or with no change in dose; 2 patients had resolution within 4 days with the dose unchanged. The incidence of treatment-emergent lipase elevation was 41% (grade 3 or 4: 18%). Pancreatitis was the DLT from AP24534-07-101and has been reported in the expanded access program.

Hemorrhage
Hemorrhagic events have been reported with ponatinib (mostly in leukemic patients with grade 4 thrombocytopenia).

Treatment-emergent hemorrhagic events occurred in 25.6% (115/449) of patients, the majority (87, 19.4%) of which were grade 1/2. The most common hemorrhagic events were epistaxis (7.1%), petechiae (3.1%), and ecchymosis (2.2%).

In AP24534-10-201, serious bleeding events were observed in 5.8% (26/449) of patients treated with ponatinib, including 5 fatalities (1 event each of subdural hematoma, traumatic intracranial hemorrhage, hemorrhagic gastritis, intracranial hemorrhage, and hemorrhagic cerebral infarction. One fatality (hemorrhagic gastritis) was assessed by the investigator as possibly related to ponatinib. The incidence of serious bleeding events was higher in patients with accelerated phase-CML, blast phase-CML, and Ph+ALL. The most commonly reported serious bleeding events included: gastrointestinal hemorrhage, subdural hematoma (3 patients each, 0.7%); cerebral hemorrhage, hemorrhoidal hemorrhage, retroperitoneal hematoma, epistaxis, post-procedural hemorrhage, traumatic intracranial hemorrhage, gastric hemorrhage (2 patients each, 0.4%). Three patients had their doses reduced or interrupted due to single events each of ear hemorrhage, gingival bleeding, and subarachnoid hemorrhage. Two patients had study drug

discontinued following single events each of cerebral hemorrhage and intracranial hemorrhage. Interrupt ponatinib for serious or severe hemorrhage and evaluate

Fluid Retention

Ponatinib is associated with edema and occasionally serious fluid retention. Patients should be weighed and monitored regularly for signs and symptoms of fluid retention. An unexpected rapid weight gain should be carefully investigated and appropriate treatment provided. Interrupt, reduce the dose of, or discontinue ponatinib according to the recommendations for non-hematologic toxicity.

One or more fluid retention AEs occurred in 125 (27.8%) patients in this study. The most common events were peripheral edema (16.7%), pleural effusion (7.6%), and pericardial effusion (3.8%). In AP24534-10-201, serious fluid retention events were observed in 4% (18/449) of patients treated with ponatinib. One instance of brain edema in a blast phase-CML patient with post-craniotomy was fatal. Serious fluid retention events in more than 1 patient included: pleural effusion (6/449), pericardial effusion (6/449, 1%), and ascites (2/449, <1%). In most cases, patients were able to continue ponatinib therapy without dose reductions or interruptions. Ponatinib was discontinued for three patients, due to pericardial effusion in two, and pleural effusion in one.

Cardiac Arrhythmias

Supraventricular tachyarrhythmias have been reported in patients treated with ponatinib. Supraventricular tachyarrhythmias occurred in 5% (25/449) of ponatinib-treated patients. Atrial fibrillation was the most common supraventricular tachyarrhythmia and occurred in 20 patients. All patients with serious atrial fibrillation had risk factors, confounding events, or both. The other supraventricular tachyarrhythmias were atrial flutter (4 patients), supraventricular tachycardia (4 patients), and atrial tachycardia (1 patient). For 13 patients, the event led to hospitalization. Three patients (0.4%) died due to cardiac arrest. One was assessed as related to ponatinib. This patient had a history of sinus bradycardia and left bundle branch block; the cardiac arrest followed a 2-day history of severe diarrhea and dehydration. The second patient had a past history of MI and died in the setting of an AMI and lobar pneumonia. The third patient had pleural effusions and pulmonary hypertension. One patient discontinued therapy due to grade 3 atrial fibrillation that was considered related to treatment. Advise patients to report signs and symptoms of rapid heart rate (palpitations, dizziness).

Symptomatic bradyarrhythmias have also been reported. Symptomatic bradyarrhythmias that led to a requirement for pacemaker implantation occurred in 1% (3/449) of ponatinib treated patients. The cardiac rhythms (1 case each) identified were complete heart block, sick sinus syndrome, and atrial fibrillation with bradycardia and pauses. Advise patients to report signs and symptoms suggestive of slow heart rate (fainting, dizziness, or chest pain).

In AP24534-07-101, SAEs of atrial fibrillation were reported in 7% of patients, with none considered treatment related. No cardiac arrest was reported in that trial.

Prolonged QTcF

A QT assessment was performed in 39 patients with cancer who received 30 mg, 45 mg, or 60

mg ponatinib once daily. No large changes in the mean QTc interval (i.e., > 20 ms) from baseline were detected in the study. However, a small increase in the mean QTc interval (i.e., < 10 ms) cannot be excluded because of study design limitations. If a prolongation of QTcF is observed, it is important to perform serum electrolyte analysis (including potassium, calcium, and magnesium) and correct any significant abnormalities with supplements if below normal limits. It is also necessary to review all concomitant medications and discontinue medications that are known or suspected to cause QT prolongation.

If no contributing reason is identified and the reason for QTcF prolongation is believed to be due to ponatinib, dose interruption and reduction guidelines for general non-hematologic toxicities should be followed. Additionally, weekly ECG monitoring is recommended for 4 weeks upon resumption of study drug, then monthly for 6 months, and then every 3 months for the remainder of the study, or more frequently as clinically indicated. Echocardiogram and ECG results for all sites will be reviewed by the lead investigator at *The Ohio State University (OSU).*

Myelosuppression
Neutropenia, anemia, and thrombocytopenia have all been commonly reported either together or individually in leukemia patients treated with ponatinib. Ponatinib has not been studied in solid tumor patients and whether (or to what extent) myelosuppression will occur in these patients is unknown. While myelosuppression can occur any time during treatment, its onset most commonly occurs within the first month on treatment.

Obtain complete blood counts every 2 weeks for the first 3 months and then monthly or as clinically indicated, and adjust the dose as recommended.

In AP24534-10-201, grade 3 or 4 myelosuppression, reported as an AE, occurred in 52% (262/449) of patients treated with ponatinib. The most commonly reported grade 3/4 myelosuppression AEs were platelet count decrease (43.9%), neutrophil count decrease (24.9%), febrile neutropenia (5.1%) and anemia (22.3%). The incidence of these events was greater in patients with advanced disease than in patients with CP-CML and patients frequently experienced multiple occurrences of these events.. SAEs of myelosuppression events occurred in 10% of patients, with febrile neutropenia and decreased platelet count the 2 most common SAEs, in 3% of patients each. In AP24534-10-201, decreased platelet count led to the discontinuation of 17 patients, making it the most common AE leading to discontinuation. Most patients who experienced grade 3 or 4 decreased platelet count had their first occurrence within the first 3 months of treatment. Most patients recovered from decreased platelet counts with dose interruptions or reductions or with no change to the regimen.

In AP24534-07-101, the incidences of AEs of myelosuppression were similar overall, with incidences of SAEs of febrile neutropenia and decreased platelet count were slightly higher, in 15% and 5% of patients, respectively. Myelosuppression events were reported as SAEs in the expanded access program.

Compromised Wound Healing and Gastrointestinal Perforation
Based on the mechanism of action, ponatinib could potentially compromise wound healing.

Interrupt ponatinib for at least 1 week prior to major surgery. The decision when to resume ponatinib after surgery should be based on clinical judgment of adequate wound healing. Serious GI perforation (fistula) was observed in one patient 38 days post-cholecystectomy in AP24534-10-201. No formal studies of the effect of ponatinib on wound healing have been conducted.

Tumor Lysis Syndrome
Two patients (<1%) treated with ponatinib in AP24534-10-201 developed serious tumor lysis syndrome (TLS). Both cases occurred in patients with advanced CML. Hyperuricemia occurred in 7% (304/449) of patients; the majority had CP CML (19 patients).TLS is likely specific to patients with CML and is unlikely in the solid tumor patients.

Constitutional Symptoms/Joint Pain
Certain constitutional symptoms such as myalgia, arthralgia, headache, weakness, fatigue, asthenia, and low grade fever have been commonly reported with ponatinib. These symptoms have been reported mainly at the initiation of treatment, are typically short lived (<2 weeks), and are seldom, if ever, reported beyond the first month of treatment. These AEs are most commonly low grade (grade 1 and 2) and are self-resolving without the need for dose interruption or dose reduction when they do occur. Most patients can be maintained on the current dose of ponatinib, uninterrupted, and their symptoms can be managed with a short course of oral analagesics, corticosteroids, and/or anti-pyretics as clinically indicated. If dose interruption is indicated, patients can resume the same dose of ponatinib typically without recurrence of symptoms once the original episode has improved or resolved.

Embryo-Fetal Toxicity
Although no studies have been conducted, ponatinib may cause fetal harm, and women who are pregnant should be prohibited from using ponatinib. Ponatinib showed embryo-fetal toxicity in rats at exposures lower than human exposures at the recommended human dose. Advise women to avoid becoming pregnant while taking ponatinib.

Overdosage

Overdoses with ponatinib were reported in clinical trials. One patient was accidentally administered the entire contents of a bottle of study medication via nasogastric tube. The investigator estimated that the patient received 540 mg of Iclusig. Two hours after the overdose, the patient had an uncorrected QT interval of 520 ms. Subsequent ECGs showed normal sinus rhythm with uncorrected QT intervals of 480 and 400 ms. The patient died 9 days after the overdose from pneumonia and sepsis. Another patient accidentally self-administered 165 mg on cycle 1 day 2. The patient experienced fatigue and non-cardiac chest pain on day 3. Multiple doses of 90 mg per day for 12 days in a patient resulted in pneumonia, systemic inflammatory response, atrial fibrillation, and a moderate pericardial effusion.

In the event of an overdose, stop ponatinib, observe the patient and provide appropriate supportive treatment.

Ponatinib use in specific populations

Pregnancy

Based on its mechanism of action and findings in animals, ponatinib can cause fetal harm when administered to a pregnant woman. Ponatinib was studied for effects on embryo-fetal development in pregnant rats given oral doses of 0.3, 1, and 3 mg/kg/day during organogenesis. At the maternally toxic dose of 3 mg/kg/day (equivalent to the AUC in patients receiving the recommended dose of 45 mg/day), ponatinib caused embryo-fetal toxicity as shown by increased resorptions, reduced body weight, external alterations, multiple soft tissue and skeletal alterations, and reduced ossification. Embryo-fetal toxicities also were observed at 1 mg/kg/day (approximately 24% the AUC in patients receiving the recommended dose) and involved multiple fetal soft tissue and skeletal alterations, including reduced ossification. There are no adequate and well-controlled studies with ponatinib in pregnant women. Advise women to avoid becoming pregnant while taking ponatinib. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

Pediatric Use

The safety and efficacy of ponatinib in patients less than 18 years of age have not been established.

Nursing

It is unknown whether ponatinib is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ponatinib, a decision should be made whether to discontinue nursing or to discontinue ponatinib, taking into account the importance of the drug to the mother.

Geriatric use

One hundred and fifty-five of 449 patients (35%) in the CML clinical trial of ponatinib were 65 years of age and over. Forty-six percent of patients ≥ 65 years had vascular occlusion events. Patients of age ≥ 65 years are more likely to experience adverse reactions including vascular occlusion, decreased platelet count, peripheral edema, increased lipase, dyspnea, asthenia, muscle spasms, and decreased appetite. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Hepatic Impairment

The Mass-Balance study (AP24534-11-104) confirmed that ponatinib elimination in humans primarily occurs via the liver. AP24534-12-109, Phase-1 study compared the PK of 30-mg ponatinib in subjects with chronic hepatic impairment with those of matched healthy subjects. The study was designed as open-label, single-dose, parallel-group, and nonrandomized. Eighteen subjects with hepatic impairment (6 each in Child-Pugh categories A, B, and C, corresponding to mild, moderate, and severe impairment, respectively) were matched to 9 healthy subjects. The study demonstrated that ponatinib or metabolite AP24600 exposure appeared to be comparable, albeit slightly higher, in subjects with mild hepatic impairment (Child-Pugh A) compared to healthy subjects. In contrast, lower plasma exposures of ponatinib and AP24600 were observed in subjects with either moderate or severe hepatic impairment (Child-Pugh B and C,

respectively) relative to healthy control subjects. PK data alone do not suggest the need for a starting dose adjustment for ponatinib in subjects with varying degrees of hepatic impairment. No clinically meaningful differences were observed in ponatinib PK in subjects with chronic hepatic impairment compared to matched healthy subjects. Ponatinib should be used with caution in patients with moderate or severe hepatic impairment.

Renal Impairment

Although renal excretion is not a major route of elimination, ponatinib has not been studied in patients with renal impairment. The potential for moderate or severe renal impairment to affect hepatic elimination has not been determined.

2.3 Rationale

The FGF-FGFR signaling pathway plays a critical role in regulating physiologic processes such as embryogenesis, angiogenesis and cell survival. *FGFR* genes are proto-oncogenes and their activation secondary to genomic alterations such as gene amplification, chromosomal translocation, and point mutation can mediate the development and growth of cancers.[1] A rapidly expanding list of cancers with genomic FGFR alterations is provided in Table 1. Therefore, inhibition of the FGF-FGFR signaling pathway presents a viable therapeutic strategy for multiple malignancies. In addition to their role in inhibiting angiogenesis and tumorigenesis, FGFR inhibitors can also ameliorate resistance to other therapies. Inhibition of FGFR has been demonstrated to overcome resistance to endocrine therapy in patients with breast cancers.[31] They have also been shown to enhance sensitivity of resistant tumors to chemotherapy.[32] FGFR inhibitors are purported to be an effective therapeutic option for relapsed tumors that have been treated previously with EGFR or VEGFR inhibitors due to secondary FGFR activation.[11]

Currently FGFR inhibitors, both selective and non-selective are being evaluated as cancer therapies. Several small molecule tyrosine kinase inhibitors (TKI) have been studied, and they share characteristics as ATP-competitive VEGFR2 inhibitors due to structural similarity of VEGFR and FGFR kinase domains. However, potential toxicities associated with pan-FGFR/VEGFR inhibition have also led to monoclonal antibodies targeting specific FGFRs (e.g. IMC-A1 (Imclone), R3Mab (Genentech)).[33, 34] Preclinical as well as early clinical studies have demonstrated that genomic FGFR alterations predict sensitivity and response to the use of FGFR inhibitors. Guagnano *et al*. have shown that genetic alterations in FGFR predict sensitivity to BGJ398 (Novartis), a selective pan-FGFR inhibitor.[35] Currently, BGJ398 is being evaluated in a Phase 1 study for patients with advanced solid tumors harboring amplifications (*FGFR1/2*) or mutations (*FGFR3*).[36] Dovitinib (TKI258, Novartis), a combined FGFR and VEGFR inhibitor, has recently been shown to be effective in patients with *FGFR1* amplified advanced breast cancers.[37] Similarly, *FGFR2* amplification in gastric cancers predicted sensitivity to selective FGFR inhibitor AZD4547 (AstraZeneca) [38], and this agent is being investigated in a phase-2 trial in patients with advanced gastric adenocarcinoma with *FGFR2* polysomy or amplification[39, 40].

We propose to evaluate ponatinib (Takeda), a pan-FGFR inhibitor, in patients with any cancer histology and molecular eligibility with defined genomic *FGFR* alterations. Ponatinib is FDA approved for the treatment of CML and Philadelphia chromosome positive ALL) for

whom no other tyrosine kinase inhibitor (TKI) therapy is indicated .[25] In addition to BCR-ABL, it is also a potent inhibitor of FGFR family members and other kinases including KIT, RET, PDGFRα, and FLT3 Gozgit *et al.* have shown ponatinib to be more potent (1 to 2 log scale) than previous FGFR inhibitors with activity across multiple FGFRs (FGFR 1-4) and types of genomic alterations.[17] Also, ponatinib has been shown to have activity against secondary gatekeeper mutations that mediated resistance in tyrosine kinases (e.g. T315I in BCR-ABL; T670I in KIT).[25] We and others (Gozgit *et al.)* have shown that ponatinib produces a robust, dose-dependent, growth inhibition across multiple cancer cell lines harboring *FGFR* alterations, compared to wild type FGFR, supporting these findings. **We hypothesize that activating genomic FGFR alterations predict response to ponatinib.** In addition, we hypothesize that activating genomic alterations in *KIT, RET, PDGFRα, ABL1, FLT3* will predict response to ponatinib given the activity of this drug in preclinical studies.

To evaluate this, we propose a single arm phase-2 study of ponatinib in patients with any cancer histology and molecular eligibility with activating *FGFR* alterations (amplifications, mutations, translocations) as well as *KIT, PDGFRα, FLT3, RET, ABL1* alterations. While enrollment of multiple tumor subtypes facilitates accrual rate of patients with genetic *FGFR* alterations as these are rare, importantly, we can assess whether tumor subtypes with *FGFR* alterations would indeed respond to FGFR inhibition. For instance, *BRAF* mutant colon cancers did not show sensitivity to BRAF inhibition as melanomas with similar mutation.[41] This was demonstrated to be due to EGFR-mediated reactivation of MAP kinase pathway, and combined EGFR and BRAF inhibition was able to improve response.[42] As yet, no tumor specific context for FGFR response has been recognized and our trial could help ascertain if there is any. Further, we can compare primary non-responders versus responders to identify additional pathways that render patients resistant to FGFR inhibition despite the presence of an FGFR alteration. As stated previously, ponatinib has also been demonstrated to be a potent inhibitor of other kinases altered in cancers including PDGFRα, FLT3, RET, ABL1 and KIT.[43, 44] Therefore, we plan to evaluate the activity of ponatinib in cancers that harbor genomic alterations in these kinases as a separate cohort.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients with histologically or cytologically confirmed diagnosis of refractory metastatic solid tumor for whom no other standard treatment options are available.

3.1.2 Patients must have tumor suitable for biopsy (as assessed by trained specialists in interventional radiology) and medically fit to undergo a biopsy or surgical procedure; OR archival tumor specimen of biopsied tumor; OR if patients do not have a tumor suitable for biopsy but have another tissue (preferably progressive metastatic site) available for molecular evaluation (*biopsy will be performed through OSU-13053 study or the UM Precision Cancer Study*).

3.1.3 Patients must have activating genomic alterations in *FGFR* (mutations, fusions or amplifications (> 6 copies)) or activating genomic alterations in *KIT, PDGFRα, RET, ABL1* and *FLT3* by any validated CLIA-certified molecular testing (FISH, PCR or sequencing data are acceptable). CLIA validated results from other institutions; diagnostic labs (e.g. foundation medicine) are acceptable.

3.1.4 Patients with solid tumors must have measurable disease (RECIST 1.1), defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. Note: This trial is open only to patients with solid tumors.

3.1.5 Patients older than or equal to 18 years of age (The safety and efficacy of ponatinib in patients less than 18 years of age have not been tested).

3.1.6 ECOG performance status ≤ 1 (Karnofsky ≥ 80%, see Appendix A).

3.1.7 Life expectancy of greater than 3 months.

3.1.8 Patients with multiple malignancies remain eligible.

3.1.9 Patients with an inherited cancer syndrome or a medical history suggestive of an inherited cancer syndrome remain eligible.

3.1.10 Patients must have controlled blood pressure with a systolic blood pressure < 140 mmHg and diastolic < 90 mmHg (for patients with an elevated initial BP reading (hypertensive range), a repeat measurement at least 2 minutes later should be performed, and the two readings should be averaged to obtain a BP reading). Any hypertensive at-home blood pressure reading will be confirmed in clinic. Patients on anti-hypertensive medications are eligible, if blood pressure is controlled. Study drug dosing will be interrupted for any reading ≥ 160/100, as outlined in management table in Section 6 of the protocol.

3.1.11 Ponatinib can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. For this reason women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and through 4 months after the end of treatment. For females of childbearing potential, a negative pregnancy test must be documented prior to registration.

3.1.12 Patients must have normal organ and marrow function as defined below:

- Absolute neutrophil count ≥1,500/mcL
- Platelets ≥75,000/mcL
- Total bilirubin ≤1.5 × upper limit of normal (ULN), unless due to Gilbert's syndrome (<5 if liver involvement with primary tumor)
- Serum lipase and amylase ≤1.5 × ULN

- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- LVEF ≥ 50% by ECHO or MUGA
- Serum creatinine ≤1.5 mg/dL *OR* calculated creatinine clearance (Cockroft-Gault formula) ≥60 mL/min *OR* 24-hour urine creatinine clearance ≥60 mL/min

3.1.13 Patient has the ability to swallow oral medication and keep a pill diary

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

3.2 Exclusion Criteria

3.2.1 Patients with hematological malignancies.

3.2.2 Patients who have not received any prior treatment.

3.2.3 Patients with known ponatinib-resistant gene alterations
- PDGFRA D842V mutation
- cKIT D816V mutation
- FLT3 D835V/Y/H/F or Y842C mutations
- FGFR3 K652E mutation

3.2.4 Major surgery (e.g. thoracic, abdominal, vascular, neurosurgery) within 28 days prior to registration on study.

3.2.5 History of acute pancreatitis within one year of study entry or history of chronic pancreatitis.

3.2.6 History of alcohol abuse

3.2.7 Have uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).

3.2.8 Patients who are receiving any other investigational agents.

3.2.9 Patients with history of clinically significant bleeding disorder.

3.2.10 Pregnant women are excluded from this study because ponatinib can affect embryo-fetal development. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ponatinib breastfeeding must be discontinued.

3.2.11 Patients who are incarcerated are not eligible.

3.2.12 Patients with any history of arterial thromboembolic disease. *Any patient with a history of MI, stroke, TIA, unstable angina or peripheral vascular disease will not be eligible.*

3.2.13 Patients with history of recurrent venous thromboembolism (deep venous thrombosis or pulmonary embolism) or history of venous thromboembolism within 6 months prior to registration on study will not be eligible

3.2.14 Patients with history of active hepatitis B or C infection or chronic hepatitis with Child Pugh B or C hepatic dysfunction.

3.2.15 Patients with prolonged corrected QT interval, defined as QTc >450 msec

3.2.16 Use of antiplatelet agents other than low-dose aspirin as described in the protocol.

3.2.17 GI bleed within 30 days prior to registration on study .

3.2.18 History of allergic reactions attributed to compounds of similar chemical or biologic composition to ponatinib.

3.2.19 Patients with history of atrial arrhythmia (requiring any anti-arrhythmic therapy) or patients with any history of ventricular arrhythmia are excluded

3.2.20 Clinically significant, uncontrolled intercurrent illness including, but not limited to:
- Symptomatic or active infection
- Uncontrolled hypertension (Diastolic blood pressure > 90 mm Hg; Systolic >140 mm Hg). Patients with hypertension should be under treatment on study entry to effect blood pressure control.
- Psychiatric illness/social situations that would limit compliance with study requirements.

3.2.21 Patients with history of congestive heart failure are excluded.

3.2.22 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with ponatinib.

3.2.23 Patients on medications known to be associated with Torsades de Pointes

3.2.24 Patients who received the last administration of an anti-cancer therapy including, chemotherapy, immunotherapy/biologic therapy, targeted therapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) or within 5 half-lives, whichever is shorter, prior to entering the study.

3.2.25 Patients who have not recovered ($\leq$ CTCAE grade 1) from adverse events (with the exception of alopecia) due to agents administered more than 4 weeks earlier.

3.2.26 Patients taking medications or herbal supplements that are known to be strong CYP3A4 inhibitors within at least 14 days prior to registration are excluded

3.2.27 Patients with symptomatic or progressive brain metastases are ineligible. Subjects with treated brain metastases are eligible if they have no radiographic or other signs of progression in the brain for $\geq$ 4 weeks after completion of local therapy.

3.2.28 Patients with macular edema, retinal vein occlusion or retinal hemorrhage are excluded.

3.2.29 Patients who have received prior FGFR targeted therapy.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. It is expected that the patients entering this study will reflect the demographics of our clinical population and geographic area. We expect that some participants will be racial/ethnic minorities which reflects the catchment area.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study centrally at the *The Ohio State University*. OSU patients will be registered by the OSU Clinical Research Specialist/Coordinator. External participating site patients will be registered by the OSU Multi-Site Coordinator. External sites should alert the Multi-Site Coordinator by e-mail or phone as soon as a potential patient is identified for screening. The required registration forms can be found in the protocol Supplemental Forms packet.

Following registration, patients should begin protocol treatment within 5 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, a written explanation documenting the reason for delay will be required before proceeding with therapy. The Multi-Site Coordinator should be notified of any cancellations as soon as possible. The patient's registration may be cancelled, pending approval by the Principal Investigator who will determine whether the patient will be replaced.

4.2 External Participating Site Registration Process

External participating site patients will have eligibility verified and will be centrally registered at The Ohio State University by the OSU Multi-Site Coordinator. Participating sites should call or email the OSU Multi-Site Coordinator to verify enrollment availability prior to consenting patients.

Following registration, patients should begin protocol treatment within 5 business days. Issues that may cause treatment delays should be discussed with the OSU Principal Investigator and OSU Multi-Site Coordinator as soon as possible. The OSU Multi-Site Coordinator must be notified immediately if a patient does not receive protocol therapy.

Only patients deemed eligible by the participating site research team should be submitted for eligibility verification and registration by the OSU Multi-Site Coordinator.

To request patient registration, the documents below must be completed by the participating site research team and faxed to the OSU Multi-Site Coordinator. The OSU secure e-mail system may be used, if needed. Contact the OSU Multi-Site Coordinator for more information. Regular e-mail must not be used to send patient registration documents.

Required documents for registration:

- Enrollment Form (refer to Supplemental Forms packet)
- Signed Eligibility Checklist (refer to Supplemental Forms packet)
- Signed informed consent document (and HIPAA if separate form)
- Documentation of consent process
- Source documents verifying every inclusion & exclusion criteria
- Source documents for every required screening item as listed in the Protocol Calendar. Screening tests must be within the specified window.
- Other signed and dated documents used as source documentation

The OSU Multi-Site Coordinator will confirm receipt of the registration documents with the participating site contact listed on the Enrollment Form. If confirmation is not received within 2 hours, it is strongly recommended that the participating site call the OSU Multi-Site Coordinator to confirm registration documents were received.

Registration requests will be processed as soon as possible and no later than 1 business day after receipt of the registration documents, pending there is no additional information needed to complete eligibility verification. Registration will occur upon OSU confirmation that the patient meets eligibility criteria.

The Multi-Site Coordinator will securely email the participating site contact listed on the Enrollment Form with the registration confirmation and the patient's assigned study number.

5. TREATMENT PLAN

5.1 Agent Administration

Ponatinib would be administered as a single agent at a starting dose of 45 mg oral once daily on an outpatient basis. In clinical trials involving CML and ALL the starting dose of ponatinib was 45 mg administered orally once daily. However, 59% of the patients required dose reductions to 30 mg or 15 mg once daily during the course of therapy. The optimal dose of ponatinib in solid tumors has not been identified. All subjects should receive a copy of the Ponatinib Medication Guide (Appendix D).

Reported adverse events and potential risks are described in **Section 7**. Appropriate dose modifications are described in **Section 6**. Details regarding administration of study drugs are detailed in **Section 8**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy. The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

Ponatinib at a dose of 45 mg should be taken orally once daily with or without food for a 28 day cycle. Tablets should be swallowed whole. Patients should not crush or dissolve the tablets. Continue treatment as long as the patient does not show evidence of disease progression or unacceptable toxicity **(Section 5.3)**.

Patients treated with ponatinib are recommended to have concomitant thrombo-prophylaxis with ASA (81 or 325 mg daily), if tolerated. Patients with documented allergy to aspirin do not require an alternate agent and are still eligible. ASA should be held when platelets drop to 75000 or below.

5.2 General Concomitant Medication and Supportive Care Guidelines

- Aspirin, at a dose of 81mg once daily, should be taken orally beginning on the first day of ponatinib administration as a prophylactic for hypertension. Aspirin should be discontinued when ponatinib is discontinued, unless a clinical indication suggests otherwise.

- Nausea/Vomiting – prophylactic pre-medications are not planned as ponatinib is not highly emetogenic. However, if patients experience nausea during a treatment cycle, anti-emetics may be used per institutional guidelines.

- Cytopenias – prophylactic growth factors (e.g. G-CSF, erythropoietin) are not permitted, however, if patients require admission for fever and neutropenia and the treating physician feels that the administration of growth factors may be beneficial then they can be given according to ASCO guidelines. Use of recombinant erythropoietin is not allowed. Platelets and red cell transfusions can be given as necessitated.

- Short courses (up to a maximum of 3 weeks) of oral corticosteroids intended to treat study treatment related rash or diarrhea are allowed. Oral steroids should be used with caution and subjects monitored for steroid-induced hyperglycemia.

- Loperamide or lomotil is recommended for supportive care of diarrhea.

- The use of bisphosphonates for skeletal metastasis is permitted.

  Because there is a low potential for interaction with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 iso-enzymes.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,

- Unacceptable adverse event(s)

- Intercurrent illness that prevents further administration of treatment,

- Patient decides to withdraw from the study, or

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Duration of Follow Up

Patients will be followed every 3 months for 52 weeks after removal from study or until death, whichever occurs first, in order to document time of progression (if patient did not progress while on study), survival, and to document subsequent alternate therapy received. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in **Section 5.3** applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

Patients must be discontinued from the trial in the event of myocardial infarction, stroke,

development or progression of arterial disease necessitating revascularization, or other vascular occlusive events.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Modifications for Ponatinib

A maximum of two ponatinib dose level reductions are allowed. If a third dose level reduction is required, treatment will be permanently discontinued. The starting dose for ponatinib is 45 mg oral daily.

Patients who experience a vascular (arterial or venous) occlusive event should be immediately discontinued from the study and ponatinib should not be restarted. For serious reactions other than arterial or venous occlusion, do not restart until the serious event has resolved.

Dose Modifications

Dose Level	Ponatinib Dose/Schedule
0	45 mg daily
-1	30 mg daily
-2	15 mg daily

Dose Modification for Nausea

Nausea and vomiting are reported with ponatinib. The use of an antiemetic prophylactically is not recommended. However, if a patient is symptomatic, appropriate antiemetic medications may be used as clinically indicated.

CTCAE Grade	Action and Dose Modification
≤ Grade 1	No change in dose
Grade 2	Occurrence at 45 mg: • Interrupt ponatinib and resume at 45 mg after recovery to ≤ Grade 1 Occurrence at 30 mg: • Interrupt ponatinib and resume at 30 mg after recovery to ≤ Grade 1 Occurrence at 15 mg: Discontinue ponatinib
Grade 3	Occurrence at 45 mg: • Interrupt ponatinib and resume at 30 mg after recovery to ≤ Grade 1 Occurrence at 30 mg: • Interrupt ponatinib and resume at 15 mg after recovery to ≤ Grade 1 Occurrence at 15 mg: Discontinue ponatinib
Grade 4	Off protocol therapy
*Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: Anti-emetics.	

Dose Modification for Vomiting

CTCAE Grade	Action and Dose Modification
≤ Grade 1	No change in dose
Grade 2	Occurrence at 45 mg: • Interrupt ponatinib and resume at 45 mg after recovery to ≤ Grade 1 Occurrence at 30 mg: • Interrupt ponatinib and resume at 30 mg after recovery to ≤ Grade 1 Occurrence at 15 mg: Discontinue ponatinib
Grade 3	Occurrence at 45 mg: • Interrupt ponatinib and resume at 30 mg after recovery to ≤ Grade 1 Occurrence at 30 mg: • Interrupt ponatinib and resume at 15 mg after recovery to ≤ Grade 1 Occurrence at 15 mg: Discontinue ponatinib
Grade 4	Off protocol therapy
*Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: Anti-emetics.	

Dose Modification for Diarrhea

Diarrhea is a common side effect of ponatinib. The use of anti-diarrheal medications is permitted. Patients who experience ≥ grade 2 diarrhea may begin loperamide (4 mg orally x 1, then 2 mg orally after each loose stool).

CTCAE Grade	Action and Dose Modification
≤ Grade 1	No change in dose
Grade 2	Occurrence at 45 mg: • Interrupt ponatinib and resume at 45 mg after recovery to ≤ Grade 1 Occurrence at 30 mg: • Interrupt ponatinib and resume at 30 mg after recovery to ≤ Grade 1 Occurrence at 15 mg: Discontinue ponatinib
Grade 3	Occurrence at 45 mg: • Interrupt ponatinib and resume at 30 mg after recovery to ≤ Grade 1 Occurrence at 30 mg: • Interrupt ponatinib and resume at 15 mg after recovery to ≤ Grade 1 Occurrence at 15 mg: Discontinue ponatinib
Grade 4	Off protocol therapy

CTCAE Grade	Action and Dose Modification
**Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours. Adjunct antidiarrheal therapy is permitted and should be recorded when used.	

Dose Modifications for Hepatic Toxicity

Hepatotoxicity, most commonly manifested by reversible transaminase and alkaline phosphatase elevation and hyperbilirubinemia, has been observed in patients taking ponatinib. Monitoring of hepatic function is recommended and management of laboratory abnormalities should be managed with dose interruption and/or dose reduction according to the dose modification table.

CTCAE Grade	Action and Dose Modification
Elevation of liver transaminases > 3 x ULN* or alkaline phosphatase > 2.5 x ULN (Grade 2 or higher; or alkaline phosphatase > 4x ULN if related to metastatic disease limited to liver [e.g. cholangiocarcinoma])	Occurrence at 45 mg: • Interrupt ponatinib and monitor hepatic function • Resume ponatinib at 30 mg after recovery to ≤ Grade 1 (< 3 × ULN) Occurrence at 30 mg: • Interrupt ponatinib and resume at 15 mg after recovery to ≤ Grade 1 Occurrence at 15 mg: • Discontinue ponatinib
Elevation of AST or ALT ≥ 3 x ULN concurrent with an elevation of bilirubin > 2 x ULN and alkaline phosphatase > 2 x ULN	Discontinue ponatinib

Dose Modifications for Myelosuppression

While myelosuppression can occur any time during treatment, its onset most commonly occurs within the first month on treatment. Ponatinib has not been studied in solid tumor patients and whether (or to what extent) myelosuppression will occur in these patients is unknown.

	Action and Dose Modification
Absolute Neutrophil Count (ANC) < 1 x 10^9/L Or Platelets < 50 x 10^9/L	First Occurrence • Interrupt ponatinib and resume initial dose after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L Second Occurrence • Interrupt ponatinib and resume at 30 mg after recovery

	Action and Dose Modification
	to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L Third Occurrence • Interrupt ponatinib and resume at 15 mg after recovery to ANC ≥ 1.5 x 10^9/L and platelet ≥ 75 x 10^9/L

Dose Modifications for Hemorrhage
Concomitant use of ponatinib with anticlotting agents should be approached with caution in patients who may be at risk of bleeding events. Serious bleeding events, including fatalities have been reported in patients treated with ponatinib. Most hemorrhagic events, but not all, occurred in patients with grade 4 thrombocytopenia. Interrupt ponatinib for serious or severe hemorrhage and evaluate.

CTCAE Grade	Action and Dose Modification
Grade 1	No intervention
Grade 2	Occurrence at 45 mg: • Interrupt ponatinib and resume at 30 mg after recovery to ≤ Grade 1 Occurrence at 30 mg: • Interrupt ponatinib and resume at 15 mg after recovery to ≤ Grade 1 Occurrence at 15 mg: • Discontinue ponatinib
Grade 3 or 4	**Permanently discontinue ponatinib**

Dose Modifications for Pancreatitis / Lipase Elevations
Pancreatitis (symptomatic abdominal pain associated with pancreatic enzyme elevation) and/or elevations in lipase and amylase are known AEs associated with ponatinib. Most cases of pancreatitis or elevated pancreatic enzymes occur within the first 2 months of treatment with ponatinib. Patients with low-grade (1 or 2) elevation in enzymes can be continued without dose reduction but should be monitored closely with serial enzyme level determinations. Patients can continue with ponatinib treatment at the same or a reduced dose once the event has improved to grade 1 or resolved. See below for dose-modification guidelines.

CTCAE Grade	Action and Dose Modification
Asymptomatic Grade 1 or 2 elevation of serum lipase	Consider interruption or dose reduction of ponatinib
Asymptomatic Grade 3 or 4 elevation of lipase (> 2 X ULN*) or asymptomatic radiologic pancreatitis (Grade 2 pancreatitis)	Occurrence at 45 mg: • Interrupt ponatinib and resume at 30 mg after recovery to ≤ Grade 1 (< 1.5 x ULN) Occurrence at 30 mg: • Interrupt ponatinib and resume at 15 mg after recovery to ≤ Grade 1 Occurrence at 15 mg: • Discontinue ponatinib
Symptomatic Grade 3 pancreatitis	Occurrence at 45 mg: • Interrupt ponatinib and resume at 30 mg after complete resolution of symptoms and after recovery of lipase elevation to ≤ Grade 1 Occurrence at 30 mg: • Interrupt ponatinib and resume at 15 mg after complete resolution of symptoms and after recovery of lipase elevation to ≤ Grade 1 Occurrence at 15 mg: • Discontinue ponatinib
Grade 4 pancreatitis (> 5 X ULN of lipase)	Discontinue ponatinib

*ULN = Upper Limit of Normal for the lab

Dose Modifications for Skin Rash

Skin rashes have been commonly reported in patients taking ponatinib. The vast majority of the skin events are nonserious, either self-limiting or manageable with antihistamines or topical steroids, and do not result in discontinuation. In more severe cases, a short course of oral corticosteroids may be used until the rash has improved or resolved. In patients treated with ponatinib, the most common skin manifestations are a diffuse maculopapular rash that is non-pruritic or an acneiform dermititis. Occasionally, patients treated with ponatinib have been reported to have a dry, flaky or exfoliative type of rash or psoriasiform dermatitis. Rarely, an erythema multiforme type of rash has been associated with ponatinib.

CTCAE Grade	Action and Dose Modification
Grade 2 persistent* despite optimal symptomatic therapy, but not clinically significant	No change, continue ponatinib therapy, continue monitor every 2 weeks.

CTCAE Grade	Action and Dose Modification
Grade 2 persistent* despite optimal symptomatic therapy, is clinically significant	Hold ponatinib Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg: Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
Grade 3 persistent* despite optimal symptomatic therapy, but not clinically significant	No change, continue ponatinib therapy, continue monitor every 2 weeks.
Grade 3 persistent* despite optimal symptomatic therapy, is clinically significant	Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib

**Persistent rash is defined as 7 days.*

Guidelines for Supportive Care of Rash	
Type of Care	**Action**
Prevention/Prophylaxis	• Avoid unnecessary exposure to sunlight. • Apply broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15 at least twice daily. • Use thick, alcohol-free emollient cream (*e.g.*, glycerine and cetomacrogol cream) on dry areas of the body at least twice daily.
Symptomatic Care[a]	• Pruritic lesions: Cool compresses and oral antihistamine therapies. • Fissuring lesions: Monsel's solution, silver nitrate, or zinc oxide cream. • Desquamation: Thick emollients and mild soap. • Paronychia: Antiseptic bath, local potent corticosteroids in addition to antibiotics; if no improvement, consult dermatologist or surgeon. • Infected lesions: Appropriate bacterial/fungal culture-driven systemic or topical antibiotics.

Guidelines for Supportive Care of Rash	
Type of Care	**Action**
[a] Patients who develop rash/skin toxicities should be seen by a qualified physician and should receive evaluation for symptomatic/supportive care management.	

Dose Modifications for Hypertension

Patients receiving ponatinib have experienced hypertension and blood pressure should be monitored at each visit. In subjects with an initial BP reading within the hypertensive range, a second reading should be taken at least 2 minutes later, with the two readings averaged to obtain a final BP measurement. The averaged value should be recorded in the eCRF.
For patients who develop HTN or worsening HTN during study treatment, antihypertensive medication should be initiated or optimized to achieve target blood pressure before interruption or dose reduction of the study treatment at the discretion of the investigator. If hypertension is persistent despite adequate anti-HTN therapy including titration of anti-HTN medication or introduction of additional anti-HTN medications, or if grade 4 HTN develops, dose interruption, reduction or discontinuation is recommended. Patients with prior history of hypertension (on anti-hypertensive agents) should monitor/record their BP at home while on ponatinib therapy. Patients will be provided with a diary to record their at-home assessments.

Patients will obtain blood pressure assessments twice per week at home, using a blood pressure cuff supplied by Takedafor purposes of the research study. Any reading within the hypertensive range will be confirmed in clinic.

Event	Management Guideline	Dose Modification
Definitions used in the table: - Persistent hypertension: Hypertension detected in two separate readings during up to three subsequent visits. - Well-controlled hypertension: Blood pressure of SBP ≤140 mmHg and DBP ≤90 mmHg in two separate readings during up to three subsequent visits. - Symptomatic hypertension: Hypertension associated with symptoms (*e.g.*, headache, light-headedness, vertigo, tinnitus, episodes of fainting) that resolve after the blood pressure is controlled within the normal range. - Asymptomatic hypertension: SBP >140 mmHg and/or DBP >90 mmHg in the absence of the above symptoms.		

Event	Management Guideline	Dose Modification
(Scenario A) • Asymptomatic and persistent SBP of ≥140 and <160 mmHg, or DBP ≥90 and <100 mmHg, or Clinically significant increase in DBP of 20 mmHg (but still below 100 mmHg).	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. If BP is not well-controlled within 2 weeks, consider referral to a specialist and go to scenario (B).	Continue ponatinib at the current dose.
(Scenario B) • Asymptomatic SBP ≥160 mmHg, or DBP ≥100 mmHg, or Failure to achieve well-controlled BP within 2 weeks in Scenario A.	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP.	• Interrupt ponatinib. • Once BP is well-controlled, restart ponatinib at a reduced dose.
(Scenario C) • Symptomatic hypertension or Persistent SBP ≥160 mmHg, or DBP ≥100 mmHg, despite antihypertensive medication and dose reduction of study treatment	• Adjust current or initiate new antihypertensive medication(s). • Titrate antihypertensive medication(s) during the next 2 weeks to achieve well-controlled BP. • Referral to a specialist for further evaluation and follow-up is recommended.	• Interrupt ponatinib. • Once BP is well-controlled, restart ponatinib at a reduced dose.
(Scenario D) Refractory hypertension unresponsive to above interventions or hypertensive crisis.	Continue follow-up per protocol.	Discontinue ponatinib.

Dose Modifications for Ocular Toxicity

Ocular toxicities have occurred in clinical trials of ponatinib. Serious ocular toxicities leading to blindness or blurred vision have occurred in ponatinib-treated patients. Patients are required to have a standard ophthalmic exam performed by an ophthalmologist at baseline and as clinically warranted. The exam will include indirect fundoscopic examination, visual acuity (corrected), visual field examination, tonometry, and direct fundoscopy.

Retinal toxicities including macular edema, retinal vein occlusion, and retinal hemorrhage have occurred in ponatinib-treated patients.

Grade	Management Guideline	Dose Modification
Grade 1 Asymptomatic or symptomatic but not limiting ADL; intervention not indicated.	• Consult ophthalmologist within 7 days of onset. • Exclude ME, RVO, or RH. • Consult retinal specialist if available in case of ME, RVO, or RH • Continue follow up examination(s) (by retinal specialist if available) for ME, RVO, or RH	• Continue ponatinib at the same dose level until ophthalmologic examination can be conducted.* • If ophthalmologic examination cannot be performed within 7 days of onset, interrupt ponatinib until ME, RVO, or RH can be excluded and symptoms resolve. • If ME, RVO, or RH excluded restart ponatinib at same dose level. • If ME: **Permanently discontinue ponatinib**. • If RVO: **Permanently discontinue ponatinib**. • If RH: **Permanently discontinue ponatinib**.
Grade 2 and 3 Grade 2 defined as: Symptomatic with moderate decrease in visual acuity (20/40 or better; limiting instrumental ADL; local or non-invasive intervention indicated. Grade 3 defined as: Symptomatic with marked decrease in visual acuity or marked visual field defect (worse than 20/40 but better than 20/200); severe pain or medically significant; operative intervention indicated.	• Consult ophthalmologist immediately. • Exclude ME, RVO, or RH. • Consult retinal specialist in case of ME, RVO, or RH for follow-up exam. • Continue follow up examination(s) (by retinal specialist if available) for ME, RVO, or RH.	• Interrupt ponatinib until signs and symptoms have resolved to baseline. • If ME, RVO, or RH excluded and symptoms resolved to baseline, restart ponatinib reduced by one dose level. • If ME: **Permanently discontinue ponatinib**. • If RVO: **Permanently discontinue ponatinib**. • If RH: **Permanently discontinue ponatinib**.
Grade 4 Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse).	• Consult ophthalmologist immediately. • Exclude ME and RVO. • Continue follow up examination(s) (by retinal specialist if available) for ME and RVO.	**Permanently discontinue ponatinib.**
ME = macular edema; RVO = retinal vein occlusion; RH = retinal haemorrhage. SAE = serious adverse event * If visual changes are clearly unrelated to study treatment (*e.g.*, allergic conjunctivitis), monitor closely but ophthalmic examination is not required. * If ocular toxicities do not resolve within 14 days, permanently discontinue ponatinib.		

Dose modification for neuropathy

CTCAE Grade	Action and Dose Modification
Grade 1 or transient Grade 2	No intervention
Grade 2 lasting ≥7 days	Hold ponatinib Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg: Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
Grade 3 or 4	Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib

Dose Modifications for reduced left ventricular ejection fraction (LVEF).
Severe congestive heart failure (CHF) and left ventricular (LV) dysfunction have been reported in patients taking ponatinib. Patients should be monitored carefully for signs or symptoms consistent with cardiac failure. ECHOs must be performed at regular intervals as outlined in the Study Calendar. The same procedure (either ECHO or MUGA, although ECHO is preferred) should be performed at baseline and at follow-up visit(s). Consider discontinuation of ponatinib in patients who develop serious CHF.

Symptoms	LVEF-drop (%) or CTCAE grade	Action and Dose Modification
Asymptomatic	Absolute decrease of >10% in LVEF compared to baseline and ejection fraction below the institution's LLN.	• Interrupt ponatinib and repeat ECHO within 4 weeks. • If the LVEF **recovers** within 4 weeks (defined as LVEF ≥LLN and absolute decrease ≤10% compared to baseline): – Restart treatment with ponatinib at reduced dose by one dose level. – Repeat ECHO 4 and 12 weeks after re-start; continue in intervals of 12 weeks thereafter. • If LVEF **does not** recover within 4 weeks: – Consult with cardiologist. – **Permanently discontinue Ponatinib.** – Repeat ECHO after 4, 8, 12 weeks or until resolution.
Symptomatic[b]	• Grade 3: resting LVEF 39-20% or >20% absolute reduction from baseline • Grade 4: Resting LVEF ≤20%.	• **Permanently discontinue ponatinib.** • **Report as SAE.** • **Consult with cardiologist.** • Repeat ECHO after 4, 8, and 12weeks or until resolution.
[a] Symptoms may include: dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.		

Treatment delays at the start of treatment that are unrelated to drug will require restaging of the patient and re-initiating treatment. If at any time during the course of the trial, treatment is delayed over 3 weeks due to events unrelated to drug, treatment will resume as normal once the patient is deemed stable to continue.

Dose Modifications for General Non-hematologic Toxicities

CTCAE Grade	Action and Dose Modification

Grade 1 or transient Grade 2	No intervention
Grade 2 lasting ≥7 days with optimal care	Hold ponatinib Resume at 45 mg after recovery to ≤ grade 1 Recurrence at 45 mg: Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib
Grade 3 or 4	Hold ponatinib Resume at 30 mg after recovery to ≤ grade 1 Recurrence at 30 mg: Hold ponatinib Resume at 15 mg after recovery to ≤ grade 1 Recurrence at 15 mg: Discontinue ponatinib

Dose Modification for concurrent strong CYP3A inhibitors

The recommended dose should be reduced to 30 mg once daily when administering ponatinib with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole). Patients taking concomitant strong inhibitors may be at increased risk for adverse reactions.

7. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Expected adverse events include the adverse reactions that have at least possible relationship to ponatinib and are considered expected in ponatinib clinical studies. To mitigate the inherent risks in clinical studies of ponatinib, patients should be monitored closely while receiving treatment. A list of AEs (**Section 7.2**) for ponatinib is listed.

7.1 Definitions

7.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal

relationship with the treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. Any worsening of a preexisting condition, which is temporally associated with the use of the study drug (ie, occurs after the first dose of study drug), is also an AE.

AEs include:

- Abnormal test findings
- Changes in physical examination findings
- Other untoward medical events, regardless of their relationship to the study drug, such as injury, events that require surgery, accidents, or apparently unrelated illnesses
- Hypersensitivity

Additionally, AEs may include signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug abuse
- Drug misuse
- Drug interactions
- Drug dependency
- Exposure in utero

7.1.2 Serious Adverse Event

The Investigator will determine the seriousness of an AE based on the following.
An AE is considered a SAE if at least one (1) of the following conditions applies:

- *Death*: An AE that results in death is any patient death within 30 days of the last dose of study drug administration. The cause of death or AE that resulted in a fatal outcome is the SAE.

- *Life-threatening AE*: An AE that places the patient, in the view of the Investigator or Takeda, at immediate risk of death from the event as it occurred (ie, this does not include an event that had it occurred in a more severe form, might have caused death).

- *Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions* is defined as any substantial disruption of a person's ability to conduct normal life functions.

- *Inpatient hospitalization or prolongation of existing hospitalization*: Hospitalization refers to admission of a patient into a hospital for any length of time.

- *A congenital anomaly/birth defect*: A fixed, permanent impairment established at or before birth.

- *Overdose*: Any AE associated with an overdose of study drug. An overdose of study drug is defined as an occurrence of administered dose exceeding that which is prescribed by the investigator per protocol.

- *Important medical event*: Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not result in death, be life-threatening, or require hospitalization. However, if it is determined that the event may jeopardize the patient and/or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical events should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

AEs reported from clinical trials that require hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a health care facility meets these criteria. Adverse events that require emergency room care that do not result in hospital admission are not SAEs unless assessed by the investigator to be an important medical event. Hospitalization does not include the following:

- Hospice facilities
- Respite care
- Skilled nursing facilities
- Nursing homes
- Routine emergency room admissions
- Same day surgeries (as outpatient/same day/ambulatory procedure)

Hospitalization or prolongation of hospitalization in the absence of a precipitating AE is not in itself a SAE. Examples include:

- Social admission (eg, patient has no place to sleep)
- Protocol-specified admission during a clinical trial (eg, for a procedure required by the trial protocol)
- Optional admission not associated with a precipitating AE (eg, for elective cosmetic surgery that was planned prior to study enrollment [appropriate documentation is required for these cases])

7.1.3 Abnormal Test Findings

Test results meeting ≥ grade 3 CTCAE v4 criteria will be reported to the principal investigator and will be reported as adverse events.

7.2 Adverse Reactions for Ponatinib

The following adverse events and reactions described in this section can be found described in further detail in the prescribing information for ponatinib.

- Vascular Occlusion
- Heart Failure
- Hepatotoxicity
- Hypertension
- Pancreatitis
- Neuropathy
- Ocular Toxicity
- Hemorrhage
- Fluid Retention
- Cardiac Arrhythmias
- Myelosuppression

The adverse events described in this section were identified in a single-arm, open-label, international, multicenter trial in 449 patients with CML or Ph+ALL who disease was considered to be resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy including those with the BCR-ABL T315I mutation. All patients received a starting dose of 45 mg ponatinib once daily. At the time of analysis, the median duration of treatment with ponatinib was 337 days in patients with CP-CML, 362 days in patients with AP-CML, 89 days in patients with BP-CML, and 81 days in patients with Ph+ ALL. The median dose intensity was 37 mg or 83% of the expected 45 mg dose. The events of arterial ischemia, cardiac failure, and peripheral neuropathy reported in the tables below include data from an additional 13 months of follow-up (median duration of treatment CP-CML: 672 days, AP-CML: 590 days, BP-CML: 89 days, Ph+ ALL: 81 days).

Adverse reactions reported in more than 10% of all patients treated with ponatinib in this trial are presented in the table below. Overall, the most common non-hematologic adverse reactions (≥ 20%) were hypertension, rash, abdominal pain, fatigue, headache, dry skin, constipation, arthralgia, nausea, and pyrexia.

Adverse Reactions Occurring in >10% of Patients, Any Group

	CP-CML (N=270)		**AP-CML (N=85)**		**BP-CML (N=62)**		**Ph+ ALL (N=32)**	
System Organ Class	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**
Cardiac or Vascular disorders								
Hypertension (a)	68	39	71	36	65	26	53	31
Arterial ischemia (b)*	20	11	19	9	10	5	3	0
Cardiac Failure (c)*	7	4	6	4	15	8	6	3
Gastrointestinal disorders								
Abdominal pain (d)	49	10	40	8	34	6	44	6
Constipation	37	2	24	2	26	0	47	3
Nausea	23	1	27	0	32	2	22	0
Diarrhea	16	1	26	0	18	3	13	3
Vomiting	13	2	24	0	23	2	22	0
Oral mucositis (e)	10	1	15	1	23	0	9	3

	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
System Organ Class	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**
GI hemorrhage (f)	2	<1	8	1	11	5	9	6
Blood and lymphatic system disorders								
Febrile neutropenia	1	<1	4	4	11	11	25	25
Infections and infestations								
Sepsis	1	1	5	5	8	8	22	22
Pneumonia	3	2	11	9	13	11	9	3
Urinary tract infection	7	1	12	1	0	0	9	0
Upper respiratory tract infection	11	1	8	0	11	2	0	0
Nasopharyngitis	9	0	12	0	3	0	3	0
Cellulitis	2	1	4	2	11	3	0	0
Nervous system disorders								
Headache	39	3	28	0	31	3	25	0
Peripheral neuropathy (g)*	16	2	11	1	8	0	6	0
Dizziness	11	0	5	0	5	0	3	0
Respiratory, thoracic, and mediastinal disorders								
Pleural effusion	3	1	11	2	13	0	19	3
Cough	12	0	17	0	18	0	6	0
Dyspnea	11	2	15	2	21	7	6	0
Skin and subcutaneous tissue disorders								
Rash and related conditions	54	5	48	8	39	5	34	6
Dry skin	39	2	27	1	24	2	25	0
Musculoskeletal and connective tissue disorders								
Arthralgia	26	2	31	1	19	0	13	0
Myalgia	22	1	20	0	16	0	6	0
Pain in extremity	17	2	17	0	13	0	9	0
Back pain	15	1	11	2	16	2	13	0
Muscle spasms	12	0	5	0	5	0	13	0
Bone pain	12	<1	12	1	11	3	9	3
General disorders and administration site conditions								
Fatigue or asthenia	39	3	36	6	35	5	31	3
Pyrexia	23	1	31	5	32	3	25	0
Edema, peripheral	13	<1	19	0	13	0	22	0
	CP-CML (N=270)		**AP-CML (N=85)**		**BP-CML (N=62)**		**Ph+ ALL (N=32)**	
Pain	8	<1	7	0	16	3	6	3
Chills	7	0	11	0	13	2	9	0
Metabolism and nutrition disorders								
Decreased appetite	8	<1	12	1	8	0	31	0
Investigations								
Weight decreased	6	<1	7	0	5	0	13	0

	CP-CML (N=270)		AP-CML (N=85)		BP-CML (N=62)		Ph+ ALL (N=32)	
System Organ Class	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**	**Any Grade (%)**	**CTCAE Grade 3 / 4 (%)**
Psychiatric disorders								
Insomnia	7	0	12	0	8	0	9	0

Events) for assessment of toxicity.
Treatment-emergent, all causality events
(a) derived from blood pressure (BP) measurement recorded monthly while on trial
(b) includes cardiovascular, cerebrovascular, and peripheral vascular ischemia
(c) includes cardiac failure, cardiac failure congestive, cardiogenic shock, cardiopulmonary failure, ejection fraction decreased, pulmonary edema, right ventricular failure
(d) includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort
(e) includes aphthous stomatitis, lip blister, mouth ulceration, oral mucosal eruption, oral pain, oropharyngeal pain, pharyngeal ulceration, stomatitis, tongue ulceration
(f) includes gastric hemorrhage, gastric ulcer hemorrhage, hemorrhagic gastritis, gastrointestinal hemorrhage, hematemesis, hematochezia, hemorrhoidal hemorrhage, intra-abdominal hemorrhage, melena, rectal hemorrhage, and upper gastrointestinal hemorrhage
(g) includes burning sensation, skin burning sensation, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensorimotor neuropathy, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy
* represents an additional 13 months of follow-up

Serious Adverse Reactions

	N (%)
Cardiovascular disorders	
Arterial ischemic event*	53 (11.8%)
Cardiovascular	28 (6.2%)
Cerebrovascular	18 (4.0%)
Peripheral vascular	16 (3.6%)
Hemorrhage	22 (4.9%)
CNS hemorrhage	10 (2.2%)
Gastrointestinal hemorrhage	10 (2.2%)
Cardiac failure*	22 (4.9%)
Effusions(a)	13 (2.9%)
Atrial fibrillation	11 (2.4%)
Venous thromboembolism	10 (2.2%)
Hypertension	8 (1.8%)
Gastrointestinal disorders	
Pancreatitis	23 (5.1%)
Abdominal pain	17 (3.8%)
Blood and lymphatic system disorders	
Febrile neutropenia	13 (2.9%)
Thrombocytopenia	13 (2.9%)
Anemia	12 (2.7%)
Infections	
Pneumonia	24 (5.3%)
Sepsis	11 (2.4%)
General	
Pyrexia	14 (3.1%)

(a) includes pericardial effusion, pleural effusion, and ascites
* represents an additional 13 months of follow-up

Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of grade 3 or 4 thrombocytopenia, neutropenia, and anemia was higher in patients with AP-CML, BP-CML, and Ph+ ALL than in patients with CP-CML (see Table below).

Incidence of Clinically Relevant Grade 3/4* Hematologic Abnormalities

Laboratory Test	CP-CML (N=270) (%)	AP-CML (N=85) (%)	BP-CML (N=62) (%)	Ph+ ALL (N=32) (%)
Hematology				
Thrombocytopenia (platelet count decreased)	36	47	57	47
Neutropenia (ANC decreased)	24	51	55	63
Leukopenia (WBC decreased)	14	35	53	63
Anemia (Hgb decreased)	9	26	55	34
Lymphopenia	10	26	37	22

ANC=absolute neutrophil count, Hgb=hemoglobin, WBC=white blood cell count
*Reported using NCI-CTC-AE v 4.0

Incidence of Clinically Relevant Non-Hematologic Laboratory Abnormalities

Laboratory Test	Safety Population N=449	
	Any Grade* (%)	CTCAE Grade 3/4 (%)
Liver function tests		
ALT increased	53	8
AST increased	41	4
Alkaline phosphatase increased	37	2
Albumin decreased	28	1
Bilirubin increased	19	1
Pancreatic enzymes		
Lipase increased	41	15
Amylase increased	3	<1
Chemistry		
Glucose increased	58	6
Phosphorus decreased	57	8
Calcium decreased	52	1
Sodium decreased	29	5
Glucose decreased	24	0
Potassium decreased	16	2
Potassium increased	15	2
Sodium increased	10	<1
Bicarbonate decreased	11	<1
Creatinine increased	7	<1
Calcium increased	5	0
Triglycerides increased	3	<1

ALT=alanine aminotransferase, AST=aspartate aminotransferase.
*Graded using NCI-CTC-AE v 4.0

7.3 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
  If the AE is not defined in the CTCAE, the Investigator will determine the severity of the AE based on the following definitions:

  Mild (Grade 1): The AE is noticeable to the patient, but does not interfere with routine activity. The AE does not require discontinuing administration or reducing the dose of the study drug.

  Moderate (Grade 2): The AE interferes with routine activity, but responds to symptomatic therapy or rest. The AE may require reducing the dose, but not discontinuing administration of the study drug.

  Severe (Grade 3): The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuing administration or reducing the dose of the study drug.

  Life Threatening (Grade 4): The AE requires discontinuing administration of the study drug. The patient is at immediate risk of death.

  Death (Grade 5): The patient dies as a direct result of the complication or condition induced by administration of the study drug.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

The Investigator must provide attribution for all AEs (serious and non-serious). In addition, if the investigator determines a Serious Adverse Event (SAE) is associated with trial procedures, the investigator must record this causal relationship in the source documents and on the SAE form, and report such an assessment in accordance with the SAE reporting requirements.

7.4 Exchange of Safety Information

a) From The Ohio State University to Takeda:

- Serious adverse events, as defined in FDA regulations 21 CFR 312.32 are to be reported

to Takeda or Takeda's designee no later than at time of submission to the FDA per the time frames outlined in 21 CFR 312.32.

- OSU will provide a copy of any aggregate safety reports which have been submitted by the institution to the appropriate regulatory authorities in accordance with Applicable law, within 7 calendar days.
- Reports of pregnancies in female subjects and female partners of male subjects and pregnancy outcomes will be promptly provided to Takeda (no more than 10 calendar days after PI awareness).
- Study institution will promptly respond to Takeda queries on SAE and make available Medical Records or Study Data as Takeda may deem necessary to investigate and/or report on an adverse event.
- Reports of non-serious adverse events will be routinely collected during the course of the trial in an appropriately configured database and provided to Takeda with dedicated outputs.
- Provide Takeda with a list of any / all events within a reasonable timeframe of Takeda's request to support Takeda's management of the product safety profile (e.g. investigation of a potential new signal).
- Submit a final study report to Takeda, to include, when applicable, a list of all adverse events and special situation reports, when available, but within no more than 1 year of study completion. If study involves a publication, OSU will provide draft publication to Takeda at least 1 month prior to submission of final publication.
- OSU will provide reports of all vascular occlusive events to Takeda or Takeda's designee within 2 business days of awareness of the vascular occlusive event. OSU should expect follow-up queries from Takeda that will need a response. OSU will respond to Takeda queries as soon as possible after additional information is known at OSU, or made available by external participating sites.

Adverse Events of Special Interest (AESIs)

Vascular occlusive events have been identified as AESIs for ponatinib. These include arterial and venous thrombotic and occlusive adverse events that meet the criteria for SAEs (cross-refer to the section where the serious criteria are described and defined) and those adverse events that do not meet the SAE criteria. AESIs require ongoing monitoring by investigators and rapid identification and communication by the investigator to the study sponsor. All AESIs, whether SAEs or not, must be reported within 2 business days of the study sponsor awareness to Takeda. Takeda has determined that the events listed below (whether considered serious or non-serious by investigators) should be considered AESIs:

A. Myocardial infarction: Defined by the Third Universal Definition of Myocardial Infarction
B. Angina (newly diagnosed or worsening of existing angina or unstable angina)
C. Coronary artery disease (CAD) (newly diagnosed or worsening of existing CAD) or symptoms that may reflect cardiovascular disease
D. Cerebrovascular ischemic disease including ischemic or hemorrhagic stroke, vascular stenosis, transient ischemic accident (TIA), cerebrovascular occlusive disease documented on diagnostic neuroimaging, or symptoms that may reflect cerebrovascular disease

E. New onset or worsening of peripheral artery occlusive disease (eg, renal artery, mesenteric artery, femoral artery) or symptoms that may reflect peripheral vascular disease
F. Retinal vascular thrombosis, both venous and arterial
G. Venous thromboembolism where significant compromise of organ function or other significant consequences could result (eg, pulmonary embolism, portal vein thrombosis, renal vein thrombosis) or symptoms that may reflect venous thrombosis

Takeda may request additional information to the study sponsor on observed AESIs and this information should be provided in a timely fashion (ie, within 2 business days of the study sponsor awareness). All serious adverse events whether "reportable" as defined in this protocol or not, must be reported to Takeda. All expedited (7/15 day) reports will be sent to Takeda simultaneously or within 24 hours of study sponsor's submission to the competent authorities. Non-expedited SAE reports (except for AESIs) can be batched by the study sponsor and sent to Takeda on a monthly basis. Also, any event of a vascular occlusive nature, either serious or non-serious, must be reported to Takeda **within 2 business days** of the study sponsor's awareness.

The study PI or designee is responsible forTakeda reporting SAE reports to Takeda:

Toll-Free Fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

b) From Takeda to The Ohio State University:

- Investigator's Brochures and other reference safety information
- Takeda agrees to promptly notify Investigator in writing promptly of information that could affect the safety or medical care of current or former subjects, influence the conduct of the Study, or alter the IRB's approval.

c) From The Ohio State University to External Participating Sites:

- Investigator's Brochures and other reference safety information (e.g. safety reports)
- Serious adverse events
- Other non-serious, but notable toxicities

7.5 Serious Adverse Event Reporting Procedures

7.5.1 *Serious Adverse Event Reporting Period*

The Ohio State University will be solely responsible for reporting serious adverse events to the OSU IRB, FDA, and Takeda. Participating sites are only permitted to report directly to OSU and must report serious adverse events to the OSU PI and Multi-Site Coordinator within 24 hours of knowledge of the event. Serious adverse events are to be reported to the OSU IRB (per policy), FDA (per 21CFR312.32), and Takeda Drug Safety and Pharmacovigilance or its designated representative beginning from the time the patient is first administered investigational product

through and including 30 days after permanent discontinuation of the investigational product. Any SAEs occurring any time after the reporting period must be promptly reported to the OSU IRB (per policy), FDA (per 21CFR312.32) and Takeda Drug Safety and Pharmacovigilance or its designated representative if a causal relationship to the investigational product is suspected. When expedited reporting applies, OSU will provide Takeda with the submitted report of any expedited report concurrent to agency submission (no more than 1 business day/3 calendar days after the submission).

Patients must be followed for all AEs from the date the patient is first administered investigational product until at least 30 Days after the End of Treatment, and for all serious or study drug-related toxicities until the AEs are resolved or until patient contact discontinues.

7.5.2 *Immediate Reporting of Serious Adverse Events*

NOTE: External participating sites are NOT permitted to report directly to the FDA or The Ohio State University Office of Responsible Research Practices (ORRP [OSU IRB]). All reports must be sent to the OSU Principal Investigator and Multi-Site Coordinator for review and submission to the FDA and ORRP. Sites must also report to their IRB according to their institutional guidelines.

The Investigator or designee must notify the OSU PI and Multi-Site Coordinator within 24 hours of knowledge of an SAE. OSU will then notify the OSU IRB (per policy), FDA (per 21CFR312.31) and Takeda Drug Safety and Pharmacovigilance or its designated representative. A complete SAE report using the FDA MedWatch 3500A Mandatory Reporting Form must be submitted to OSU within 3 business days. Additional or follow-up information on a SAE must also be reported immediately (ie, within 24 hours of new SAE information) and on the MedWatch 3500A form. Should the FDA, OSU IRB, or Takeda require additional data on the event, the Investigator will be asked to provide those data to OSU in a timely fashion.

All SAEs should be reported to the OSU IRB using the most current version of the Event Reporting Form (available at http://go.osu.edu/Buck-IRB) and within time frames outlined in the IRB policy. SAEs reported from participating institutions will be reported to the IRB by the Multi-Site Coordinator. Participating institutions are responsible for reporting to their local IRB per their institutional guidelines.

7.5.3 *Information to be Provided by the Investigator for a Serious Adverse Event*

SAEs are to be reported using the FDA MedWatch 3500A Mandatory Reporting Form. Information about the SAE that must be provided includes (refer to the SAE Cover Sheet in the Supplemental Forms packet):

- Investigator identification
- Patient identification (eg, study assigned sequence ID)
- Information on study drug and concomitant therapies (eg, start/stop date, dose and frequency of study drug)
- Description of event

- Severity of the SAE
- Relationship of the SAE to the study drug, the patient's disease, or other contributing factors
- Outcome of the SAE

7.5.4 *Follow-up information on a Serious Adverse Event*

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained by the Investigator. For all SAEs, the investigator is obligated to pursue and provide information to the OSU PI. In addition, an investigator may be requested by the OSU PI to obtain specific information in an expedited manner. This information may be more detailed than that captured on the SAE form. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes such as concomitant medication and illnesses must be provided.

7.5.5 *Required Follow-up for Serious Adverse Events*

There should be routine follow-up for 30 days after permanent discontinuation of study drug in all patients in order to monitor for the occurrence of SAEs. If an SAE continues after the 30-day evaluation period, then the patient must be followed until the event resolves or stabilizes. The medical monitor may specify a longer period of time, if required to assure the safety of the patient.

7.5.6 *Takeda Responsibility for Expedited Safety Reports*

Takeda will notify investigators of all reportable SAEs. This notification will be in the form of an expedited safety report. The OSU Multi-Site Coordinator will distribute safety reports to the external participating sites. Upon receiving such notices, the investigator must review and retain the notice with other study-related documentation. The OSU PI and Institutional Review Board (IRB) will determine if the informed consent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information.
Suspected serious adverse reactions and other significant safety issues reported from the study shall be reported to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited safety reports and/or in aggregate reports), by Takeda or its designated representative.

7.5.7 *Pregnancy and other safety issues*

Females of childbearing potential and fertile males will be informed as to the potential risk of conception while participating in this study and will be advised that they must use effective contraception during the dosing and for a period of at least 4 months thereafter. A pregnancy test will be performed on each pre-menopausal female of childbearing potential prior to the first dose of study drug. A negative pregnancy test must be documented prior to administration of study drug.

If a patient is confirmed pregnant during the trial, study drug administration must be discontinued immediately. Information regarding a pregnancy must be immediately forwarded to the OSU PI, who will report the information to Takeda Drug Safety and Pharmacovigilance or its designated representative. OSU will notify Takeda of any pregnancy (patient or partner) while on drug (no more than 10 calendar days after PI awareness).

The Investigator must immediately report follow-up information to Takeda Drug Safety and Pharmacovigilance regarding the course of the pregnancy, including perinatal and neonatal outcome, regardless of whether the patient has discontinued participation in the study. If the pregnancy results in the birth of a child, additional follow-up information may be requested. If the pregnancy results in spontaneous abortion or stillbirth, the event should be reported as an SAE. Pregnancy outcomes must be collected for the female partners of any males who took study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

7.5.8 *Adverse error monitoring and reporting*

Adverse effects related to ponatinib will be monitored using a custom database and aggregate reports of AE (including type, CTCAE grade, duration, attribution and outcome) will be reported to the OSU DSMC, per policy.

OSU will notify Takeda of any safety findings that the PI determines may impact the risks/benefits of the drug (no more than 1 business day/3 calendar days after determination).

7.5.9 *Data safety monitoring plan*

Continuous evaluation of safety, data quality and data timeliness will be carried out. The PI will conduct continuous review of data and patient safety at their regular disease group meetings (at least monthly) and the discussion will be documented in the minutes. The PI of the trial will review toxicities and responses of the trial where applicable at these disease group 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 Takeda, to determine if the trial should be terminated before completion.

Serious adverse events and responses will also be reviewed by the OSUCCC –James Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report (quarterly) that will be reviewed by the committee per the DSMC plan. All reportable serious adverse events will also be reported to the Institutional Review Board (IRB) of record as per the policies of the IRB.

A mandatory monthly trial and safety review teleconference will be held for all participating sites. It will be expected that representatives from all participating sites be present for each call. Meeting minutes will document the attendance and discussions. Safety related information and data completion status will be minimally reviewed each month.

8. PHARMACEUTICAL AGENT INFORMATION

A list of the adverse events and potential risks associated with the investigational agent ponatinib administered in this study can be found in **Section 7.1**.

8.1 Ponatinib

The drug substance AP24534 (ponatinib) HCl is the mono-hydrochloride salt of the active moiety AP24534 free base.

Chemical name: 3-(Imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-(4-((4-methylpiperazin-1 yl) methyl)-3-(trifluoromethyl)phenyl) benzamide, hydrochloride salt

CAS Registry number: 1114544-31-8 (HCl salt)
943319-70-8 (free base)

Molecular Formula: $C_{29}H_{28}ClF_3N_6O$

M.W.: 569.02.

Approximate Solubility: The free base of AP24534 has solubility in hydrochloric acid-potassium chloride at pH 1.7 of 2.64 mg/mL. The free base of AP24534 has an aqueous solubility of less than 0.0001 mg/mL.

Mode of Action: orally-available TKI that is a potent inhibitor of BCR-ABL along with FGFR family members and other kinases including KIT, RET, PDGFRα, ABL1 and FLT3.

Description: Ponatinib HCl is an off-white to yellow crystalline, anhydrous solid

How Supplied: Ponatinib for investigational use is supplied as 15 mg and 45 mg round, white, film-coated tablets. Inactive ingredients in the capsule blend are colloidal silicon dioxide, lactose anhydrous, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The capsule shell contains gelatin and titanium dioxide. The tablet formulation includes inactive ingredients lactose monohydrate, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, polyethylene glycol, talc, polyvinyl alcohol, and titanium dioxide.

Storage and Handling: Ponatinib drug product is recommended for storage at controlled room temperature (20°C to 25°C [68°F to 77°F]).

Route of Administration: Oral, with or without food. Tablets should be swallowed whole. Should not be crushed or dissolved.

Potential Drug Interactions: Based on in vitro studies ponatinib is a substrate of CYP3A4/5 and to a lesser extent CYP2C8 and CYP2D6. Ponatinib also inhibits the P-glycoprotein (P-gp),

ATP-binding cassette G2 (ABCG2) [also known as BCRP], and bile salt export pump (BSEP) transporter systems in vitro.

Availability: Ponatinib is an investigational agent supplied by Takeda

9. BIOMARKER AND CORRELATIVE STUDIES

Integral

The primary hypothesis of the correlative component is that genomic alterations in FGFR (as well as KIT, RET, PDGFRα, ABL1 and FLT3) predict sensitivity and response to ponatinib. To corroborate the hypothesis, patients will have mandatory research biopsies and tumor sequencing to detect genomic alterations in these genes as well as the rest of the exome and transcriptome. Research biopsies and genomic sequencing are supervised and carried out in a companion tissue collection study, OSU precision study (OSU-13053/2013C0152), PI: Roychowdhury), or University of Michigan precision study (HUM00055952, *Determining feasibility of dissemination of molecular profiling data to patients with cancer. IRB FWA00004969),* PI: Dr. Arul Chinnaiyan. These IRB approved tissue collection and cancer profiling studies enroll eligible patients who have advanced or refractory metastatic cancer, to undergo mandatory tumor biopsy, integrated sequencing, bioinformatics analysis, and return of clinically significant sequence results to the treating oncologists and patients. An outline of the Precision Cancer Study process is shown in Figure 2. Importantly, the study includes CLIA-certified gene testing for the top ~200 cancer genes so that these results can be utilized for clinical-decision making such as trial eligibility. Patients with targetable molecular alterations can subsequently be treated with agents that target the respective genomic alterations.

The pilot version of the Precision Cancer Study opened at University of Michigan's Comprehensive Cancer Center in April 2011, under the direction of Dr. Roychowdhury and Dr. Chinnaiyan, and has enrolled 200 adult patients with advanced cancer to date.[45] The success rate for tumor biopsy was 89%, and there were no significant procedural complications (expected complication rate is <1 %).[46, 47] Therefore, the Precision Cancer Study would screen and identify candidate patients with tumors that harbor activating genomic alterations in *FGFR* (mutations, amplifications, fusions) or other genomic alterations (*KIT*, *RET*, *PDGFRα*, *ABL1* and *FLT3*) for the Phase 2 ponatinib therapeutic trial. OSU-13053 has been enrolling up to 4 metastatic cancer patients (any histology) every 2 weeks, scaling to 4 every week later this spring. To enable a clinically pertinent and feasible approach we use a CLIA-certified customized cancer gene panel (220 genes) that captures targetable genetic alterations such as point mutations (e.g. *BRAF* V600E mutation), copy number variations (e.g. *ERBB2* amplification) and gene fusions (e.g. *ALK*). In addition, patients will also undergo parallel "research sequencing" that entails whole "exome" and "transcriptome" sequencing.

A similar precision study is in place at University of Michigan (MI-ONCOSEQ/ HUM00067928; PI- Arul Chinnaiyan) that supervises research tumor biopsies, genomic sequencing strategies, and return of results. This study would screen and identify patients with tumors that harbor activating genomic alterations in *FGFR* (mutations, amplifications, fusions) and other genomic alterations (*KIT*, *RET*, *PDGFRα*, *ABL1* and *FLT3*), and is mandatory for enrollment into the trial at University of Michigan (sub-site).

Integrated

Patients who have activating genomic alterations in *FGFR, KIT, RET, PDGFRα, ABL1* or *FLT3* would be treated with ponatinib until disease progression. Eligible patients can undergo repeat tumor biopsies at the time of disease progression, and their tumors would be subjected to genomic (exome and transcriptome) and proteomic (RPPA) analysis and compared with pre-treatment analyses to evaluate for candidate mechanisms of resistance.

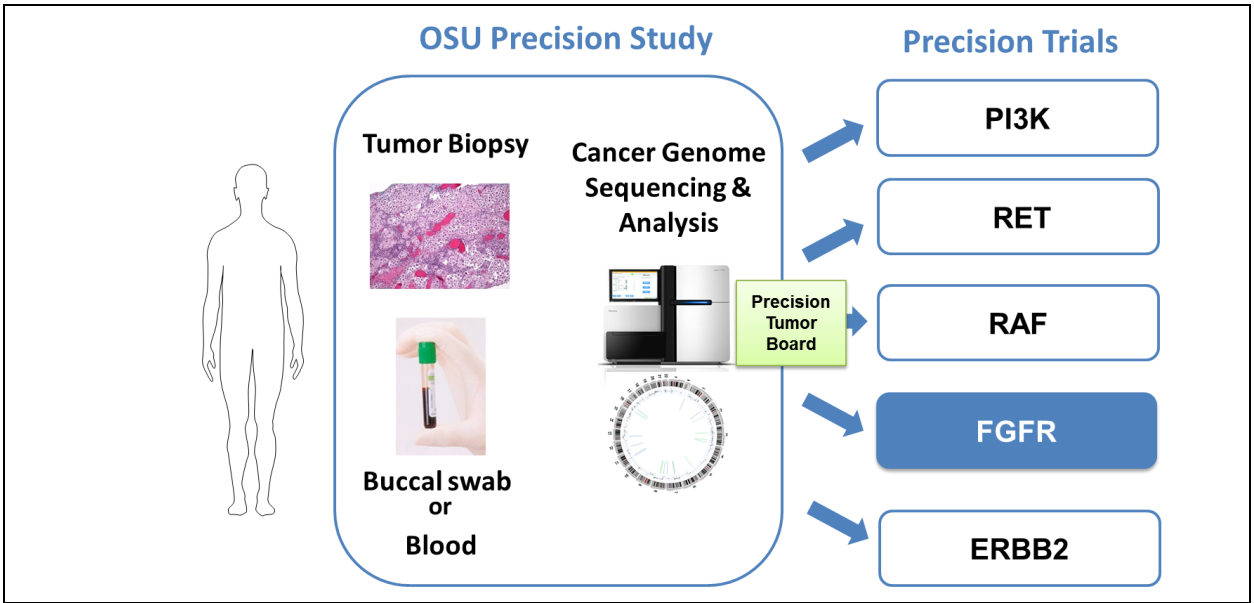

Figure-2: Precision cancer study process is shown. Patients with advanced or refractory metastatic cancer would undergo tumor biopsy and integrating sequencing. Patients with targetable alterations can subsequently be enrolled in trials that target the respective genomic alterations.

9.1 Collection of Specimens

Biospecimens will be collected at the beginning of the study. Consent and tissue management is supervised by the OSU Precision Cancer Study (OSU-13053, PI: Roychowdhury). Biospecimens included in this protocol may be fresh, frozen or fixed. Biospecimens may be collected through The Ohio State University outpatient and inpatient facilities. Generally, most procedures will occur through the Department of Radiology (Interventional procedures). However, some procedures could occur through other areas such as dermatology (skin biopsy) or operating rooms (undergoing a standard of care procedure that is anticipated to yield excess tissue). Previously collected tissue blocks, can also be used for sequencing. For complete details, please refer to the Precision Cancer Study protocol (OSU-13053). The Precision Cancer Study uses a secure Custom Database/LIMS to catalog, store, and track specimens.

9.1.1 Blood and Tissue Procurement:

A) Blood

Where possible, blood samples will be drawn from patients scheduled to have venipuncture for routine clinical purposes. When this is not possible, blood draws will occur at times other than those needed for routine clinical care. Generally, blood draws for research purposes will be 4 tablespoons of blood (amounts to 4-5 10mL tubes). Exception includes patient with hematological malignancies who require leukapheresis procedure as part of their routine clinical care, the leftover leukapheresis product may be collected and banked for the study
Blood Processing: Generally, the processing and storage of blood samples will involve the following: blood will be drawn into one or more tubes that contain EDTA, heparin or citrate for the collection and stored as serum, white blood cells or whole blood. To preserve patient and donor confidentiality, samples are given a specimen ID number. Serum and white blood cells will be separated from other cellular components by centrifugation, allocated into tubes, catalogued, and frozen at –80° C or viably in liquid nitrogen freezers. Samples may be processed for DNA, RNA, and/or protein.

B) Buccal smear
Buccal smears are a source of normal tissue for comparison to tumor samples. Three buccal smears will be obtained at the time of diagnosis or at routine follow-up evaluations. Samples are given a specimen ID number.
Buccal Smear Processing: Swabs will be processed for nucleic acid and/or protein and stored at -20° C or -80° C respectively.

C) Previously collected and processed biospecimens
Fixed or frozen specimens may also be obtained from participants. In some cases, patients referred to The Ohio State University clinics with a cancer diagnosis from outside hospitals will bring hematoxylin and eosin stained slides for routine review by pathologists. To preserve patient and donor confidentiality, samples are given a specimen identification number which will be entered into the sample database. Authorized study personnel will contact the institution where tissue was already obtained and request the appropriate sample. A copy of the informed consent will be provided to such institutions to allow release of the tissue or cut slides for research purposes. To preserve patient and donor confidentiality, samples are given a specimen ID (generated in Custom Database/LIMS) which will be entered into the sample database.

D) Tumor tissue biopsy
Tumor tissue or fluids will be collected from patients through the least invasive approach. Patients will receive informed consent detailing risks and benefits of the specific procedure. The list of possible procedures includes but is not limited to: percutaneous needle biopsy (liver, lung, breast, soft tissue mass), lymph node biopsy, bone marrow biopsy and aspirate, thoracentesis for pleural fluid and paracentesis for peritoneal fluid. When patients undergo tumor biopsy, they will receive a routine clinical consent as provided by the health care professional who performs the procedure. Generally, this will be staff from the Department of Radiology. This consent process will describe the procedure, risks, benefits, and alternatives.

Tissue Biopsy Processing. Freshly excised tissue will be placed in OCT medium and frozen immediately at -80 C. An H&E slide will be prepared for review by an OSU pathologist. To preserve patient and donor confidentiality, samples are given a specimen ID number. Patients who have progression of their cancer may choose to be re-consented for additional tissue

procurement including tumor biopsy and other samples. This is subject to the same eligibility and consent requirements.

Some clinical sites may not be completing pretreatment tumor biopsy due to resource limitations. These sites will provide the most recent archival tumor specimen available.

9.2 Laboratory Correlative Studies

Genome and Transcriptome Sequencing

Pretreatment tumor biopsy or archival specimen will undergo sequencing would as part of the **OSU Precision Cancer Study** (OSU-13053), a companion study to this trial. This study supervises collection of research tumor biopsies/archival specimens, germline tissue collection (blood, buccal swabs), genomic sequencing strategies, and return of results. This study shares data and samples for patients who subsequently participate in a therapeutic study such as this Phase 2 ponatinib trial. An integrative sequencing strategy, clinical and research would be utilized for this study. Clinical sequencing would be performed in CLIA-certified lab (Roychowdhury Lab) for a custom cancer panel of 220 genes. Research sequencing includes whole exome and transcriptome sequencing (RNASeq) of tumor to identify potentially informative mutations, amplifications, or gene fusions to evaluate for biomarkers of sensitivity and mechanisms of resistance. The custom cancer panel includes assessment of both DNA and RNA for 220 oncogenes (including *FGFR1*, *FGFR2*, *FGFR3*, and *FGFR4*) and tumor suppressors and is designed to detect point mutations, copy number changes, and gene fusions. The list of genes is shown in Figure 3.

A similar study is in place at University of Michigan (MI-ONCOSEQ/ HUM00067928; PI- Arul Chinnaiyan) that supervises collection of research tumor biopsies/archival specimens, genomic sequencing strategies, and return of results. This study would screen and identify patients with tumors that harbor activating genomic alterations in *FGFR* (mutations, amplifications, fusions) and other genomic alterations (*KIT*, *RET*, *PDGFRα*, *ABL1* and *FLT3*) for enrollment at University of Michigan.

CLIA Sequencing: Targeted gene sequencing is accomplished by solution-based hybridization capture with custom baits (Agilent) of both tumor (biopsy or archival specimen) and normal DNA (Blood). This is used to generate somatic point mutations and copy number changes using published tools (Varscan2, MuTect)[45, 48]. Targeted gene sequencing from RNAseq libraries is utilized to identify gene fusions involving FGFRs and analyzed using published fusion tools (Tophat2, Chimerscan)[49, 50]. All sample collection, processing, sequencing, and analysis will be completed in Dr. Roychowdhury's CLIA-certified lab.

Research Sequencing: For research sequencing, we would use Agilent's SureSelect whole exome capture and Illumina's TruSeqRNA protocols to prepare libraries for sequencing as previously described.[45] Libraries will be submitted to a vendor for sequencing on an Illumina HiSeq2000 instrument (Beijing Genomics Institute). Bioinformatics analysis will be performed in the lab to derive annotated single nucleotide variation, copy number alterations, and gene expression using existing tools as previously described (Exome: BWA, Varscan2, MuTect; RNAseq: Tophat2, Cufflinks).[45]

ABL1	CDK4	ESR1	FLT4/VEGFR3	MAP2K4	PAK7	ROCK1
ABL2	CDK6	EZH2	FOXL2	MAP3K1	PALB2	RPA1
AKT1	CDK8	FANCA	GNA11	MAP3K13	PAX5	RPTOR
AKT2	CDKN1B	FANCC	GNAQ	MCL1	PDGFRA	RUNX1
AKT3	CDKN2A	FANCD2	GNAS	MDM2	PDGFRB	SETD2
ALK	CDKN2B	FANCE	GRIN2A	MDM4	PDK1	SF3B1
APC	CDKN2C	FANCF	HGF	MEN1	SOX2	SH2B3
AR	CEBPA	FANCG	HRAS	MET	PIK3C2G	SMAD2
ARAF	CHEK1	FANCL	HSP90AA1	MITF	PIK3C3	SMAD3
ARID1A	CHEK2	FBXW7	IDH1	MLH1	PIK3CA	SMAD4
ASXL1	CHUK	FGF1	IDH2	MLST8	PIK3CG	SMO
ATM	CRBN	FGF10	IGF1	MPL	PIK3R1	SPOP
ATR	CREBBP	FGF12	IGF1R	MRE11A	PIK3R2	SRC
AURKA	CRKL	FGF14	IGF2R	MSH2	STK12	STAT3
AURKB	CRLF2	FGF17	IKBKE	MSH6	SUFU	STAT4
AXL	CTNNA1	FGF18	IKZF1	MTOR	PRDM1	STK11
BACH1	CTNNB1	FGF19	INHBA	MYC	PRKAR1A	TET2
BAP1	CYP17A1	FGF2	INSR	MYCN	PRKDC	TGFBR2
BARD1	DDR2	FGF22	IRF4	MYD88	PTCH1	TNKS
BCL2	DNMT3A	FGF23	JAK1	NCOR1	PTCH2	TNKS2
BCL2A1	DOT1L	FGF3	JAK2	NF1	PTEN	TOP1
BCL2L1	EGFR	FGF4	JAK3	NF2	PTK2	TP53
BCL2L2	EPHA3	FGF5	JUN	NFKB1	PTK2B	TRRAP
BCL6	EPHA5	FGF6	KDR/VEGFR2	NFKBIA	PTPN11	TSC1
BLM	EPHA6	FGF7	KIT	NOTCH1	PTPRD	TSC2
BRAF	EPHA7	FGF8	KRAS	NOTCH2	RAD50	TYK2
BRCA1	EPHB1	FGF9	LRP1B	NOTCH3	RAD51	VHL
BRCA2	EPHB4	FGFR1	LRP6	NOTCH4	RAF1	WT1
CARD11	EPHB6	FGFR2	LRRK2	NRAS	RARA	
CCND1	ERBB2	FGFR3	LTK	NTRK1	RB1	
CCND2	ERBB3	FGFR4	MAGED1	NTRK2	RET	
CCND3	ERBB4	FLT1/VEGFR1	MAP2K1	NTRK3	RHEB	
CCNE1	ERG	FLT3	MAP2K2	PAK3	RICTOR	

Figure 3: Gene Panel List

Reverse Phase Protein Assay (RPPA)

In addition to genome and transcriptome sequencing we would also perform RPPA to assess protein expression and modifications that characterize canonical pathways in cancers. This assay will be run at MD Anderson Cancer Center RPPA-Functional Proteomics Core Facility. Sections of the OCT embedded core biopsies/archival tumor specimens will be evaluated by a pathologist to verify tumor content. Tissue will then be cut out of the OCT and protein will be extracted using standard methods. The protein will be denatured, diluted and arrayed on nitrocellulose coated slides. The slides will be probed with a set of over 200 validated antibodies and spot density determined by MicroVigene software. Samples will be normalized for protein loading and concentrations will be determined using the Super Curve Fitting program. Supervised and un-supervised hierarchical clustering analysis will then be performed. Some of the proteins of interest that are included in this assay are; PI3KCA, total and phosphorylated forms of Akt, mTOR, Cyclin D1, ERK, MEK, p70-S6 kinase etc. RPPA data at the time of

disease progression to ponatinib would be compared with data prior to treatment with ponatinib to evaluate for putative mechanisms of resistance to FGFR targeting.

Data Integration: Using the exome sequencing, transcriptome sequencing, and RPPA, we can systematically characterize candidate mechanisms of resistance in the FGFR pathway at the time of disease progression with ponatinib. Putative changes of interest would likely include splice variants in FGFR, increased FGFR gene expression, point mutations or copy number variation in FGFR signaling pathways (PI3-kinase or MAP kinase).

9.3 Specimen Storage and Disposal

Specimens will be stored in designated and secure facilities at The Ohio State University. The Precision Cancer Study uses a secure Custom Database/LIMS to catalog, store, and track specimens. The Study stores specimens in monitored and locked freezers that are in a secure facility.
Generally, frozen tissue will be stored in secured -80ºC freezers. Storage and retrieval of fixed and paraffin embedded specimens will be handled using routine procedures of the Pathology Department affiliated with the hospital at which the specimen was collected. Disposal of biospecimens will be considered under certain circumstances including but not limited to reduced specimen integrity, exhausted capacity or insufficient funds for long-term maintenance or storage of low priority biospecimens. Determination of the integrity and priority of biospecimens is at the discretion of study personnel. The discarding of research specimens is also subject to any institutional policy and the informed consent under which the specimen was obtained.

9.4 Sites Performing Correlative Studies

- Integrated sequencing analysis (exome and transcriptome sequencing) would be performed at The Ohio State University (Dr.Roychowdhury Lab) and University of Michigan (Dr.Arul Chinnaiyan's Lab). Methodologies for exome and transcriptome sequencing are identical.

- The RPPA assay will be performed by MD Anderson Cancer Center RPPA-Functional Proteomics Core Facility.

9.5 Potential risks and procedures for minimizing risks

9.5.1 Risks of blood draws

All blood draws will be performed by trained personnel that use standard sterile techniques. Infection is unlikely since stringent aseptic techniques are followed during all venipuncture procedures.

9.5.2 Risks of biopsy

The risks of this study relate primarily to the risk of a biopsy. In general, these procedures are associated with a small risk of pain, bleeding, infection, and damage to adjacent organs. The magnitude of this risk depends somewhat upon the site of the procedure. Potential risks according to site are:

Risks of core breast biopsy:

- Likely: local discomfort and minor bleeding.
- Less likely: moderate or major bleeding, need for blood transfusion, hospitalization due to bleeding or other complications, infection, pneumothorax, damage to adjacent organs.

Risks of skin/chest wall punch biopsy:

- Likely: local discomfort and minor bleeding.
- Less likely: moderate or major bleeding, or infection

Risks of lymph node or soft tissue core needle biopsy:

- Likely: local discomfort and minor bleeding.
- Less likely: moderate or major bleeding, need for blood transfusion, hospitalization due to bleeding or other complications, infection, pneumothorax, damage to adjacent organs.
- Additional risks may be present if i.v. conscious sedation is required.

Risks of liver core needle biopsy:

- Likely: local discomfort and minor bleeding
- Less likely: moderate or major bleeding, need for blood transfusion, hospitalization due to bleeding or other complications, infection, bowel perforation or damage to adjacent organs
- Additional risks may be present if i.v. conscious sedation is required.

Lung biopsy core needle biopsy:

- Likely: local discomfort and minor bleeding
- Less Likely: moderate or major bleeding, need for blood transfusion, lung collapse, hospitalization due to bleeding or other complications, infection, damage to nearby organs, allergic reaction to the numbing medicine

Bone Marrow Biopsy:

- Likely: local discomfort and minor bleeding
- Less Likely: Nerve injury, blood collection at the site

In order to minimize the risk of a biopsy, only qualified personnel will perform these procedures. Prior to the procedure, the physician performing the procedure will discuss the risks with each study participant, answer any questions, and obtain separate procedure consent. For biopsies of lesions that are not superficial and clearly palpable, imaging studies such as CT, ultrasound, or MRI will be used to guide the biopsy in order to minimize the risk of damage to adjacent structures. After lymph node biopsies, patients will be observed for approximately 2 hours (range 2-4 hours) after the procedure, or per institutional standard guidelines. After liver biopsies,

patients will be observed for approximately 4 hours (range 4-6 hours) after the procedure, or per institutional standard guidelines. Less than the goal quantity of tissue is acceptable for each type of biopsy, and will be left to the clinical judgment of the physician performing the procedure.

All grade 3 or 4 events attributable to any of the study procedures will be reported to the Principal Investigator within 24 hours of occurrence. Adverse events will be reported by the PI to the IRB consistent with standard procedures.

9.5.3 Anesthesia Risk

Risks of local anesthesia

All biopsy procedures require local anesthesia using lidocaine, xylocaine, or related compounds. There is a small risk of an allergic reaction associated with these drugs.

In order to minimize the risk of local anesthesia, only qualified personnel will perform the biopsy procedure. Patients will be queried if they have had previous allergic reactions to local anesthetics.

Risks of intravenous conscious sedation

Certain biopsy procedures, such as lymph node or liver biopsies, may require intravenous conscious sedation (IVCS). IVCS is a minimally depressed level of consciousness that retains the patient's ability to maintain a patent airway independently and continuously and respond appropriately to physical stimulation and verbal commands.

The risks of intravenous conscious sedation include: inhibition of the gag reflex and concomitant risk of aspiration, cardiopulmonary complications (myocardial infarction, cardiac arrhythmias, hypoxemia), and allergic reactions to the sedative or analgesic medications. These risks are small but real; for example, in a prospective study of 14,149 patients undergoing IVCS during upper gastrointestinal endoscopies, the rate of immediate cardiopulmonary events was 2 in 1000. The 30-day mortality was 1 per 2,000 cases. In this study, there was a strong association between lack of monitoring and use of high-dose benzodiazepines with adverse outcomes. There was also an association between the use of local anesthetic sprays to the oropharynx and the development of pneumonia.

In order to minimize the risk of intravenous conscious sedation, only qualified personnel will be responsible for conscious sedation as per institutional protocols. A minimum of two individuals will be involved in the care of patients undergoing conscious sedation—the physician performing the biopsy procedure, and the individual (M.D. or R.N.) who monitors the patients and his/her response to both the sedation and the procedure, and who is capable of assisting with any supportive or resuscitative measures. The room where the procedure utilizing IVCS takes place will have adequate equipment to provide supplemental oxygen, monitor vital signs, and maintain an airway should this be necessary. An emergency cart will also be immediately accessible to the room where the procedure is to take place, and emergency support services will be available on page. Patients will be screened and evaluated for their fitness to undergo conscious sedation

by a trained physician. Following the procedure, patients will be observed closely in the recovery room according to standard institutional guidelines.

9.5.4 Risk of imaging studies

Some biopsy procedures require imaging studies, either to plan or guide the procedure. Imaging studies that may be used in obtaining tissue samples include CT scans and ultrasound. CT scans will expose study participants to controlled amounts of radiation. The total dose of radiation from these tests is not anticipated to cause any adverse effects. There is also a risk of an allergic reaction to the intravenous contrast dye used during CT imaging, as well as a risk of experiencing feelings of anxiety or claustrophobia while undergoing a CT scan. There are no anticipated risks with the use of ultrasound.

In order to minimize these risks, patients will be queried, as per standard institutional practice, regarding their history of reactions to intravenous contrast dye. If a patient has had such a reaction, she/he will be premedicated, or dye will not be used, as per standard institutional practice. If a patient has previously experienced anxiety or claustrophobia while undergoing a CT scan, anxiolytics may be considered as indicated.

10. STUDY CALENDAR

Baseline evaluation must be conducted within 2 weeks prior to start of ponatinib therapy. Imaging studies 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. Appropriate delays in study treatment or procedures are allowed to adjust for holidays or weekends. Each cycle is **28** days.

Study Assessments[1]	**Screen**	**During Ponatinib Therapy**		**Final Study Visit[3]**	**Follow-Up[9]**
Informed Consent	X				
Baseline Demographics	X				
Ophthalmic Exam[2]	X	As clinically indicated			
Medical History / Interim History	X	Day 1 (± 3 days) of each cycle		X	
Concomitant Medications	X	Continuous			
Physical Exam	X	Day 1 (± 3 days) of each cycle		X	
ECOG Performance Status	X	Day 1 (± 3 days) of each cycle		X	
Vital Signs (BP, HR,Temperature, weight)	X	Day 1 (± 3 days) of each cycle		X	
Blood Pressure (at home)[4]		Twice per week during cycle			
Chemistry[5]	X	Day 1 (± 3 days) of each cycle		X	
Triglycerides	X				
CBC, Diff, Plt	X	Every 2 weeks for first 2 cycles	Day 1 (± 3 days) from cycle 3		
Liver Function Testing		Cycle 1 Day 1	Once per month, or more frequent if clinically indicated		
Serum Amylase, Serum Lipase	X	Every 2 weeks for first 2 cycles	Day 1 (± 3 days) from cycle 3		
Pregnancy Test[6]	X				
12-Lead ECG	X	Repeated as Clinically Indicated			
LVEF (ECHO)	X	Repeated every 3 cycles ± 7 days or as Clinically Indicated			
Research Biopsy(s) [7]	Research biopsies on eligible	Research biopsies will be attempted on all patients at time of progression			

	patients prior to the study			
Study Agents		Ponatinib will be administered daily		
Tumor measurements[8]	X	Staging will occur after every 2 cycles ± 7 days or as Clinically Indicated		
Adverse Events		Continuous		

1. Assessments scheduled on days of dosing must be done prior to administration of study drug(s), unless otherwise specified.
2. Ophthalmic exam will include indirect and direct fundoscopy, visual acuity, visual field examination, tonometry and color fundus photos. Additional ophthalmic exams will be performed if symptomatically warranted.
3. Final Study Visit must occur 21 days (±7 days) after last dose of study drug.
4. Blood pressure cuff will be provided by Takeda. Patients will record readings in diary (Appendix B) and bring with them to clinic visits.
5. Including alkaline phosphatase, total bilirubin, albumin, creatinine, glucose, potassium, SGOT, SGPT, sodium, magnesium, chloride, bicarbonate, phosphate.
6. Perform only in women of child-bearing potential.
7. Research biopsies will be performed as part of the OSU Precision Cancer Trial (or through MI-ONCOSEQ for study enrollment at University of Michigan). Blood, buccal samples must also be obtained per **Section 9**.
8. Radiologic documentation must be provided for patients removed from the study due to progressive disease for solid tumors. CT chest/abdomen/pelvis is preferred. Bone scan, MRI or PET may be used at the discretion of treating physician.
9. Patients discontinuing for toxicity are followed until resolution of the toxicity, as outlined in **Section 5.4**. Patients who have discontinued protocol therapy will be followed every 3 months for 52 weeks or until death, whichever occurs first, in order to document time of progression (if patient did not progress while on study), survival, and to document subsequent alternate therapy received. For patients with resolution of toxicity to protocol therapy, telephone follow-up is permitted.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with ponatinib

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area may be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target**

lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which

greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-	No	SD	Documented at least once ≥4

	PD/not evaluated			wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

11.1.7 Response Review

All responses will be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images will occur.

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

With the advent of genomic profiling and targeted therapies, focusing on patients with a specific target (or genomic alteration) of interest regardless of disease type or histology is a new paradigm that cancer research is beginning to adopt. This is a Phase-2, "basket" study for patients with advanced cancers (stage 4, any histology) who have disease progression with at least one prior regimen, identified with predefined genomic alterations. Two separate cohorts will be accrued in parallel, defined by genomic *FGFR,* as well as *KIT, PDGFRα, ABL1, RET,* and *FLT3* alterations.
Cohort A will consist of patients identified with activating mutations or fusions in *FGFR* as well as patients with *FGFR* amplifications.
Cohort B will consist of patients identified with rare gene targets (*KIT, PDGFRα, RET, ABL1,* and *FLT3* alterations) for whom there may be downstream targeting and efficacy associated with ponatinib.
Our goal is to assess efficacy outcomes in these two cohorts when treated with ponatinib.

(a) Definition of primary outcome/endpoint:
The primary endpoint for each of the cohort in this study is overall response. Overall response is defined as the number of patients who achieve any response in the first 6 cycles of treatment. All eligible patients, selected by a CLIA approved assay, who have received at least one dose of ponatinib will be evaluable for response. Response for tumors would be assessed using the RECIST 1.1 criteria (using CT scans or calipers by clinical exam) where response will be defined as a partial or complete response.

(b)Definition of secondary outcomes/endpoints:
-Toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment per NCI CTCAE v4.0
-Overall survival is defined as the time from treatment initiation to death.
-Progression-free survival defined as the time from treatment initiation to progression or death

12.2 Analysis of Primary Objectives

Cohort A: *FGFR* mutations, fusions or amplifications

This cohort will utilize a two-stage Simon minimax phase II study design. In the relapsed/refractory setting for the multiple eligible disease types who have an *FGFR* mutation, fusion or amplification given the targeted nature of this regimen and preliminary data that support its use in those with *FGFR* mutations, fusions or amplifications, a true ORR of at least 20% would be considered promising in this patient population. Therefore, this study is designed to detect an ORR of at least 20% vs. the null hypothesis that the true ORR is at most 5%, representing a response by chance alone. Based on preclinical data, we expect that those with *FGFR* amplification may not be as susceptible to the targeting effects of ponatinib as those with *FGFR* mutation/fusions. We also expect that those patients identified with *FGFR* amplifications will be much more prevalent than those identified with *FGFR* mutations/fusions. To accommodate the possible confounding scenario of accruing a large majority of FGFR amplification only patients vs. mutations/fusions, we will stratify accrual, with planned enrollment of an equal number of *FGFR* amplification only and of FGFR mutation/fusion patients. Also, no more than 10 patients would be enrolled for a specific tumor type.

Decision Rule: The largest response rate where this treatment regimen would be considered ineffective in this population is 5%, and the smallest response rate that would warrant subsequent studies with this proposed regimen in this patient population is 20%. The following two-stage Simon minimax phase II study design requires a maximum of 30 evaluable patients to test the null hypothesis that the true response rate is at most 5%.

Constraining the Type I error rate to 5% and with at least 80% power, this two-stage Simon minimax study design will require 30 evaluable patients to test these hypotheses regarding the ORR with ponatinib in this patient population. As described above, to address possible confounding that could result from accruing a large majority of *FGFR* amplification only patients, a subpopulation that may not be as susceptible to the targeting of ponatinib, we will restrict accrual of the FGFR amplification only patients to 15, and accrue 15 patients identified as having FGFR mutations/fusions. No more than 10 patients would be enrolled for a single tumor type regardless of *FGFR* alteration.

Under this design, the first stage will enroll 10 evaluable patients. If we observe at least one response in the first stage, the study will proceed to the second stage and enroll an additional 20 evaluable patients. Given the expected greater prevalence rate of the *FGFR* amplifications, we expect that it is not unlikely that the first 10 patients accrued in this cohort will be all amplification only patients. If this is the case and no responses are observed, then we will consider this adequate early evidence that the regimen is not sufficiently active in the *FGFR* amplification only patients. At this point, we would keep accrual open, but only to the *FGFR* mutation/fusion patients. An interim decision rule would not be implemented in this subgroup of patients. If there are 0 responses in the first 10 all amplification patients, accrual of patients with FGFR amplifications would cease. Subsequently, 20 patients would be enrolled and enrollment would be restricted to patients with FGFR mutations and fusions.

In the final analysis, if we see at least 4 patients who have a response to treatment out of the 30 evaluable patients, we will consider this sufficient evidence that this combination regimen has promising activity in this patient population. Otherwise, if 3 or fewer patients have a response in the first 6 cycles of therapy, we will consider this regimen to not be sufficiently active in this population.

Analysis Plan: As described above, the proportion of responses for the purposes of this decision rule will be calculated out of all eligible patients who receive any treatment. Assuming the number of responses is binomially distributed, 95% binomial confidence intervals will also be calculated for the estimate of the proportion of responses.

Cohort B: KIT, PDGFRα, RET FLT3, ABL1 alterations

Design Summary: As mentioned above, this cohort will consist of patients identified with rare gene targets for whom there may still be downstream targeting and efficacy associated with ponatinib; these patients will include those identified with *KIT, PDGFRα, RET, ABL1,* and *FLT3* alterations. Given the variable types of genetic alterations that may be accrued to this cohort in addition to the multiple disease types, this cohort will be a pilot evaluation without a corresponding formal decision rule. This cohort will be open to accrual for the timeframe that Cohort A is open to accrual, with up to a maximum of 15 patients being accrued to this cohort. Our analyses for this cohort will be largely exploratory and descriptive, focusing on identifying the composition of patients who enrolled to this cohort in terms of their genetic alteration and disease type along with biomarker evaluations and clinical outcomes. While this cohort does not have specific endpoints associated with it, it provides a mechanism to make ponatinib available to those with rare genetic alterations and collects valuable preliminary data for ponatinib single agent therapy in the various types of patients who may be enrolled.

12.3 Sample Size/Accrual Rate

This trial would be conducted at two institutions to accrue up to 45 patients across all cohorts: 30 for Cohort A, and up to 15 for Cohort B. We have a Precision Cancer Study (Ohio State) that evaluates a pool of 400 patients per year with metastatic cancer through research tumor biopsies and comprehensive clinical tumor sequencing. From this pool, we would enrich patients with *FGFR* alterations. We expect to see actionable FGFR alterations in approximately 5% of 400 patients screened a year (200 this year) with advanced solid tumors with any histology. Similar precision trial is in place at University of Michigan (MI-ONCOSEQ), screening 400 patients a year. By combining screening from OSU and UM, we expect to see approximately 40 patients enrolled per year (5% of 800 screened). Quarterly review of accrual at each site would be carried out to identify the number of patients enrolled for therapy. Accrual should be complete in 12 to 18 months.

12.4 Analysis of Secondary Objectives

- Frequency and severity of adverse events and tolerability of the regimen will be collected and summarized by descriptive statistics. As per NCI CTCAE v4.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns for each of the cohorts as well as across cohorts. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and classified as either “unrelated” or “unlikely to be related” to study treatment in the event of an actual relationship developing. The incidence of severe (grade 3+) adverse events or toxicities will be described. We will also assess tolerability of the regimen through

assessing the number of patients who required dose modifications and/or dose delays. In addition, we will capture the proportion of patients who go off treatment due to adverse reactions or even those who refuse further treatment for lesser toxicities that inhibit their willingness to continue participation on the trial. All patients who have received at least one dose of any of the therapeutic agent will be evaluable for toxicity and tolerability.

- Overall and Progression Free Survival as time-to-event outcomes. Kaplan-Meier curves will be used to estimate the survival distributions of overall survival and progression-free survival for each cohort. Each of these variables is measured from the date of study registration to the date of event (ie, death and/or disease progression) or the date of last follow-up if no event has occurred.
- Clinical benefit rate (CBR) at 6 months. The 6-month CBR will be calculated by the number of patients who have achieve a response and/or are progression-free and alive at 6 months divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for CBR will be calculated.
- Correlative markers will be explored in this trial in relation to clinical outcomes of interest, and in particular in relation to the primary endpoint of overall response. Given the limited overall sample size as well as the relatively limited expected proportion of responses, these analyses will be largely exploratory and hypothesis-generating in nature. Correlative gene and protein markers will be summarized univariately in a quantitative manner and also summarized by clinical outcome group (e.g. response vs. no response). Graphical analyses will be largely used to assess potential patterns and relationships; e.g. side-by-side boxplots to assess differences in continuous marker levels between those with vs. without the clinical improvement (e.g. response vs. no response). Overall, hypothesis testing will largely be avoided given the sample size limitations but we will still obtain important preliminary data that can inform future studies and help better understand the mechanisms of this treatment regimen in this patient population.
- We would also evaluate and summarize the logistical aspects of the trial, including the rate of participation and enrollment of those screened and identified with the eligible genetic alterations. Also, of those enrolled, we will characterize the composition of the cohorts. Disease group-specific outcomes will also be summarized and described, although we will not be powered for any formal evaluation within a disease or histology subset. Still, these will be used as valuable preliminary data for hypothesis generation and designing future trials with this regimen and/or this treatment approach.

12.5 Reporting and Exclusions

12.5.1 Evaluation of Toxicity

All patients would be evaluable for toxicity from the time of their first treatment with ponatinib.

12.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3)

stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.).

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B MEDICATION DIARY

PATIENT ID: _____			PATIENT INITIALS (F M L): ___ ___ ___		DOSE PONATINIB _____ daily	CYCLE # _____
Date	**Day of Cycle**	**Day of Week**	**Time**	**Dose Missed**	**Patient Comments**	**Blood Pressure ###/## mmHg Take Twice Weekly**
Example1: 1/22/14	1	Mon	3 : 15 □ AM □ PM	☐		
Example 2: 1/23/14	2	Tues	_____:_____ □ AM □ PM	☒	Forgot to take my pills and didn't remember until the next day	
	1		_____:_____ □ **AM** □ **PM**	☐		
	2		_____:_____ □ **AM** □ **PM**	☐		
	3		_____:_____ □ **AM** □ **PM**	☐		
	4		_____:_____ □ **AM** □ **PM**	☐		
	5		_____:_____ □ **AM** □ **PM**	☐		
	6		_____:_____ □ **AM** □ **PM**	☐		
	7		_____:_____ □ **AM** □ **PM**	☐		
	8		_____:_____ □ **AM** □ **PM**	☐		
	9		_____:_____ □ **AM** □ **PM**	☐		
	10		_____:_____ □ **AM** □ **PM**	☐		
	11		_____:_____ □ **AM** □ **PM**	☐		
	12		_____:_____ □ **AM** □ **PM**	☐		
	13		_____:_____ □ **AM** □ **PM**	☐		
	14		_____:_____ □ **AM** □ **PM**	☐		
	15		_____:_____ □ **AM** □ **PM**	☐		

PATIENT ID: _____			PATIENT INITIALS (F M L): ____ ____ ____		DOSE PONATINIB _____ daily	CYCLE # _____
Date	**Day of Cycle**	**Day of Week**	**Time**	**Dose Missed**	**Patient Comments**	**Blood Pressure ###/### mmHg Take Twice Weekly**
	16		_____:_____ □ AM □ PM	☐		
	17		_____:_____ □ AM □ PM	☐		
	18		_____:_____ □ AM □ PM	☐		
	19		_____:_____ □ AM □ PM	☐		
	20		_____:_____ □ AM □ PM	☐		
	21		_____:_____ □ AM □ PM	☐		
	22		_____:_____ □ AM □ PM	☐		
	23		_____:_____ □ AM □ PM	☐		
	24		_____:_____ □ AM □ PM	☐		
	25		_____:_____ □ AM □ PM	☐		
	26		_____:_____ □ AM □ PM	☐		
	27		_____:_____ □ AM □ PM	☐		
	28		_____:_____ □ AM □ PM	☐		

DIRECTIONS: **Take by mouth daily with or without food. You will take the medication once per day, at the same time each day. If you miss a dose of your medication, you should take it as soon as you remember that day up to 6 hours past the scheduled time. If more than 6 hours has passed since the scheduled time, do NOT take the missed dose. Please inform your study doctor of any new medications you are taking.**

PLEASE REMEMBER: **bring this calendar and all pill bottles with you when you return to the clinic at the end of this cycle. Sign and date below. Thank you!**

Patient Signature:	**Date:**

OFFICIAL USE ONLY	Med. Amt. Dispensed:	Date Dispensed:	Completed By:
	Med. Amt. Returned:	Date Returned:	Date:

APPENDIX C INFORMATION ON POSSIBLE DRUG INTERACTIONS

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The patient _____ is enrolled on a clinical trial using the experimental agent ponatinib. This clinical trial is sponsored by Takeda. This form is addressed to the patient, but includes important information for others who care for this patient.

The agent **ponatinib** can interact with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Ponatinib interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question are **CYP3A4, CYP2C8 and CYP2D6**. CYP 3A4 is responsible for breaking down ponatinib in your liver.
- Ponatinib must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of these enzymes.
    - Substances that increase the activity of CYP 3A4 ("inducers") could reduce the effectiveness of **ponatinib** and should be avoided, while substances that decrease this enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
    - Co-administration with drugs that block acid production (e.g. antacids, proton pump inhibitors can reduce the absorption of **ponatinib.** They should be avoided unless the benefits outweigh the possible risk.

- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4, CYP2C8, CYP2D6, BCRP, and p-glycoprotein.**
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small and

located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

- Be careful:
    - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
    - If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
    - If you take herbal medicine regularly: Avoid these until the study is over. You should not take herbal supplements including, but not limited to, St. John's wort, kava, ephedra (ma huang), gingko biloba, yohimbe, saw palmetto, or ginseng. You should abstain from taking any herbal and dietary supplements for at least 2 weeks prior to the first dose of the study drug.

Other medicines can be a problem with your study drugs. You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you.
Your study doctor's name is Sameek Roychowdhury, MD. PhD and he can be contacted at.

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the agent **ponatinib.** This clinical trial is sponsored by Ariad Pharmaceuticals. **Ponatinib** can interact with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	➢ **Ponatinib** interacts with specific liver enzymes called **CYP3A4, CYP2C8, CYP2D6** , and must be used very carefully with other medicines that interact with these enzymes. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP3A4, CYP2C8, CYP3A or BCRP**." ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is **Sameek Roychowdhury** and can be contacted at (614) 293-6196

APPENDIX D PONATINIB MEDICATION GUIDE

Ponatinib- (ponatinib hydrochloride tablet), film coated
Takeda, Inc.

What is the most important information I should know about ponatinib?

Ponatinib can cause serious side effects, including:

Blood clots or blockage in your blood vessels (arteries and veins). Blood clots or blockage in your blood vessels may lead to heart attack, stroke, or death. A blood clot or blockage in your blood vessels can prevent proper blood flow to your heart, brain, bowels (intestines), legs, eyes, and other parts of your body. You may need emergency surgery or treatment in a hospital. Get medical help right away if you get any of the following symptoms:

- chest pain or pressure
- pain in your arms, legs, back, neck or jaw
- shortness of breath
- numbness or weakness on one side of your body
- trouble talking
- headache
- dizziness
- severe stomach area pain
- decreased vision or loss of vision

Blood clots or blockage in your blood vessels can happen in people with or without risk factors for heart and blood vessel disease, including people 50 years of age or younger. Talk to your healthcare provider if this is a concern for you.

Heart problems. Ponatinib can cause heart problems, including heart failure which can be serious and may lead to death. Heart failure means your heart does not pump blood well enough. Ponatinib can also cause irregular slow or fast heartbeats and heart attack. Your healthcare provider will check your heart function before and during your treatment with ponatinib. Get medical help right away if you get any of the following symptoms: shortness of breath, chest pain, fast or irregular heartbeats, dizziness, or feel faint.

Liver problems. Ponatinib can cause liver problems, including liver failure, which can be severe and may lead to death. Your healthcare provider will do blood tests before and during your treatment with ponatinib to check for liver problems. Get medical help right away if you get any of these symptoms of liver problems during treatment:

- yellowing of your skin or the white part of your eyes (jaundice)
- dark "tea-colored" urine
- sleepiness

See "What are the possible side effects of ponatinib?" for information about side effects.

What is ponatinib?

Ponatinib (Iclusig®) is a prescription medicine approved to treat adults who have:

- a specific type of abnormal gene (T315I-positive) chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML), T315I-positive Philadelphia chromosome positive acute lymphoblastic leukemia (Ph + ALL)
- chronic phase, accelerated phase, or blast phase CML or Ph+ ALL who cannot receive any other tyrosine kinase inhibitor (TKI) medicines

It is not known if ponatinib is safe and effective in children less than 18 years of age.

What should I tell my healthcare provider before taking ponatinib?

Before you take ponatinib, tell your healthcare provider if you:

- have a history of blood clots in your blood vessels (arteries or veins)
- have heart problems, including heart failure, irregular heartbeats, and QT prolongation
- have diabetes
- have a history of high cholesterol
- have liver problems
- have had inflammation of your pancreas (pancreatitis)
- have high blood pressure
- have bleeding problems
- plan to have any surgical procedures
- are lactose (milk sugar) intolerant. ponatinib tablets contain lactose.
- drink grapefruit juice
- have any other medical conditions
- are pregnant or plan to become pregnant. ponatinib can harm your unborn baby. You should not become pregnant while taking ponatinib. Tell your healthcare provider right away if you become pregnant or plan to become pregnant.
- are breastfeeding or plan to breastfeed. It is not known if ponatinib passes into your breast milk. You and your healthcare provider should decide if you will take ponatinib or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription medicines and over-the-counter medicines, vitamins, and herbal supplements. Ponatinib and other medicines may affect each other causing side effects.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ponatinib?

- Take ponatinib exactly as your healthcare provider tells you to take it.

- Your healthcare provider may change your dose of ponatinib or tell you to stop taking ponatinib.
- Do not change your dose or stop taking ponatinib without talking to your healthcare provider.
- Swallow ponatinib tablets whole. Do not crush or dissolve ponatinib tablets.
- You may take ponatinib with or without food.
- If you miss a dose of ponatinib, take your next dose at your regular time. Do not take 2 doses at the same time to make up for a missed dose.
- If you take too much ponatinib, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of ponatinib?

Ponatinib may cause serious side effects, including:

- See "What is the most important information I should know about ponatinib?"
- High blood pressure. Your blood pressure should be checked regularly and any high blood pressure should be treated while you are taking ponatinib. Tell your healthcare provider if you get headaches, dizziness, chest pain or shortness of breath.
- Inflammation of the pancreas (pancreatitis). Symptoms include sudden stomach-area pain, nausea, and vomiting. Your healthcare provider should do blood tests to check for pancreatitis during treatment with ponatinib.
- Neuropathy. Ponatinib may cause damage to the nerves in your arms, brain, hands, legs, or feet (Neuropathy). Tell your healthcare provider if you get any of these symptoms during treatment with ponatinib:
    - muscle weakness, tingling, burning, pain, and loss of feeling in your hands and feet
    - double vision and other problems with eye sight, trouble moving the eye, drooping of part of the face, sagging or drooping eyelids
- Effects on the eye. Serious eye problems that can lead to blindness or blurred vision may happen with ponatinib. Tell your healthcare provider if you get any of the following symptoms: perceived flashes of light, light sensitivity, floaters, dry or itchy eyes, and eye pain. Your healthcare provider will monitor your vision before and during your treatment with ponatinib.
- Severe bleeding. Ponatinib can cause bleeding which can be serious and may lead to death. Tell your healthcare provider if you get any signs of bleeding while taking ponatinib including:
    - vomiting blood or if your vomit looks like coffee-grounds
    - pink or brown urine
    - red or black (looks like tar) stools
    - coughing up blood or blood clots
    - unusual bleeding or bruising of your skin
    - menstrual bleeding that is heavier than normal
    - unusual vaginal bleeding
    - nose bleeds that happen often
    - drowsiness or difficulty being awakened

    - confusion
    - headache
    - change in speech
- Fluid retention. Your body may hold too much fluid (fluid retention). Tell your healthcare provider right away if you get any of these symptoms during treatment with ponatinib:
    - swelling of your hands, ankles, feet, face, or all over your body
    - weight gain
    - shortness of breath and cough
- Low blood cell counts. Ponatinib may cause low blood cell counts. Your healthcare provider will check your blood counts regularly during treatment with ponatinib. Tell your healthcare provider right away if you have a fever or any signs of an infection while taking ponatinib.
- Possible wound healing problems. If you need to have a surgical procedure, tell your healthcare provider that you are taking ponatinib. You should stop taking ponatinib at least 1 week before any planned surgery.
- A tear in your stomach or intestinal wall (perforation). Tell your healthcare provider right away if you get:
    - severe pain in your stomach-area (abdomen)
    - swelling of the abdomen
    - high fever

The most common side effects of ponatinib include:

- skin rash
- stomach-area (abdomen) pain
- tiredness
- headache
- dry skin
- constipation
- fever
- joint pain
- nausea

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of ponatinib. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ponatinib?

Store ponatinib at room temperature between 68°F to 77°F (20°C to 25°C). Keep ponatinib and all medicines out of the reach of children.

General information about ponatinib

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ponatinib for a condition for which it was not prescribed. Do not give ponatinib to other people, even if they have the same symptoms you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about ponatinib that is written for health professionals.

For more information, go to www.iclusig.com or call 1-855-552-7423.

What are the ingredients in ponatinib (Iclusig®)?

Active ingredient: ponatinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, sodium starch glycolate (type B), colloidal silicon dioxide and magnesium stearate. The tablet coating consists of talc, polyethylene glycol, polyvinyl alcohol and titanium dioxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured for:
ARIAD Pharmaceuticals Inc (a wholly owned subsidiary of Takeda Pharmaceutical Company Limited) .
40 Landsdowne Street
Cambridge, MA 02139-4234

Revised: March 2017

APPENDIX E COVID-19 PRECAUTIONS

Due to the emerging pandemic for *SARS*-CoV-2 virus, it has become necessary to enact social distancing and limit hospital and outpatient facility interactions and visits for vulnerable patient populations. Patients receiving active therapy to control their metastatic cancer are particularly vulnerable.

This study involves patients receiving an oral targeted therapy that can either control cancer growth (stable disease) and shrink cancer disease (partial or complete responses), thereby prolonging life and maintaining quality of life. It is vital that these patients continue to receive these therapies, but also important that we mitigate the risk of virus transmission for patients, providers, and family members. In the coming weeks and months, as governments manage the *SARS*-CoV-2 virus pandemic, it is quite possible that travel between states and cities may be limited, or that cities may have curfews. This amendment seeks to mitigate risk and enable ongoing care as feasible.

This appendix proposes the following changes for this investigator-initiated trial:

- Convert whenever possible all outpatient office visits to tele-medicine (video and phone) as necessary to continue monitoring, care, and treatment. Patients with concerning symptoms or labs from tele-medicine visits may be escalated to in-person evaluations as needed in the appropriate setting. This will serve to triage patients based on needs versus risk.
    - For example, some patients on this study may be on a well-tolerated and effective therapy dose for 6 to 30 months, and have little need to be seen in-person in the clinic if there are no changes or new issues.
- Patients will continue to have necessary blood work and scans to monitor for toxicities and disease status. Basic study procedures such as blood draws, radiographic scans, ECHO, ECG can be done by patients' local providers. These results will be reviewed by the Study Team centrally.
- ECHO and ECGs are for data collection, but are not expected to find rare abnormalities. These can be deferred unless prompted by symptoms or clinical concern.
- We will provide the option for oral therapies to be shipped to patients from our Investigational Drug Pharmacy or patients/family members could pick them up.
- Depending on circumstances, local healthcare providers in another city may be required to assess and evaluate patients, and the PI will communicate with these providers to facilitate care as it relates to study treatment.
- On-treatment biopsies, as well as post-progression studies or biopsies, may be deferred depending on the availability of resources in the healthcare system.

Our Team has over 5 years of experience treating and managing patients with this oral therapy, and we are confident that this will ensure ongoing therapy that is beneficial and safe.

Time Frame: This amendment is expected to span a duration of 6 months, and will re-assess the clinical situation prior to the end of this period.

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