A phase Ib/II study of BGJ398 in combination with imatinib mesylate in patients with untreated advanced gastrointestinal stromal tumor (GIST)

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MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

A phase Ib/II study of BGJ398 in combination with imatinib mesylate in patients with untreated advanced gastrointestinal stromal tumor (GIST)

In current standard of care, prolonged efficacy of imatinib mesylate is limited in patients with locally advanced/unresectable or metastatic Gastrointestinal Stromal Tumors (GISTs). Importantly, imatinib induces mainly cytostatic effects in the majority of patients with limited apoptotic effect and affords little, if any, hope to cure a patient with locally advanced or metastatic disease. About 50% of patients respond to imatinib in the first-line setting, but nearly all patients with advanced disease will develop imatinib-resistance with a median time to progression of 20-24 months after initiation of therapy[1-4]. Second and third line options have very limited efficacy with response rate of 4-10% and median Progression Free Survival (PFS) rates of 4-6 months [5-7].

This is a phase Ib/II study of a FGFR inhibitor (BGJ398-Novartis) in combination with imatinib mesylate (Gleevec - Novartis) as a first line therapy in patients with untreated locally advanced or metastatic GIST. The study is designed to specifically target the FGFR and MAPK pathways in conjunction with c-KIT in GIST. We believe that this novel combination strategy will prove to be more effective than single agent imatinib and provide an effective therapeutic regimen that will help patients with advanced GIST. The combination therapy will do this by targeting the MAPK pathway, a major pathway implicated in the development of resistance to single agent imatinib, and a critical lineage specific survival factor of GIST and its precursor ICC-*ETV1*. Moreover, we believe that the combination therapy will significantly enhance apoptosis and potentiate the efficacy of treatment. We believe this strategy will also effectively address many of the imatinib-resistance mechanisms that are in part mediated by FGFR signaling.

The primary goal of the phase Ib study is to assess the tolerability and safety of the combination therapy. Once the highest tolerable dose is identified or the clinical doses of imatinib (400 mg daily) and BGJ398 (125 mg qd – three weeks on and one off) are reached, the phase II portion of the study will be initiated. The primary endpoint of the phase II portion is to assess Response Rate (RR) (complete response (CR) + partial response (PR)) by RECIST 1.1.

The phase Ib portion of the study will be performed in standard 3+3 fashion. The phase Ib portion of the study will be open to all patients with locally advanced or metastatic GIST who have progressed on imatinib. An initial cohort of three eligible patients with locally advanced or metastatic GIST will initiate treatment with BGJ398 at 75 mg daily (three weeks on and one off) and imatinib at 400 mg daily for 4 weeks (1 cycle). Depending on the toxicity, dose levels of imatinib (400 mg daily) + BGJ398 will be investigated as outlined below (Table 1). As imatinib 400 mg PO QD is standard of care for metastatic GIST, this dose will remain constant (barring individual dose modifications outlined in section 9.2a).

Table 1: The dose escalation schema:

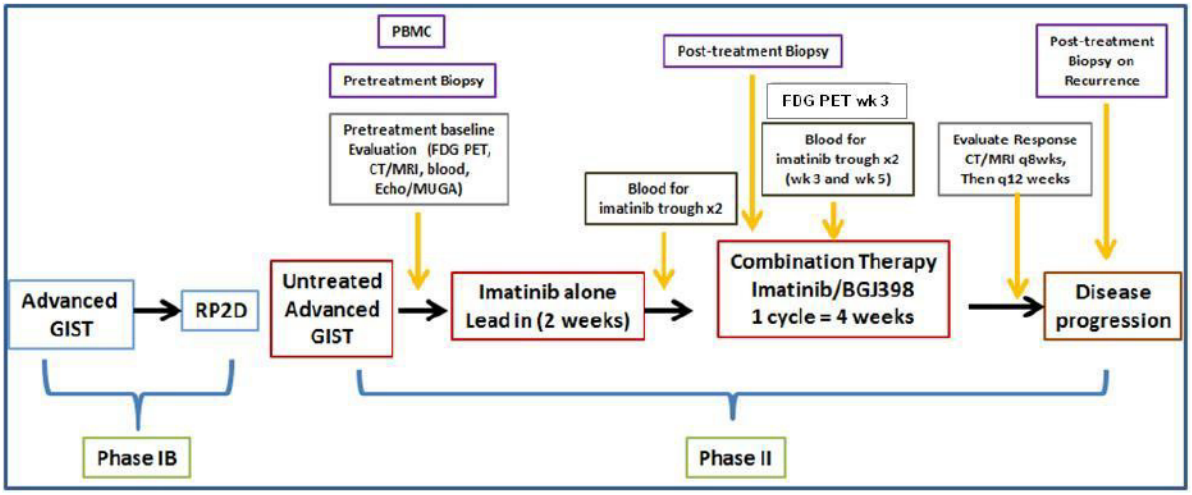
Dose Level	Imatinib	BGJ395
-2	400mg daily	25 mg qd

-1	400 mg daily	50 mg qd
1	400 mg daily	75 mg qd
2	400 mg daily	100 mg qd
3	400 mg daily	125 mg qd

Any adverse event that meets criteria in section 9.1 that occurs prior to the second cycle (i.e. before C2D1) will be considered a Dose Limiting Toxicity (DLT) for the purposes of dose escalation to the next dose level. Any adverse event that occurs after the first cycle may require a dose reduction for the patient but will not impact the assessment of dose level safety.

The phase II portion of the study will be used to confirm the safety and tolerability of the combination and to assess additional efficacy signals of the combination in patients with untreated locally advanced or metastatic GIST. Response Rate (RR) by RECIST 1.1 will be the primary endpoint. Secondary endpoints will include RR by Choi criteria and EORTC criteria for partial response on FDG PET (25% reduction in PET SUVmax) 3 weeks (C1D21) after combination treatment, PFS, OS and resectability rates. Also, the trial will be rich in molecular correlates/exploratory endpoints that will include MAP kinase, FGFR, and KIT signaling pathway inhibition, evaluation of FGF2 and FGFR levels on tumor tissue, FGF2 serum levels, ETV1 inhibition assessed by ETV1 protein levels, and its transcriptional activity based on a custom *ETV1*-dependent gene signature. This combined analysis will be critical to properly design future clinical trials of this combination in patients with locally advanced or metastatic GIST.

The trial phase Ib/II schema is outlined below: (Schema 1):



All participants on the Phase II portion will have a 2-week lead in of imatinib alone. Blood will be drawn at the end of this period to establish steady-state trough imatinib serum levels. After blood for imatinib levels are obtained, BGJ398 at the recommended Phase II dose (RP2D) and schedule will be added to the regimen. The initiation of BGJ398 will not be contingent on the imatinib level; rather,

BGJ398 can be started after the blood draws for imatinib levels are performed. The start of the combination therapy will be considered Cycle 1, Day 1.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Hypothesis: Targeting the MAPK pathway and FGFR signaling by combining BGJ398 and imatinib will be a safe and a more effective therapeutic strategy than imatinib alone in patients with untreated locally advanced or metastatic GIST.

Primary Objective:

Phase Ib study: to assess the safety and tolerability of treatment with BGJ398 (an FGFR inhibitor) in combination with imatinib and to determine the MTD and the recommended Phase II dose (RP2D) and schedule of the combination therapy in locally advanced or metastatic GIST patients.

Phase II study: to assess the efficacy (RR = complete response (CR) + partial response (PR)) at 32 weeks of the combination therapy of BGJ398 and imatinib in patients with untreated locally advanced or metastatic GIST, using RECIST 1.1.

Secondary Objectives:

Phase Ib study: to assess the pharmacokinetics of BGJ398 and imatinib; to estimate RR (CR + PR) by 32 weeks by both RECIST 1.1 and CHOI criteria, progression free survival (PFS) and clinical benefit rate (CR+PR+SD) at 32 weeks of the combination therapy of BGJ398 and imatinib in all locally advanced or metastatic GIST patients who have received prior therapy with imatinib.

Phase II study: to assess the RR (CR + PR) of the combination therapy of BGJ398 and imatinib by CHOI criteria, and by EORTC criteria for partial response on FDG PET (25% reduction in PET SUVmax), PFS, overall survival (OS), clinical benefit rate (CR+PR+SD) at 32 weeks and resectability rates in patients with untreated locally advanced or metastatic untreated GIST.

Correlative Objective*:*

We will analyze the molecular and signaling effects of imatinib in combination with BGJ398 using tumor biopsy specimens collected pre- and post-treatment (C1D8), and (if feasible) upon disease progression. Biopsies will be performed on a minimum of 20 patients from the Phase II portion of the study across all sites. In addition, blood and serum will be collected throughout the trial. All of these samples will be used to analyze the pharmacodynamic effects of BGJ398 in combination with imatinib on the following and correlate with clinical response to help identify promising prognostic or predictive biomarkers for further study:

- ETV1 protein level by western blot (WB)
- ETV1-dependent transcriptome (expression profile of *ETV1*-dependent gene targets) by nanostring.
- Expression of genes implicated in GIST pathogenesis and signaling, including KIT, ETV1, FGFR1, -2, -3, and -4; DUSP6, SPRY2, and SPRY4.
- Cell proliferation (Ki-67) and apoptosis (cleaved caspase-3) by IHC

- MAP kinase pathway and other pathways downstream of KIT signaling using standard antibodies (phospho-ERK, phospho-KIT, phospho-MEK, phospho-AKT) by IHC
- *KIT/PDGFRA* mutational status in matched tumor biopsy specimens collected prior to therapy, after combination therapy and upon disease progression. FGFR and FGF2 expression on tumor samples by IHC and FGF2 ligand levels in collected serum by ELISA.
- Protein expression of FGF2, sVEGFR1, sVEGFR2, VEGF-A, -C, -D, cKIT, PLGF, and Tie2 in tumor tissues utilizing commercially available immunoassay kits

We will also monitor the effect of BGJ398 on imatinib serum levels by measuring the steady-state imatinib serum trough levels at the end of the 2-week lead in imatinib alone phase and after the combination of BGJ398 and imatinib therapy at week 3 and week 5 (C1W3 and C2W1).

3.0 BACKGROUND AND RATIONALE

3.1 Targeting ETV1 in GIST

3.1.1. KIT inhibition by TKIs in GIST: although effective, tumor resistance invariably occurs

Gastrointestinal stromal tumor (GIST) represents one of the most common subtypes of human sarcomas. GIST is thought to arise from the Interstitial Cells of Cajal (ICCs), which highly express the *KIT* receptor tyrosine kinase (RTK) [8]. The majority of GISTs harbor activating mutations in the *KIT* RTK, and to a lesser extent in the *PDGFRA* RTK and *BRAF* serine/threonine kinase [9-11], and these mutations are thought to function as oncogenic "driver" mutations required for growth and survival of GIST. These observations have provided the scientific rationale for the clinical success of using tyrosine kinase inhibitors (TKIs), e.g. imatinib mesylate (Gleevec®), in the management of advanced GISTs.

Imatinib has become the first line standard of care in advanced GIST, with a response rate (RR) of approximately 45-50% and overall disease control in 80% to 85% of patients, as well as a median progression free survival (PFS) of 20 to 24 months [3, 4, 12]. Despite the early clinical success, the majority of patients develop resistance to imatinib within 2-3 years of treatment [3, 13]. Two second line therapeutic options exist in current standard of care for GIST patients that have progressed on 400mg of imatinib per day. One strategy entails increasing the imatinib dose from 400mg to 800mg daily, which has a median time to progression (TTP) of 12 weeks and primarily benefits patients with *KIT* exon 9 mutations [4, 13, 14]. Alternatively, patients can switch therapy from imatinib to sunitinib malate, another multi-targeted TKI that inhibits *VEGF/PDGFR/KIT*, which has a median TTP of 27.3 weeks [15]. Recently, the FDA approved regorafenib as a third-line treatment for GIST based on a randomized placebo controlled Phase III trial in which regorafenib showed a 3.9 month improvement in PFS over a placebo and a response rate of 4.5% [7]. The limited response rate of sunitinib in the second line setting and the documented lack of efficacy seen with TKIs in the third line setting clearly indicate that a general disease resistance to this class of inhibitors develops once disease progression occurs on imatinib. Despite these clinical observations, progress has been slow in identifying and applying novel treatment strategies for patients with imatinib (and hence other TKI) resistant disease.

The mechanisms of imatinib resistance in GIST are complex and heterogeneous. Approximately 5% of patients have primary resistance to imatinib with progression of disease within two months of treatment. About 14% of patients develop early resistance to imatinib after approximately 4 months

of treatment. The majority of patients develop resistance to imatinib after approximately 2-3 years of treatment [12]. Secondary mutations are rare in primary resistance, but are found in about 50-67% of patients with secondary resistance [16, 17]. The rest of secondary resistance has unknown etiologies. Other causes of secondary resistance are still being defined; researchers at MSKCC recently correlated an intratumoral immune response with imatinib resistance in GIST [18]. Moreover, recent data suggest that the GIST stem/progenitors are *KIT*-low and *KIT*-independent and therefore imatinib-insensitive [19], which might account for part of the resistance mechanisms in both primary and secondary resistance settings. In addition, activation of alternative signaling pathways such as the MAP Kinase pathway and the PI3K pathway have also been correlated with the development of primary imatinib resistance [20]. In summary, although *KIT* inhibitors have revolutionized the treatment of advanced GIST, the efficacy is not indefinite and it is not curative in most advanced GIST patients [3, 4, 12, 21-24].

Here, we propose a novel strategy that combines inhibition of both KIT and FGF signaling pathways. The goal of such dual inhibition is to not only target KIT, but also the MAP Kinase pathway (via FGF signaling). We have recently discovered that the MAP Kinase pathway plays a major role in the pathogenesis and propagation of GIST by stabilizing ETV1 [25]. ETV1 is a lineage specific survival factor in GIST that cooperates with mutant KIT in oncogenesis. *ETV1* is a master regulator of an ICC-GIST-specific transcription network. The *ETV1*-dependent transcriptional program is further regulated by activated *KIT*, which prolongs ETV1 protein stability via its downstream MAP kinase signaling pathway and strongly cooperates with *ETV1* to promote tumorigenesis (Figure 1) [26]. The fact that *ETV1* is a lineage- specific transcription factor required for the survival of the ICC/GIST lineage and may define the optimal cellular context for *KIT*-mediated oncogenesis indicates that *ETV1* may also be critical for the survival and maintenance of the intrinsically imatinib-resistant, *KIT*-independent stem cell/progenitors in GIST and posits *ETV1* as a novel therapeutic target in both imatinib-sensitive and -resistant GIST. While it is challenging to target transcription factors, the observation that the ETV1 protein level is stabilized by active MAP kinase signaling has provided us with the scientific rationale to explore the therapeutic potential of targeting ETV1 protein stability by inhibiting the MAP kinase signaling pathway in both imatinib-sensitive and -resistant GISTs. This strategy if successful, shall bypass the differential efficacy of imatinib and sunitinib on GIST tumors with different *KIT* mutational status, and potentially be effective for all GISTs, including those of the GIST stem/progenitor pool.

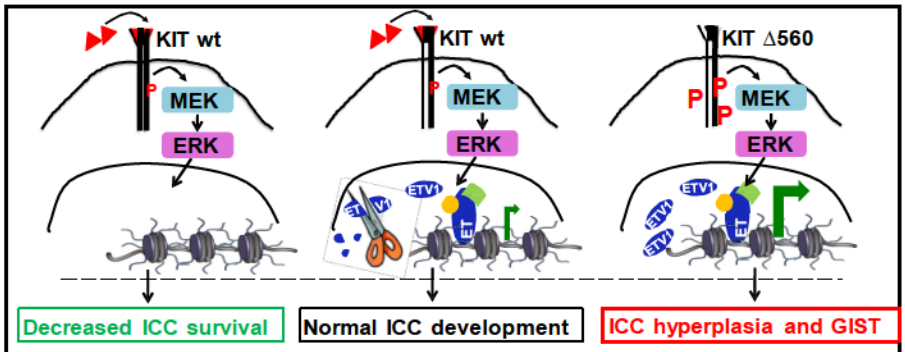
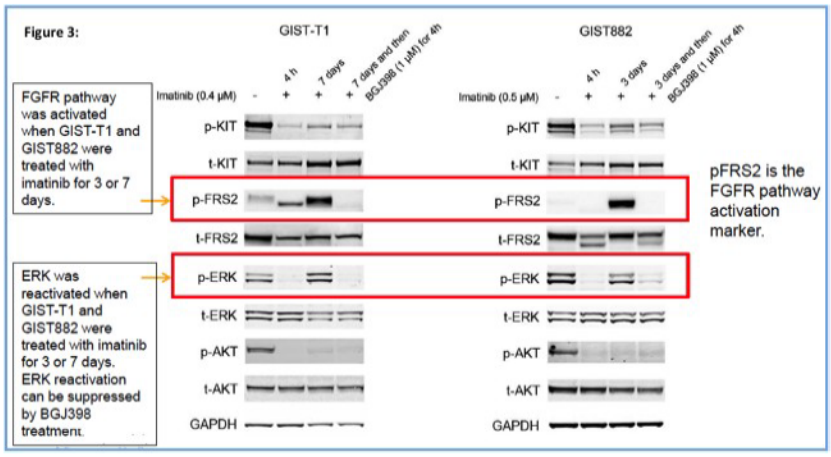
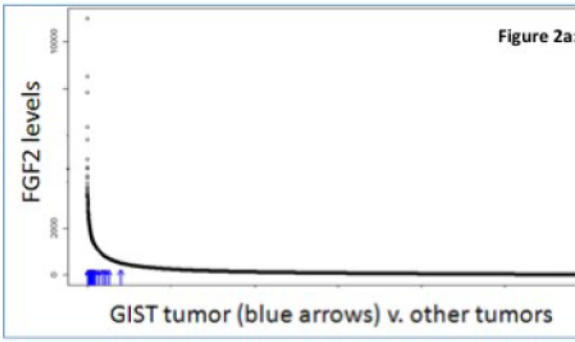


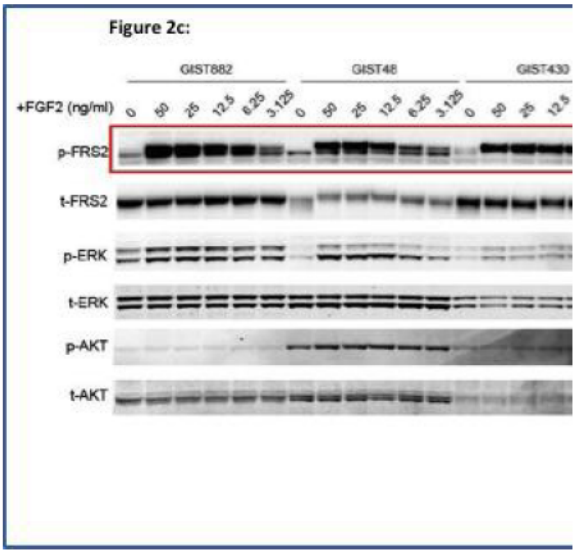
Figure 1. Model of the role of ETV1 in ICC maintenance and GIST oncogenesis. Normal level of KIT activation by KIT ligand (red triangle) stabilizes ETV1 transcription factor through the MAPK pathway, and results in physiological ETV1 transcriptional output critical for ICC development (middle). In the absence of ETV1, there is decreased ICC development, which phenocopies genetic loss of KIT signalling (left). Activating mutation of *KIT* (e.g. *KITΔ560*) leads to constitutive activation of the KIT-MAPK signalling pathway, increased stabilization and augmented ETV1 transcriptional output that promotes tumorigenesis (right).

3.1.2 Gastrointestinal Stromal Tumors Overexpress FGF

The FGF pathway has recently been identified as a possible mediator in the development of GIST resistance to imatinib. Preclinical work has established FGF2 as being highly overexpressed in GIST tumors as compared to multiple other malignancies (Figure 2a). The FGF Receptor (FGFR) is also upregulated in GIST when compared to other tumors (Figure 2b). Stimulation of GIST cells with FGF2 in vitro seems to activate the FGF pathway and downstream effectors of the MAP Kinase pathway (p-ERK) (Figure 2c). Subsequent blockade of FGF signaling with BGJ398 (Novartis, pan-FGFR inhibitor) inhibits FGF2 signaling and in FGF2 stimulated assays is able to also abrogate MAPK signaling (Figure 2d). Interestingly, imatinib is able to abrogate p-ERK signaling in FGF2 non-stimulated assays suggesting that in the absence of FGF2, MAP Kinase signaling is mediated by KIT. However, in FGF2 stimulated assays, imatinib is unable to abrogate p-ERK, suggesting that the activity of the MAP Kinase system is dependent on FGF, more so than KIT signaling, in FGF dependent tumors. Taken together, these data suggest that a number of GIST tumors have high expression of FGF2 and subsequent activity/penetrance of the FGF signaling pathway.







3.1.3 The FGF Pathway May Mediate Imatinib Resistance via MAP Kinase Signaling

To further explore how the FGF and MAP kinase pathways are interrelated and active in GIST, GIST cell lines were exposed to imatinib in culture for extended periods of time (Figure 3). After three days of exposure, the FGF signaling pathway becomes activated as noted by acquired expression of FRS2. At baseline, p-ERK is activated. However, its activity is quickly abrogated upon exposure to imatinib. However, p-ERK activity is reactivated with prolong exposure to imatinib when FGF signaling activates (day 3). Subsequent exposure to BGJ398 not only shuts off FGF signaling, but also p-ERK signaling. This strongly suggests that resistance to imatinib is mediated by MAP Kinase signaling via the FGF pathways and that inhibition of the FGF pathway with BGJ398 may not only overcome resistance but provide a mechanism to avoid imatinib resistance if the drugs are given in combination at the start of therapy. In FGF tumors, the activity of the MAP Kinase pathway as mediated by FGF signaling may play a role in cellular proliferation and the development of imatinib resistance.

3.1.4 Imatinib Plus BGJ398 Has Greater Antiproliferative Effects in GIST Than Both Imatinib and BGJ398 Alone

The combination of imatinib and BGJ398 may be more efficient in affecting the growth of GIST as opposed to imatinib alone. Cellular proliferation assays were performed on GIST cell lines in the presence and absence of FGF2 stimulation (Figure 4). Even is the absence of FGF2 stimulation, the combination of imatinib plus BGJ398 was more efficacious in killing both GIST-T1 and GIST-882 cells.

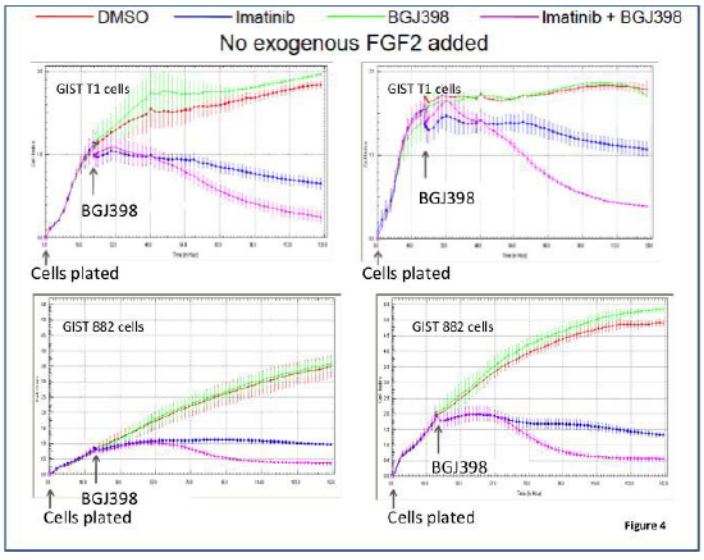


Figure 4

3.1.5 FGFR Inhibition is Superior to MEK inhibition in FGF Stimulated GIST Systems

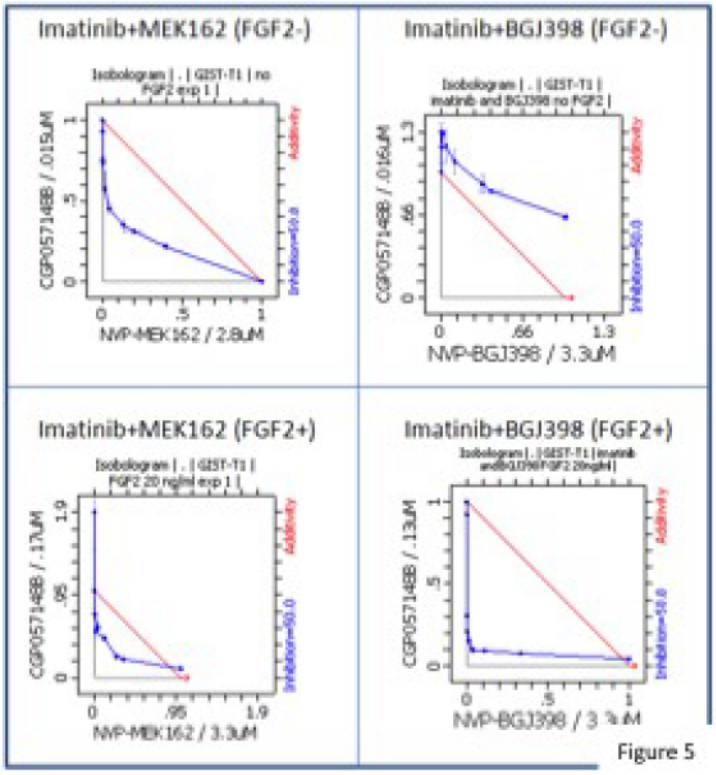


Figure 5

Since the activity of the FGF signaling pathway in GIST, for both proliferation and the development of resistance, appears to be mediated by the MAP Kinase pathway, further investigations were done to see how BGJ398 would compare to the activity of a MEK inhibitor (MEK162 – Novartis). Electrical impedance assays were performed on GIST cell line lines in the presence and absence of FGF2 stimulation (Figure 5). In the absence of FGF2, the combination of imatinib plus MEK162 seemed to have significant superiority over the combination of imatinib plus BGJ398. This suggests that the MAP Kinase pathway is actively contributing to GIST oncogenesis at baseline, possibly through ETV1 signaling and that dual inhibition with a MAP Kinase pathway inhibitor with imatinib seems to have significant synergy over imatinib alone. This warrants further clinical investigations. However, in the presence of FGF2 stimulation, the combination of imatinib and BGJ398 seems to have superiority over imatinib and MEK inhibition. In the case of FGF2 stimulation, significant synergy, more so than with imatinib and MEK162, was noted in GIST cell lines cells.

3.1.6 Summary

Overall, these data suggest that a subset of GIST rely of FGF signaling. In these tumors, proliferation and imatinib resistance is mediated via the MAPK pathway. BGJ398, a pan FGFR inhibitor, appears to abrogate FGF and MAP Kinase signaling and that dual inhibition of KIT with a FGF/MAP kinase pathway inhibitor has significant synergistic effects over single agent imatinib and may provide a way to overcome imatinib resistance as mediated through the FGF signaling. The impedance assays also suggest that the combination of imatinib and BGJ398 may have cytotoxic effects in GIST as opposed to the known cytostatic effects of imatinib alone. Therefore, targeting these GIST tumors in an upfront setting may afford the opportunity to greatly effect outcomes in excess of what is currently seen with imatinib alone, i.e. prevent imatinib resistance and possibly allow for cytotoxic effects on the cancer cells. In such, we are proposing 'A phase Ib/II study of BGJ398 in combination with imatinib mesylate in patients with untreated advanced gastrointestinal stromal tumor (GIST)'. As the true penetrance of FGF signaling in GIST is currently not known, we are proposing this novel investigator initiated trial as a means of establishing the safety and efficacy of imatinib plus BGJ398 in GIST. In addition, the trial will be rich in correlative experiments to determine the true penetrance of

FGF signaling in GIST, and hence integral biomarkers that will help select the patient population who would benefit from FGFR inhibition. In addition, as FGF signaling appears to mediate MAP Kinase signaling. This project will also be designed to evaluate the overall effects of MAP kinase signaling in GIST both in the context of ETV1 activity and FGF signaling

Strategically, we believe that this patient population will be the purest condition for the proof of concept that the combination regimen will be a more effective strategy than single agent imatinib alone. We believe that this approach will not only affect KIT, FGFR, and MAPK signaling, but also ETV1 protein stability and the FGF/MAPK pathways ability to incite resistance to imatinib therapy.

3.2 BGJ398

3.2.1 Overview of BGJ398

BGJ398 is an orally bio-available, selective and ATP competitive pan-fibroblast growth factor receptor (FGFR) kinase inhibitor which has demonstrated anti-tumor activity in preclinical, *in vitro* and *in-vivo* tumor models harboring FGFR genetic alterations. BGJ398 belongs to the pyrimidinyl aryl urea chemical class and its chemical name is 3-(2,6-Dichloro-3,5-dimethoxyphenyl)-1-{6-[4-(4-ethyl-1-piperazin-1-yl)phenylamino]-pyrimidinyl-4-yl}-1-methylurea phosphate(1:1).

As of September 24, 2013, 94 patients have been enrolled to the CGBJ398X2101 study. The MTD has been identified as 125 mg once daily (q.d.).

Please refer to the Investigator's Brochure for additional information on BGJ398.

3.2.2 Non-clinical experience

At the cellular level, BGJ398 selectively inhibits the kinase activity of FGFR1 FGFR2, FGFR3, and FGFR4 as measured by inhibition of receptor autophosphorylation with IC50 values of 3 - 7 nM for FGFR1, FGFR2 and FGFR3, and 168 nM for FGFR4. In cellular kinase selectivity assays using a panel of BaF3 cell lines rendered IL-3 independent by various tyrosine kinases, the most potently inhibited kinase, in addition to the FGFRs were VEGFR2 and FLT1 with IC50s of 1510 nM and 1591 nM, respectively.

Consistent with inhibition of FGFR autophosphorylation, BGJ398 inhibits FGFR downstream signaling and proliferation of human cancer cell lines harboring genetic alterations of the FGFRs. These include, among others, lung and breast cancer cell lines with FGFR1 gene amplification, gastric cancer with FGFR2 gene amplification, endometrial cancer with FGFR2 mutations and bladder cancer with FGFR3 mutations or FGFR3 translocations[27]. In line with its cellular activity, BGJ398 shows anti-tumor activity in multiple models bearing FGFR genetic alterations[28, 29].

3.2.2.1 *Animal drug metabolism and pharmacokinetics*

In all species tested, BGJ398 exhibited a high plasma CL and a large Vss. The compound is highly bound to plasma proteins (~ 98%) but does not preferentially distribute to red blood cells. BGJ398 is widely distributed to tissues in the rat and has a high affinity to melanin containing tissues. *In vitro* hepatic systems metabolize BGJ398 predominantly to 2 pharmacologically active metabolites: BHS697 and BQR917. Biotransformation of BGJ398 to both metabolites was observed in human hepatocyte cultures. The compound is a P-gp and BCRP substrate and also inhibits BCRP mediated transport with an IC_{50} value of 0.21µM. BGJ398 is a potent reversible inhibitor of CYP3A4 (Ki 0.26µM). The compound also reversibly inhibits CYP2C9 and CYP2C19 with Ki of 6.09µM and 4.1µM,

respectively and CYP2C8 with IC_{50} of 12µM. BGJ398 is also a time dependent inhibitor of CYP3A4 with a K_I = 37.3 µM and K_{inact} = 0.0547 min $^{-1}$. In addition CQM157, a recently identified metabolite in circulating plasma from patients, is an inhibitor of CYP2C8, CYP2C9 and CYP3A4 (IC_{50} less than 10 µM) and CYP2C19 (IC_{50} 12 µM). CQM157 is also an inhibitor of transporters P-gp, BCRP, OATP1B1 and OATP1B3 (IC50 less than 5 µM).

A distribution study following single dose administration of [^{14}C]BGJ398 in rats showed evidence that radiolabeled components (BGJ398 and /or its metabolites) cross the blood brain barrier. Concentrations of BGJ398 and its active metabolite BHS697 were also detected in rat brain following a single oral administration of 10 mg/kg of BGJ398.

3.2.2.2 *Safety pharmacology and toxicology*

BGJ398 showed no evidence of *in vitro* genotoxicity in Ames and chromosome aberration tests and no evidence of phototoxicity in a 3T3 photo-cytotoxicity test. *In vitro* safety pharmacology assessment of BGJ398 revealed a decrease in human *Ether-à-go-go*-related gene (hERG) channel activity with an IC_{50} of 2.0 µM (1121ng/ml).

In vivo safety pharmacology studies in rats and dogs did not reveal any effects on central nervous or respiratory systems and on hemodynamic or electrocardiographic parameters, respectively.

In repeated dose (oral gavage; up to 4-weeks) toxicity studies, BGJ398 did lead to increases in serum FGF23 and serum phosphorous associated with partially reversible ectopic mineralization (kidney, lung, vascular and digestive systems) along with largely reversible changes in renal function parameters and bone growth plate thickening / retention of the primary spongiosa in rats (≥ 10 mg/kg/day) and dogs (≥ 10 mg/kg/day). These effects were deemed to be on-target effects mediated by pharmacological inhibition of FGFR.

In rats, corneal changes were found upon 4 weeks of BGJ398 treatment consisting of irreversible, slight corneal opacity in dose-dependent incidence, as assessed by *in vivo* ophthalmology, associated with reversible, diffuse epithelial keratopathy at the highest dose of 10 mg/kg. In the 4-week GLP oral toxicity study in rats, the severely toxic dose in 10% (STD_{10}) was 10 mg/kg/day which resulted in premature death in one (1/30) animal. Doses of 20 mg/kg/day in rats led to vasculopathy associated with moribundity after 6 administrations. In dogs, the highest non-severely toxic dose (HNSTD) was 10 mg/kg/day leading to minimal, fully reversible retention of the primary spongiosa and minimal increase in mineralization in lung and kidney without observed functional impairment.

3.2.3 Clinical experience

3.2.3.1 *Clinical safety*

As of September 24, 2013, 94 patients have been enrolled to the CGBJ398X2101 study. The dose escalation portion of the study has been completed and the MTD has been identified as 125 mg once daily (q.d.), administered continuously. BGJ398 was administered to 43 patients evaluated at 9 different dose levels, ranging from 5 mg per day to 150 mg per day. Four dose limiting toxicities (DLTs) were reported during the dose escalation portion and occurred at the 100 mg (n=1; grade 3 AST/ALT elevation), 125 mg (n=1; hyperphosphatemia for > 14 days), and 150 mg (n=2; grade 1 corneal toxicity and grade 3 AST/ALT elevation) dose levels.

As of September 24, 2013, 51 patients have been enrolled thus far as part of one of 3 ongoing expansion cohorts at 125 mg daily. One cohort has enrolled 12 patients with FGFR1 amplified

advanced or metastatic squamous non-small cell lung carcinoma; a second cohort has enrolled 21 patients with any advanced solid tumor harboring an FGFR genetic pathway alteration. Both of these cohorts are treating patients on continuous 28-day cycles. The third cohort has enrolled 18 patients any solid tumor with any FGFR genetic pathway alteration on a new schedule of 3 weeks on drug, 1 week off, repeated in 28-day cycles.

The most frequent treatment-emergent adverse events as of the cut-off date suspected to be related to BGJ398 were hyperphosphatemia (71.3%), decreased appetite (26.6%), fatigue (25.5%), stomatitis (24.5%), alopecia (21.3%), asthenia (16%), and increases in AST (11.7%) and ALT (11.7%). The majority of adverse events were Grade 1 and 2 and reversible upon discontinuation of study drug.

Hyperphosphatemia has been seen in the majority of patients treated at doses of 100 mg q.d. and higher. Phosphate elevations are a biomarker of on-target FGFR pathway inhibition which mediates renal tubular phosphate secretion and reabsorption. The hyperphosphatemia has been managed by dietary phosphate restrictions, phosphate lowering therapy, and drug interruptions. As a result, an alternate dosing schedule of 125 mg 21 days on, 7 days off in a 28 day cycle is currently being investigated as part of Study BGJ398X2101.

3.2.3.2 *Preliminary efficacy of BGJ398*

Among patients in the Phase 1 study, anti-tumor activity was noted in several tumor types with FGFR genetic aberrations, including one PR lasting approximately 9 months in squamous NSCLC.

3.2.4 Pharmacokinetics

In Study BGJ398X2101, full PK profiles were obtained on Day 1, Day 15 and Day 28 after the first dose of study drug. As this study is ongoing, all data presented are current as of 24 September 2013 (refer to the Investigator Brochure for further details).

At 5 and 10 mg/day, plasma concentrations of BGJ398 were low (< 3.3 ng/mL) and frequently below the lower limit of quantification. Exposure (Cmax and AUC) was measurable in all treated patients starting at 20 mg/day.

The median apparent Tmax value across all dose levels tended to be 2-3 hours post-dose. At the MTD (125 mg q.d.), the median Cmax and AUC0-24 were ~80.8 ng/ml and ~694 h.ng/ml on Day 1 and ~245 ng/mL and ~3342 h.ng/mL on Day 15. At 125 mg q.d. 3 weeks on 1 week off, median Cmax and AUC0-24 were ~71.3 ng/mL and ~632 h.ng/mL on Day 1 and 251 ng/mL and 3693 h.ng/mL on Day 15.

The inter-patient variability was moderate to high for BGJ398 and % coefficient of variation (% CV) ranged from 50 – 75% at the expansion cohort of 125 mg qd on Day 15. Accumulation was observed with daily dosing. The mean AUC0-24 ratios between Cycle 1 Day 1 and Cycle 1 Day 15 ranged from 1.5 to 6.5, which indicates some change in BGJ398 exposure following multiple dosing. At doses of 60 mg and above, most individual patients showed increased exposure on Day 15 following multiple dosing (~1.5 – 13 fold relative to Day 1 exposure). Very limited data are available for patients who received continuous dosing for 28 days without dose interruptions (8 patients at doses 60 mg and above, only 7 patients with PK data). In most of these patients who received uninterrupted dosing, a further increase in exposure beyond Day 15 was observed. This is based on either AUC0-24 exposure on Day 28 or comparing predose samples after Day 15 in these patients. Refer to the BGJ398 Investigator's Brochure for further details.

In most patients, across all study days and dose levels, active metabolites were measurable. As a percentage of parent exposure, BHS697 was detected at ~10-15% and BQR917 at < 10%. Following an exploratory analysis, CQM157 was identified as a major pharmacologically active metabolite in plasma samples with in vitro potency that was similar to BGJ398. Preliminary analysis in circulating plasma following dosing with 125 mg of BGJ398 on Day 1 (n=8), showed plasma exposures to CQM157 ranged from 3% to 300% of parent BGJ398. On Day 15 (n=4), exposure to CQM157 remained the same or decreased as compared to Day1 unlike BGJ398 which showed accumulation following multiple dosing. For further information refer to the Investigator's Brochure.

3.3 Imatinib Mesylate (Gleevec STI571; NSC #716051)

3.3.1 Overview of Imatinib mesylate

Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the Bcr-Abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in chronic myeloid leukemia (CML). It inhibits proliferation and induces apoptosis in Bcr-Abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive (Ph+) chronic myeloid leukemia. Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) stem cell factor (SCF), colony stimulating factor (CSF1R) and collagen receptors (DDR), c-Kit, and inhibits PDGF- and SCF-mediated cellular events. *In vitro*, imatinib inhibits proliferation in gastrointestinal stromal tumor (GIST) cells, which express an activating c-kit mutation.

Gleevec is approved in the US for the treatment of the following indications: newly diagnosed adult patients with Ph+ CML in chronic phase; patients with Ph+ CML in blast crisis, accelerated phase or in chronic phase after failure of interferon-alpha therapy; pediatric patients with Ph+ chronic phase CML whose disease has recurred after stem cell transplant or who are resistant to interferon-alpha therapy; patients with KIT (CD117) positive unresectable and/or metastatic malignant GIST; adjuvant treatment of adult patients following resection of KIT (CD117) positive GIST; patients with relapsed/refractory Ph+ acute lymphoblastic leukemia (ALL); patients with unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberance (DFSP); patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements; patients with hypereosinophilic syndrome/chronic eosinophilic leukemia (HES/CEL); and patients with aggressive systemic mastocytosis (ASM) without the D816V c-Kit mutation or with c-Kit mutational status unknown.

3.3.2 Clinical experience with Imatinib mesylate

Efficacy results of imatinib studies in leukemias have shown dramatic rates of complete responses. These major objective clinical responses can be of variable durability, lasting from weeks to more than a year. The pathways of resistance in leukemia are being actively explored. Possible mechanisms of resistance include overexpression of the mutated BCR-Abl gene and variants, secondary gatekeeper mutations in the abl kinase as well as increased expression of alpha acid glycoprotein.

Thousands of patients with metastatic or unresectable GIST have now been treated with imatinib. The approximate response rate is 45-52% [3, 4]. Juxta- Membrane Domain mutations in the exon 11 respond best to imatinib. The response rate for GIST patients with exon 9 mutations is about 30%, as

well as for patients with GIST harboring mutant PDGFRA. Response rates are nearly 0 for GIST with wild type c-kit. Mutations in the kinase domain are known to be unresponsive (Exon 17).

Imatinib was found effective in patients with the hypereosinophilic syndrome, and investigation into the genetic basis of this disease revealed that many of these patients, as well as some with systemic mastocytosis, harbor a chromosomal deletion that gives rise to an oncogenic fusion protein (FIP1L1-PDGFRA) involving the PDGF receptor. Imatinib is now considered a first-line agent for many malignancies characterized by aberrant protein tyrosine kinase signaling via ABL, c-kit, and PDGF receptor.

Over 12,000 adults have received imatinib at doses ranging from 25-1000 mg daily. During a Phase I trial, the most commonly reported adverse events (AE) related to imatinib administration were mild to moderate nausea, edema of various locations, and musculoskeletal symptoms, all of which appeared to have possible dose-response relationships. The corresponding events from the pooled Phase II trials (Novartis 0101, 0109, 0110) were nausea, vomiting, muscle cramps, edema, diarrhea and headache. Several serious adverse events (SAE) have been reported, 77 with a suspected causality relationship to trial drug. The majority of SAEs with a suspected relationship fell into five broad categories and occurred in 1.4-3.3% of patients: rash; liver function test (LFT) abnormalities; myelosuppression; upper GI hemorrhage; fluid retention/renal failure/electrolyte imbalance. There were two deaths with suspected relationship to trial drug, due to liver failure (possibly in association with excessive consumption of acetaminophen), and fluid retention/renal insufficiency, respectively.

In patients with CML, the majority of Gleevec® -treated patients experienced adverse events at some time. Most events were of mild to moderate grade, Imatinib was discontinued for adverse events in 2.4% of newly diagnosed CML patients, 4% in accelerated phase and 5% in blast crisis. The most frequently reported adverse events (regardless of relationship) were edema, nausea, and vomiting, muscle cramps, musculoskeletal pain, diarrhea and rash. Edema was most frequently periorbital or in lower limbs and was managed with diuretics, other supportive measures, or by reducing the dose of Gleevec®.

In patients with GIST, the majority of imatinib-treated patients experienced AEs at some time. Approximately 60% of patients reported at least one grade 3/4 AE at some time during the study, and imatinib was discontinued due to AEs in 18 patients. The most frequently reported AEs were edema, nausea, diarrhea, abdominal pain, muscle cramps, fatigue, and rash, most of which were of mild-to-moderate severity. Imatinib was discontinued for AEs in 7 patients (5%) in both dose levels (400 and 800 mg/d) studied. Superficial edema, most frequently periorbital or lower extremity, was managed with diuretics, other supportive measures, or by reducing the dose of imatinib. Severe (NCI-CTCAE Grade 3/4) superficial edema was observed in 3 patients (2%), including facial edema in 1 patient. Grade 3/4 pleural effusion or ascites was observed in 3 patients (2%). Nine (6%) patients (600 mg/d (n=6); 400 mg/d (n=3)) were reported to have grade 3/4 GI or intra-tumoral hemorrhage during the study (GI bleeding (n=5); intratumoral bleeding (n=3); both GI and intratumoral bleeding (n=1). The GI localization of the tumor likely contributed to this AE in this patient population. None of these patients had thrombocytopenia at the time of haemorrhage. The small number of events and the variability in baseline clinical profiles preclude conclusions to aid the identification of patients at increased risk of hemorrhage during therapy with imatinib.

For further information regarding clinical experience with Imatinib mesylate, refer to the Investigator's Brochure.

3.3.3 Pharmacokinetics of Imatinib mesylate

3.3.3.1 Pharmacokinetics of Imatinib in healthy subjects and patients with normal hepatic and renal function

The pharmacokinetics of Gleevec® have been evaluated in healthy subjects and in population pharmacokinetic studies in over 900 patients. Imatinib is well absorbed after oral administration with C_{max} achieved within 2-4 hours post-dose. Mean absolute bioavailability is 98%. Following oral administration in healthy volunteers, the elimination half-lives of imatinib and its major metabolite, the N-desmethyl derivative, were approximately 18 and 40 hours, respectively. Mean imatinib AUC increased proportionally with increasing dose in the range 25mg - 1000mg. There was no significant change in the pharmacokinetics of imatinib on repeated dosing, and accumulation is 1.5-3 fold at steady state when Gleevec® is dosed once daily. At clinically relevant concentrations of imatinib, binding to plasma proteins in *in vitro* experiments is approximately 89-96%, mostly to albumin.

A pharmacokinetic study following continuous once daily oral administration of imatinib has been performed in two GIST patients. The preliminary results showed that the PK profiles in GIST patients are similar to that observed in CML patients. Imatinib is rapidly absorbed and a Cmax of 2.9 µg/ml was reached at steady state following a 400 mg daily dose. The terminal life was 13h and there was 1/5 fold drug accumulation after one month dosing. The AUC (0-24) values were 23,748 ng/h/ml at steady state after a 400 mg dosing, which is similar to those seen in CML patients.

The terminal half-life (t1/2) averaged to 10 to 23 hours (18 hours for the parent and 40 hours for the major metabolite (see below)) and there was a 2-3 fold accumulation of drug at steady state. These data are compatible with a schedule of once daily administration. The increase in mean plasma AUC values was proportional to dose up to 750 mg/day. The mean plasma AUC (0-24) at steady state following a continuous once daily oral dose of 750 mg was 62,259 ng/h/ml.

A food effect study has shown no significant differences in absorption when imatinib was administered either with food or in the fasting state. Since this agent has potential to irritate gastric mucosa, it is therefore strongly recommended that the agent be taken with food to decrease risk of gastric irritation.

Imatinib is hepatically metabolized and elimination is mainly in the feces, predominantly as metabolites. The major metabolite is the N-desmethylated piperzine derivative, and this metabolite shows in vitro potency similar to that of the parent drug. CYP3A4 is the major enzyme responsible for metabolism of imatinib. Other cytochrome P450 enzymes, such as CYP2D6, CYP2C9, and CYP2C19, play a minor role in its metabolism. Because of the inherent risk of either reduced activity or enhanced toxicity of concomitant medications and/or imatinib, drugs known to be metabolized by the same CYP450 isoenzymes as imatinib should be used with caution (Appendix C). Special care has to be given to the concomitant use of paracetamol (acetaminophen, Tylenol) with imatinib. Any use of this drug has to be documented in the medical records and/or captured on the appropriate case report form. Cases of reactivation of Hepatitis B can occur in patients who are chronic carriers of this virus after receiving a BCR-ABL tyrosine kinase inhibitor (TKI), such as imatinib.

3.3.3.2 Pharmacokinetics of Imatinib in patients with hepatic insufficiency

A Phase I study to investigate the effects of imatinib in patients with liver dysfunction was conducted by NCI. Results showed that exposure to both imatinib and CGP74588 was comparable between patients with mild or moderate hepatic insufficiency and those with normal hepatic function. Therefore Imatinib can be administered to patients with varying degrees of hepatic impairment with some modifications in dosing recommended. Patients with mild and moderate hepatic impairment can be treated at a starting dose of 400 mg/day, whereas, patients with severe hepatic impairment should be treated at a starting dose of 300 mg/day.

3.3.3.3 Pharmacokinetics of Imatinib in patients with renal insufficiency

Imatinib and its metabolites are not significantly excreted by the kidney. A multicenter PK study in patients with advanced malignancies and varying degrees of renal dysfunction has been conducted by US National Cancer Institute [Study P-5340]. Results show that imatinib is well tolerated over a dose range of 400-800 mg in patients with mild renal dysfunction (creatinine clearance between 40 and 59 mL/min), and a dose range of 200-600 mg daily in patients with moderate renal dysfunction (creatinine clearance between 20 and 39 mL/min). PK results showed that the AUC and C_{max} values in the mild, moderate, and severe groups were approximately 1.5-2-fold that of the normal group at steady-state. The increase in imatinib exposure was not associated with any increased clinically significant toxicity or drug-related AEs. Therefore, in patients with mild or moderate renal insufficiency, no dose modification of imatinib mesylate is required.

For severe renal dysfunction patients (creatinine clearance < 20 mL/min), only 2 patients were enrolled, and no patients in hemodialysis were enrolled into the study. Literature data (Pappas, et al 2005) showed that 400 mg daily dose was well tolerated in a patient with end stage renal disease on hemodialysis.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a multi-center single arm phase Ib/II trial to evaluate the clinical safety and efficacy of imatinib and BGJ398 in patients with locally advanced or metastatic GIST. All patients will have a diagnosis of GIST. Patients in the Phase Ib portion of the trial are required to have locally advanced or metastatic GIST and can be in any phase of treatment that has progressed on imatinib. Patients on the Phase II portion of the study are required to have locally advanced or metastatic GIST and have not received any prior systemic therapy except for adjuvant imatinib therapy completed more than 90 days prior to enrollment (untreated/treatment naïve).

The phase Ib portion of the study will be a standard 3 + 3 dose escalation with sample size ranging from 6-30 patients. Pharmacokinetic sampling for BJG398 will occur in this phase of the trial. The phase II portion of the study will assess Response Rate (Complete and Partial, RECIST 1.1) at 32 weeks as its primary endpoint. The trial will assume a 20% improvement in the historical RR of imatinib alone, from 45% to 65%. The phase II sample size will be 44 patients. At the end of the study, if > 24 patients have had a documented response by RECIST 1.1, the study will be considered positive and

the treatment regimen will be considered worthy of further investigation. The study design is based on an exact Binomial test and has a type I error of 0.08 and a type II error of 0.1.

4.2 Intervention

Patients who meet the eligibility criteria will be treated with the combination therapy of BGJ398 and imatinib. In the phase Ib portion of the study, patients will receive imatinib at 400 mg once daily and BGJ398 at the standard 3+3 escalation doses for 21 days on, 7 days off (treatment schedule A)(Table 1). Using treatment schedule A, if dose level 1 to -2 is identified as the MTD and concern exists regarding therapeutic activity of BGJ398 at this dose level, expansions with higher dose levels (1 to 3) may be considered at the MSKCC PI's discretion, with modification of the treatment schedule. In this setting BGJ398 will be administered daily for one week followed by 3 weeks off and imatinib will be taken daily throughout the 4 week cycle period (treatment schedule B). In the phase II portion of the study, patients will receive imatinib at 400 mg once daily (standard of care first line imatinib dose) and BGJ398 at the RP2D and treatment schedule identified in the phase Ib portion of the study. One cycle is 28 days. If no progression of the tumor is seen, patients will continue on therapy. Those patients who have progression of disease will proceed directly to second line therapy as per standard of care. For Phase II, study personnel will attempt to collect survival status for all patients after the end-of-study visit every 3 months via telephone, email, or other method for up to 3 years.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Imatinib Mesylate (Gleevec STI571; NSC #716051)

5.1.1 Mechanism of Action:

Imatinib is a small molecule that has been demonstrated to be a highly selective inhibitor of certain protein tyrosine kinases. Specifically, imatinib is known to inhibit the kinase action of the following:

- Abl and the chimeric BCR-Abl fusion protein found in certain leukemias such as chronic myeloid leukemia (CML).
- The platelet-derived growth factor receptor (PDGFR).
- KIT, the product of the c-kit proto-oncogene.
- Abl-related gene (ARG).

Imatinib has been extensively tested in Philadelphia chromosome-positive leukemia patients where the main target is inhibition of the dysregulated kinase activity associate with the chimeric BCR-Abl fusion protein and in patients with gastrointestinal stromal tumors (GIST) in which the main target is inhibition of the dysregulated kinase activity associated with activating mutations of KIT.

Cases of reactivation of Hepatitis B can occur in patients who are chronic carriers of this virus after receiving a BCR-ABL tyrosine kinase inhibitor (TKI), such as imatinib.

5.1.2 Formulation, Storage and Packaging

Imatinib is available in 100 mg and 400 mg scored capsule. The storage conditions for study drug will be described in the package insert, usually at room temperature-25°C (77°F).

5.1.3 Administration of Imatinib mesylate

Imatinib will be supplied by Novartis. Imatinib is available in 100 mg and 400 mg scored capsule. Preferentially and unless otherwise clinically indicated, 400mg capsule will be used. The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance) and to notify the Investigator of any deviations. Patients will be instructed to record their daily study drug administration in the patient diary provided to them. Imatinib will be dosed at 400 mg once a day by mouth. Because of the potential for intestinal irritation, the capsule should be taken during a meal and with a large glass of water (8 oz) to minimize the chance of irritating the esophageal and/or gastric mucosa. Patients should keep normal eating habits; however, low-fat (i.e. continental) breakfast is recommended avoiding xanthine (e.g. caffeine) or grapefruit containing food or beverages. Minimum of 1h should be allowed between last drug intake and going to bed. If vomiting occurs, no additional trial medication should be taken that day in an effort to replace the material that has been vomited. If a dose of imatinib is missed, the subject should take the dose as soon as possible, but only if there are 12 or more hours remaining before the next dose is due. If the next dose is due in less than 12 hours, the subject should skip the missed dose and take the next dose as scheduled. A study medication diary will be completed by the patients for each dose of Imatinib.

Instructions for dose modifications can be found in Section 9.

5.2 BGJ398

5.2.1 Mechanism of Action:

BGJ398 is an orally bioavailable, potent and selective inhibitor of the fibroblast growth factor receptors (FGFRs). The FGFR family of receptor tyrosine kinases (RTKs) consists of four members (FGF-R1, FGF-R2, FGF-R3, FGF-R4), which serve as the high affinity receptors for 22 FGF ligands. These are pleiotropic growth factors that control cell proliferation, migration, angiogenesis, apoptosis and differentiation and are involved in both developmental and adult tissue homeostasis. More recently, cancer epidemiological and molecular studies have reported various genetic alterations including gene amplifications, mutations and chromosomal translocations, as well as aberrant protein expression for this family of RTKs and ligands. Further, their link to cancer dependence has been established preclinically by means of loss of function approaches. Preclinical research studies have shown that BGJ398 selectively suppresses FGFR signaling and proliferation in cancer cells with FGFR dependency and respectively, the tumor growth of mouse and rat xenograft models associated with aberrant FGFRs expression/activation. In addition to a direct effect on the tumor cells, BGJ398 has an effect on endothelial cells by blocking bFGF-induced angiogenesis, thus providing an alternative mechanism to inhibit tumor growth. On this basis, targeted inhibition of FGFRs can be exploited for therapeutic gain.

5.2.2 Formulation, Storage and Packaging

BGJ398 will be provided by Novartis as film-coated capsule for oral use of dosage strength of 25mg and 100mg. Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, BGJ398 should be stored according to the instructions specified on the drug labels. Study medication will be dispensed by an authorized person at the investigator's site.

5.2.3 Administration of BGJ398

BGJ398 will be taken orally, using treatment schedule A (once a day for 21 days on, 7 days off) or treatment schedule B (once daily for 7 days on, 21 days off) repeating in 28 day cycles. Patients should be instructed to take the daily dose of BGJ398 in the morning, at approximately the same time each day (24 ± 2 hour interval). Patients should consume a light breakfast each day (e.g., non-grapefruit-based juice, toast and jam). This should be followed by a 2 hour fast, after which the doses of study drug should be taken. Patients should continue to fast for 1 hour after the administration of study drug.

BGJ398 should be taken with a large glass of water (~250 mL) and consumed over as short a time as possible. Patients should be instructed to swallow the capsules whole and not chew them. If for any reason a breakfast was not consumed prior to taking the dose the patient should take the dose with a full glass of water, and continue to fast for an hour after taking the dose. If the patient forgets to take the scheduled dose in the morning, he/she should not take the dose more than 2 hours after the usual time and should continue treatment the next day. Any doses that are missed should be skipped altogether and should not be replaced or made up at the next scheduled dosing.

If vomiting occurs following the dosing of study drug, re-dosing is not permitted that same day. Dosing should resume the next day.BGJ398 is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of both compounds, and limit bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. Therefore, BGJ398 should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent. Patients must avoid consuming Seville oranges or juice, grapefruit, grapefruit juice, grapefruit hybrids, or pummelos from 7 days prior to the first dose of study medication through the end of study participation. This is due to a potential CYP3A4 interaction with study medication. Normal oranges and orange juice are allowed.

The investigator or responsible site personnel should instruct the patient to take the study drug exactly as prescribed to promote compliance. All dosages prescribed and dispensed to the patient and all dose changes or missed doses during the study must be recorded. A study medication diary will be completed by the patients for each dose of BGJ398. Patients will be instructed to return unused study drug to the site at the end of each cycle.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

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

Inclusion criteria:

- Patients must have pathologically confirmed GIST.
- In the Phase Ib portion, must have locally advanced or metastatic GIST and have progressed on imatinib.
- In the Phase II portion, patients must be newly diagnosed or imatinib treatment naïve in the advanced/metastatic setting. Prior adjuvant imatinib therapy is allowed as long as disease

recurrence was documented ≥90 days after last dose of imatinib and imatinib has not yet been restarted.

- Patients must be at least 18 years of age.
- Disease must be measurable by RECIST 1.1.
- ECOG Performance Status 0 or 1.
- Adequate renal, hepatic, and hematologic function as the following: Serum Creatinine ≤ 1.5 mg/dL, Total Serum Bilirubin ≤ 1.5 x upper limit of normal (ULN) unless due to Gilbert's Disease, Serum AST (SGOT) and/or ALT (SGPT) ≤ 2.5 x ULN (or ≤ 5.0 x ULN if considered due to tumor), ANC ≥ 1500/mm^3, Platelets ≥ 100,000/mm^3, and hemoglobin ≥ 10g/dL.
- Patients of childbearing potential must have a negative blood pregnancy test within 14 days of treatment. Patients must agree to use a reliable barrier method of birth control during and for 3 months following the last dose of study drug.
- Patient must have adequate cardiac function (left ventricular ejection fraction (LVEF) ≥50% as determined by a multigated acquisition (MUGA) scan or echocardiogram; and QTc interval ≤480 ms by Fridericia's formula (QTcF).
- Patient must be able to take oral medications.
- Patients must sign an informed consent document.

6.2 Subject Exclusion Criteria

Patients meeting any of the following criteria are excluded from the study:

Exclusion criteria:

- For phase I, prior intolerance to imatinib at a dose of 400 mg daily.
- For phase II, any receipt of cytotoxic, biologic, or immune therapy aimed to treat GIST except for adjuvant imatinib systemic therapy that concluded at least 90 days prior to registration. For Phase I, patients are eligible regardless of prior therapy.
- Chronic liver disease (e.g., cirrhosis)
- Known positive serology for HIV, active Hepatitis B, and/or active Hepatitis C infection.
- Patients have a history or current evidence of Central Serous Retinopathy (CSR) or retinal vein occlusion (RVO) or major predisposing factors to CSR or RVO (e.g. uncontrolled glaucoma or ocular hypertension) in the opinion of the study ophthalmologist.
- History of retinal degenerative disease
- Active corneal disorder or keratopathy (e.g. corneal abrasion, bullous keratopathy)
- Severe and/or uncontrolled medical disease, including:
  - Uncontrolled diabetes mellitus (A1c >8)
  - Chronic Kidney Disease Stage III or higher (Creatinine Clearance <60mL/min/m^2 by Modified Diet in Renal Disease (MDRD) calculation)
  - Active, uncontrolled infection
- Known active brain metastasis unless they have been treated and shown documented radiographic stability for 28 days.
- Known other active malignancy (other than malignancies which the investigator determines are unlikely to interfere with treatment and safety analysis).
- Patients have clinically significant cardiovascular disease, including any of the following

- Any history of acute coronary syndrome including myocardial infarction, stable or unstable angina, CABG, coronary angioplasty or stenting, or known obstructive coronary artery disease
- Symptomatic chronic heart failure (New York Heart Association Criteria, Class II-IV)
- Evidence of clinically significant cardiac arrhythmias and/or conduction abnormalities < 6 months prior to screening except atrial fibrillation (AF) and paroxysmal supraventricular tachycardia (PSVT)

- Any history of thrombotic cerebrovascular accident or other arterial thrombosis
- Uncontrolled arterial hypertension (systolic blood pressure >155 mmHg or diastolic >95 mmHg) despite appropriate medical therapy.
- History and/or current evidence of uncontrolled endocrine alterations of calcium/phosphate homeostasis, e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis, etc.
- Impairment of gastrointestinal function or gastrointestinal disease (e.g., uncontrolled ulcerative disease; uncontrolled nausea, vomiting, diarrhea; chronic malabsorption syndrome).
- Patients with major surgery within 3 weeks prior to study entry or who have not recovered from side effects of such procedure.
- Women who are pregnant or lactating.
- Sexually active males, unless they use a condom during intercourse while taking the drug and for 15 days after stopping treatment. They should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
- Patients with any significant history of non-adherence to medical regimens or with inability to grant reliable informed consent.

7.0 RECRUITMENT PLAN

Both men and women and members of all races and ethnic groups are eligible for this trial. The clinical trial will be listed on the clincaltrials.gov website and on the websites of participating institutions. Patients will be identified through internal referrals and external referrals by Medical and Surgical Oncologists nationally and internationally. Patients will be recruited through the Sarcoma Disease Management Team of the Memorial Sloan-Kettering Cancer Center, Dana Farber Cancer Institute and MD Anderson Cancer Center. The Sarcoma service and the Sarcoma Disease Management Team each hold weekly interdepartmental meetings to identify study participants for open clinical trials. We will also discuss the trial and patient recruitment with several GIST patient support groups.

Patients will be recruited through the Sarcoma Disease Management Team of the participating institutions.

8.0 PRETREATMENT EVALUATION

Patients will need to have the following tests and procedures prior to entering the study:

Within 4 weeks of study start:

- Informed Consent
- Tumor imaging - CT Chest/Abdomen/Pelvis preferable
- Confirmation of disease (A biopsy will be required if patients do not have enough archived tissue to make treatment decisions). A portion of this biopsy will be collected for research purposes only after a pathological diagnosis has been made and informed consent has been obtained.
- Ophthalmology examination
- Tumor biopsy: After consent, and prior to treatment, 20 patients enrolled on the Phase II portion of the study across all sites will have a dedicated open incisional or core biopsy of their disease (see section 9.1 for detailed description of biopsy selection process). After biopsies on 20 patients are obtained, consent to a biopsy will not be mandated for enrollment. However, consent to research biopsies in subsequent patients will be encouraged if funding exists.

Within 2 weeks of study start:

- Demographics
- B-HCG (if applicable)
- Medical History
- Concurrent Medication
- Physical Exam
- Vital Signs
- Height
- Weight
- Performance Status (ECOG)
- CBC with differential, platelets
- Blood Chemistry--Comprehensive panel- (Albumin, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, sodium, glucose, potassium, total protein, sodium, alkaline phosphatase, SGOT [AST], SGPT [ALT]) plus LDH, creatinine phosphokinase (CK), magnesium, phosphorus, amylase, and lipase.
- TSH
- Hepatitis B serology—(Hep B surface antigen, Hep B surface antibody and Hep B core Antibody)
- EKG
- Urinalysis
- Baseline FDG PET scan (Phase II study only)
- Echocardiogram or MUGA

Please see Study Calendar in Section 10.0 for more information.

9.0 TREATMENT/INTERVENTION PLAN

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 11. Appropriate dose modifications of imatinib and BGJ398 are described in section 9.2. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Imatinib will be self administered orally by the patient on a daily basis throughout the treatment cycle. The standard treatment dose is 400 mg PO QD. 400 mg capsule will be used unless otherwise specified by the treating physician. BGJ398 will be taken at the RP2D and treatment schedule chosen from the Phase Ib portion of the trial. The RP2D selected may be lower than the MTD based on PK data and clinical tolerance beyond Cycle 1. BGJ398 is taken daily for a duration determined by the treatment schedule appropriate for the given dose level . In the event of dose delays of BGJ398, Day 1 of the following cycle will be defined as the day that BGJ398 is restarted. A pill diary for both medications will be provided and recorded (Appendix B). This will be used to assure compliance with the regimen.

On the Phase Ib portion, the timing of pharmacokinetic sample collections will be dependent on the treatment schedule onto which that patient is enrolled. For treatment schedule A pharmacokinetic samples will be drawn on Cycle 1, Day 1 at the following timepoints: 0, 1, 2, 4, 6, 8, and 24 hrs; and Cycle 1, Day 21 at the following timepoints: 0, 1, 2, 4, 6, and 8 hours. For treatment schedule B pharmacokinetic samples will be drawn on Cycle 1, Day 1 at the following timepoints: 0, 1, 2, 4, 6, 8, and 24 hrs; Cycle 1, Day 7 at the following timepoints: : 0, 1, 2, 4, 6, and 8 hours, Cycle 1, Day 15 at timepoint 0hr and Cycle 1, Day 21 at timepoint 0hr.

After consent, and prior to treatment, the first 20 patients enrolled on the Phase II portion of the study across all sites will have a dedicated open incisional or core biopsy of their disease. All biopsies will be performed at MSKCC or other participating institutions. Biopsies on subsequent patients will not be mandated, but encouraged if additional funding is identified. A patient may be excused from this biopsy requirement if tissue is not accessible or if investigator determines that the patient should not undergo this biopsy. If this occurs, a biopsy will be mandated in additional patients to ensure that at least 20 participants undergo a biopsy. Upon initiation of treatment, patients who underwent a pre-treatment biopsy will undergo a second biopsy after one week (C1D8) of combination of BGJ398 and imatinib treatment and at time of disease progression. All patients will undergo baseline staging FDG PET and body imaging and repeat FDG PET scans during week three of the combination therapy of treatment (C1D21) as part of standard of care. Four weeks of treatment (28 days) will be considered one cycle. Imaging with standard CT scans and response evaluations will occur every 8 weeks for the first 32 weeks regardless of treatment interruption and then on Day 1 of every 3rd cycle thereafter.

All participants on the Phase II portion will have a 2-week lead in of imatinib. Blood will be drawn at the end of this period to establish steady-state imatinib serum trough levels. After blood for imatinib levels are obtained, BGJ398 at the established Phase II dose and treatment schedule will be added to the regimen. The start of the combination therapy will mark the beginning of cycle 1 (Day 1 cycle 1). The initiation of BGJ398 will not be contingent on the imatinib level; rather, BGJ398 can be started after the blood draw from imatinib levels is performed. Blood will be drawn again approximately 3-5-weeks after the initiation of the combination therapy to establish the steady-state imatinib serum trough levels in the presence of BGJ398.

9.1 Dose Rationale:

Phase Ib: The primary endpoint of the phase 1b portion of this study is to determine the maximum tolerated dose (MTD) and the Recommended Phase 2 Dose (RP2D) and treatment schedule of BGJ398 administered in combination with imatinib in patients with GIST. The phase Ib will be pursued in standard 3+3 format, based on toxicities encountered during the first cycle of therapy.

The first three patients will be enrolled at Dose level 1(Table 1, see section 1) using treatment schedule A. Dose level 1 is chosen based on the standard of care imatinib dose of 400 mg daily in the advanced GIST patient population, and an intermediate dose level of BGJ398 (75 mg daily). This dose is below the BGJ398 MTD of 125 mg daily identified in phase I trials as monotherapy. BGJ398 dose level 1 to -2 will be administered using a schedule of BGJ398 taken daily for 3 weeks followed by one week off and imatinib taken daily throughout the 4 week cycle period (treatment schedule A).

The maximum pace of dose escalation within each cohort is outlined in Table 2. Expansions of lower dose levels may be made based on safety and tolerance considerations at the MSKCC Principal Investigator's discretion, and the selected RP2D may be lower than the MTD defined below. If dose level 1 is not found to be tolerable, then the next cohort will be enrolled at dose level -1. If dose level -1 is not found to be tolerable, then the next cohort will be enrolled at dose level -2. If dose level -2 is not found to be tolerable, then the study may be terminated based on discussions with the MSKCC Principal Investigator. If 0-1 of 6 patients experience a DLT on dose level 3, this will be the RP2D.

Table 2:

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these additional 3 patients experience DLT (1/6 total), proceed to the next dose level. • If 1 or more of this group suffer DLT (≥2/6 total), then dose escalation is stopped, and this dose is declared the MTD. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≥2	Dose escalation will be stopped. This dose level will be declared the MTD. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the MTD	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose (RP2D).

Using treatment schedule A, if dose level 1 to -2 is identified as the MTD and concern exists regarding therapeutic activity of BGJ398 at this dose level, expansions with higher dose levels (1 to 3) may be considered at the MSKCC PI's discretion, with modification of the treatment schedule. In this setting BGJ398 will be administered daily for one week followed by 3 weeks off and imatinib will be taken

daily throughout the 4 week cycle period (treatment schedule B). The higher dose level expansion will start by enrolling 3 patients into a cohort, at dose level 1, using treatment schedule B.

When using treatment schedule B the maximum pace of dose escalation within each cohort is outlined in Table2.

Upon documentation of the RP2D dose and treatment schedule of the combination, the phase II trial will open and all subsequent patients enrolled will initiate treatment at that dose and treatment schedule with any subsequent dose modifications as outlined below.

Toxicity will be assessed using the NCI CTCAE (version 4.03) unless otherwise specified. Dose Limiting Toxicity (DLT) is defined as an unexpected adverse event (AE) or abnormal laboratory value assessed as at least possibly related to the study medication, which occurs ≤28 days (1 cycle) following the first dose of BGJ398 (cycle 1), and meets any of the criteria listed in Table 3. Please note plasma assessments may substitute for serum assessments per local laboratory standards.

Table 3: Criteria for defining dose-limiting toxicities

TOXICITY	DLT CRITERIA
Hematology	CTCAE grade 4 neutropenia lasting more than 7 consecutive days
	CTCAE grade 4 thrombocytopenia
	CTCAE Grade 3 or 4 neutropenia with fever (temperature ≥ 38.5°C)
Skin and subcutaneous tissue disorders	Rash, HFSR (Hand Foot Skin Reaction) or photosensitivity CTCAE Grade 3 > 7 consecutive days despite skin toxicity treatment (as per local practice)
	Rash, HFSR or photosensitivity CTCAE Grade 4
Eye disorders	CSR (Central Serous Retinopathy) CTCAE Grade 2 for > 14 consecutive days confirmed by ophthalmologic examination
	CSR (Central Serous Retinopathy) CTCAE Grade ≥ 3, confirmed by ophthalmologic examination
	Retinal disorder other than CSR (retinal detachment/tear, retinal vascular disorder, retinopathy other) CTCAE Grade ≥ 2 confirmed by ophthalmologic examination
	Visual disturbances without ocular (retinal) changes: Blurred vision, Flashing lights, Floaters, Corneal abnormalities CTCAE Grade ≥ 3
Gastro-intestinal	≥ CTCAE grade 3 nausea or vomiting ≥ 48 hrs despite optimal anti-emetic therapy
	≥ CTCAE grade 3 diarrhea ≥ 48 hrs despite optimal anti-diarrhea treatment Pancreatitis ≥ CTCAE grade 3
Hepato-biliary	≥ CTCAE grade 3 total bilirubin
	≥ CTCAE grade 3 ALT (isolated increases in AST without concomitant increases

	in ALT will not be considered dose-limiting, because of the non-specific nature of AST)
	Serum alkaline phosphatase CTCAE Grade 4 > 7 consecutive days
Investigations (Metabolic)	Serum Lipase and/or serum amylase (asymptomatic) CTCAE grade 3 for > 7 consecutive days Serum Lipase and/or serum amylase (asymptomatic) CTCAE grade 4 Symptomatic serum lipase and/or serum amylase ≥ CTCAE grade 3
ECG QT Interval	QTcF interval ≥ 501 ms on at least two separate ECGs
Renal	Serum creatinine > 2x ULN Serum Phosphorous that requires dose interruption of BGJ398 for >14 days of first 21 days of Cycle 1
Non-hematologic events	≥ CTCAE grade 3, except for the exclusions noted below
Exceptions to DLT criteria	Grade 3 alopecia
	< 5 days of CTCAE grade 3 fatigue
	< 5 days of CTCAE grade 3 edema
	Grade 3 laboratory abnormalities that are responsive to oral supplementation or deemed by the investigator to be clinically insignificant
CTCAE version 4.03 will be used for all grading. Optimal therapy for vomiting or diarrhea will be based in institutional guidelines, with consideration of the prohibited medications listed in this protocol.	

Phase II: The RP2D doses and treatment schedule defined in the phase Ib clinical trial will be used to conduct the phase II portion of the study.

9.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed until resolution or stabilization of the event. Appropriate clinical experts (e.g. ophthalmologist, cardiologist, dermatologist) should be consulted as deemed necessary. A dose interruption of ≥ 28 days may require the patient to be discontinued from the study (with the exception of patients who undergo surgery; see section 13). Patients will continue to be followed for toxicity for 28 days following the last dose of study medication.

Patients exhibiting hypomagnesaemia, hypocalcaemia, and/or hypokalemia, should receive electrolyte replacement as indicated by national and institutional guidelines and be followed until laboratory values have normalized or as clinically indicated.

Patients on the study will be examined regularly to monitor for the possible development of CSR, as the appearance of CSR has been associated with BGJ398 treatment. Patients will receive a ophthalmological visit at baseline and 4 weeks after initiation of the study drug. If an ocular event occurs, patients will undergo ophthalmological evaluation as mandated by the study ophthalmologist. For patients developing a CSR of any grade it is recommended to follow up the CSR with an ophthalmological exam every two weeks for 8 weeks, and subsequently at approximately a 4-

week interval. Dose adjustments for ocular toxicities are outlined in Table 11. If ocular findings re-develop after rechallenge with drug, drug may be permanently discontinued based on evaluation by the study ophthalmologist.

All patients will have baseline cardiac ejection fraction evaluated by echocardiogram or MUGA studies. If a cardiac event occurs, the patients will undergo cardiac evaluation as seen appropriate by the investigator.

9.3 Dose Modification

No dose reductions will be performed for hematological toxicities Grade 1 or 2 and non-hematological toxicities grade 1. No dose reduction of imatinib will occur during the first cycle for the Phase Ib patients.

9.3.1 Imatinib:

Please refer to Table 4 and 5 for dose reduction steps and criteria for interruption and re-initiation of imatinib for drug-related toxicities.

Table 4: Dose Modification Algorithm for Imatinib

Dose Level	Imatinib Dose
1	**400 mg QD**
-1	**300 mg QD**
-2	**200 mg QD**

Table 5: Dose modifications for adverse events associated with imatinib

Hematologic toxicity	
≥ Grade 3	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 2, if recovery occurs within 14 days If toxicity persists for 15-28 days or recurs, hold therapy and resume at next lower dose level after recovery to ≤ Grade 2: I→ 300 mg QD If recurrence is seen at the reduced imatinib dose, hold therapy and resume at next lower dose level after recovery to ≤ Grade 2. I→ 200 mg QD If 4th occurrence, considerations should be had to remove subject from study if the toxicities are not manageable with appropriate supportive measures.
Note: No dose reductions will be performed for grade 3 or 4 anemia. The patient may receive blood transfusions. Use of erythropoietin alfa (EPO) is allowed at the discretion of the treating investigator. G-CSF or GM-CSF may not be used as a prophylactic but may be used as otherwise clinically indicated to support blood counts for patients in this study.	
General non-hematologic toxicity	
Grade 2 (intolerable or persisting > 7 days with optimal supportive care)	Hold therapy and resume imatinib at 400 mg QD after recovery to ≤ Grade 1, if recovery occurs within 14 days If toxicity persists for 15-28 days or recurs, hold therapy and resume at next lower dose level after recovery to ≤ Grade 1: I→ 300 mg QD If recurrence is seen at the reduced imatinib dose, hold therapy and resume at next lower dose level after recovery to ≤ Grade 1. I→ 200 mg QD If 4th occurrence, considerations should be had to remove subject from study if the toxicities are not manageable with appropriate supportive measures.

≥ Grade 3	Hold therapy and resume imatinib at 300 mg QD after recovery to ≤ Grade 1, if recovery occurs within 14 days If toxicity persists for 15-28 days or recurs, hold therapy and resume at next lower dose level after recovery to ≤ Grade 1: I→ 200 mg QD If recurrence is seen at the reduced imatinib dose, hold therapy and resume at next lower dose level after recovery to ≤ Grade 1. I→ 100 mg QD If 4th occurrence, considerations should be had to remove subject from study if the toxicities are not manageable with appropriate supportive measures.

Dose re-escalation

Every attempt to re-escalate the dose of study treatment to the initial dose level should be made. This applies to either dose reductions due to hematological or non-hematological toxicities. The dose should be re-escalated if the following criteria are met within 4 weeks after dose reduction:

- All ≥ Grade 2 non-hematologic toxicities have resolved to ≤ Grade 1
- All ≥ Grade 3 hematologic toxicities have resolved to ≤ Grade 1
- Or alternatively, all ≥ Grade 3 hematological and non-hematological toxicities have resolved to ≤ Grade 2 and are manageable with supportive therapy

Re-escalation of imatinib should be considered and are encouraged, especially if a participant undergoes one full cycle at the modified dose without experiencing the toxicity that caused the dose reduction.

9.3.2 BGJ398:

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. These changes must be recorded on the Dosage Administration Record CRF.

All dose modifications should be based on the worst preceding toxicity. The following guidelines need to be applied:

Each patient will be allowed up to 3 dose reductions, provided this is feasible based on the RP2D. Patients must discontinue BGJ398 if toxicities persist following 3 dose reductions (Table 6) unless a continuation is allowed in discussion with the MSKCC PI.

Following resolution of toxicity to baseline or ≤ grade 1, treatment is resumed at either the same or lower doses of study drugs as per the criteria in Table 6. If treatment is resumed at the same doses of study drugs, and the same toxicity recurs with the same or worse severity regardless of duration, doses must be reduced to the next lower dose level (Table 6). If treatment is resumed at the lower doses of study drugs, and the same toxicity recurs with the same or worse severity, the patient must discontinue study treatment unless a continuation is allowed in discussion with the MSKCC PI.

If a patient requires a dose delay of > 14 consecutive days of BGJ398 from the intended day of the next scheduled dose, then the patient should be discontinued from the study treatment unless a continuation is allowed in discussion with the MSKCC PI.

In exceptional situations, study treatment may continue even if the patient experienced one of the treatment stopping rules. The decision to allow for continuation of treatment will be made on a case-by-case basis following discussion between the MSKCC Principal Investigator (MPI) and the Investigator. Situations that may allow for continuation of treatment include but are not limited to the following. A dose delay of > 14 days has occurred, but the patient is clearly benefiting from study treatment (i.e., stable disease, partial response, or complete response) and it is the investigator's opinion that no safety concerns are present, after discussion with the MPI, the patient may remain on the study treatment. A third or subsequent reduction (to dose level -3) in dose may be allowed if the patient is clearly benefiting from study treatment (i.e., stable disease, partial response, or complete response) but is experiencing adverse events that prevent continued treatment at the already reduced dose.

For guidance regarding interruptions in BGJ398 therapy due to adverse events, please see Table 7. Of special note is management of hyperphosphatemia, an expected on-target drug effect. See the Renal section of Table 8 for dose interruptions for acute kidney injury accompanied by hyperphosphatemia. Recommendations for prophylaxis and dose modifications for hyperphosphatemia are outlined in Table 8. Exact timing of stopping/starting BGJ398 in the setting of elevated phosphorous levels will be left to the judgment of the treating physician, and differences in phosphate management will not be considered protocol deviations. A list of high-phosphorous foods and suggested alternatives is provided in Appendix F to guide discussions regarding appropriate dietary intake. Please note plasma assessments may substitute for serum assessments per local laboratory standards.

Table 6: Dose reduction table

Dose level	**BGJ398**	
Dose level 0	RP2D	Starting dose
Dose level -1	RP2D minus 25 mg	
Dose level -2	RP2D minus 50mg	
Dose level -3	RP2D minus 75mg	Allowed only if patients is clearly benefiting from study treatment, but is experiencing AE that prevent continued treatment at dose level -2 and applicable based on RP2D

Table 7: Criteria for interruption and re-initiation of BGJ398 treatment

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
Cardiac disorders	
Cardiac - Prolonged QTc interval by Fridericia's Formula (QTcF)	
Grade 1 and 2 : QTcF 481-500 msec (asymptomatic)	Maintain dose level of BGJ398 • ECG assessments should be performed for 2 additional cycles at the same frequency as in cycle 1, or as clinically indicated If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule. • If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in cycle 1 for all subsequent cycles.
Grade 3 : QTcF > 500msec as identified on the ECG by the investigator	• Hold BGJ398. • Monitor patient with hourly ECGs until the QTcF has returned to baseline. • Perform further monitoring as clinically indicated. • Exclude other causes of QTcF prolongation such as hypokalemia, hypomagnesaemia and decreased blood oxygenation. • Patients should receive appropriate electrolyte replacement and should not receive further BGJ398 until electrolytes are documented to be within normal limits. Once the QTcF prolongation has resolved, patients may be re-treated at one lower dose level at the investigator's discretion

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy

	• ECG assessments should be performed for 2 additional cycles at the same frequency as in cycle 1 or as clinically indicated
	  ○ If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule.
	  ○ If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in cycle 1 or as clinically indicated, for all subsequent cycles
	• Patients who experience recurrent QTcF ≥ 500msec after one dose reduction will be discontinued from study.
	NB: If ventricular arrhythmia or Torsades de Pointes is observed in a patient, he/she will be discontinued from the study.
	Whenever QTcF ≥ 501msec is observed, a plasma sample for determination of BGJ398 concentration should be obtained with the time of sample collection noted.

Cardiac disorders - others Grade ≥ 3, or congestive heart failure ≥ 2	Discontinue patient from study treatment.
Investigations-Hematology	
ANC decreased (Neutropenia) Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1or baseline, then • If resolved in ≤ 7 days, maintain dose level of BGJ398 • If resolved in > 7 days, ↓ 1 dose level of BGJ398. Hold dose of BGJ398 until resolved to CTCAE ≤ Grade 1, ↓ 1 dose level of BGJ398.
Febrile neutropenia Grade 3 (ANC < 1.0 x 10^9/L, single temperature of > 38.3°C or a sustained temperature of ≥ 38.0°C for more than one hour) Grade 4	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then • If resolved by ≤ 7 days, ↓ 1 dose level of BGJ398. • If not resolved within 7 days discontinue patient from study drug treatment. Discontinue patient from study treatment.
Hemoglobin	Hold dose of BGJ398 until resolved to CTCAE Grade ≤

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
Grade 3 (<8.0 mg/dL – 6.5 mg/dL) Grade 4 (< 6.5 mg/dL)	1 or baseline, then maintain dose level Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level
Platelet count decreased (Thrombocytopenia) Grade 3 (PLT < 50 - 25 x 10^9/L) without bleeding Grade 3 (PLT < 50 - 25 x 10^9/L) with bleeding or Grade 4 (PLT < 25 x 10^9/L)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of BGJ398. • If resolved in > 7 days, ↓ 1 dose level of BGJ398 Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level
Investigations – Renal	
Serum creatinine Grade 1 and Ca x Pi >55 mg^2/dl^2 despite sevelamer 1600 mg TID and low-phosphorous diet for at least 14 days Grade 2 (> 1.5 - 3.0 x ULN) and Ca x Pi ≤55 mg^2/dL^2 Grade 2 and Ca x Pi >55 mg^2/dl^2 despite phosphorus lowering therapy for at least 14 days Grade ≥ 3 (> 3.0 x ULN)	Monitor Cr, Ca, and Pi at least twice weekly until Cr improves or stabilizes Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of BGJ398. • If resolved in > 7 days, ↓ 1 dose level of BGJ398. Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of BGJ398. • If resolved in > 7 days, ↓ 1 dose level of BGJ398. Discontinue patient from study treatment Discontinue patient from study treatment.
Investigations – Hepatic	
Blood bilirubin (patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only) Grade 2 (>1.5 – 3.0 x ULN)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • If resolved in ≤ 7 days, maintain dose level of BGJ398. • If resolved in > 7 days, ↓ 1 dose level of BGJ398.

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
Grade ≥ 3 (> 3.0 x ULN)	Discontinue patient from study treatment. Note: If CTCAE Grade 3 or 4 hyperbilirubinemia is due to hemolysis, then ↓ 1 dose level of BGJ398 and continue treatment at the discretion of the Investigator.
AST or ALT Grade 3 (> 5.0 - 20.0 x ULN) without bilirubin elevation > 2.0 x ULN	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of BGJ398. • If resolved in > 7 days, ↓ 1 dose level of BGJ398.
Grade 4 (> 20.0 x ULN) without bilirubin elevation >2.0 x ULN	Discontinue patient from study treatment.
AST or ALT and Bilirubin AST or ALT > 3.0 – 5.0 x ULN and total bilirubin > 2.0 x ULN without liver metastasis or evidence of disease progression in the liver	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • If resolved in ≤ 7 days, ↓ 1 dose level of BGJ398. • If resolved in > 7 days, discontinue patient from study treatment.
AST or ALT > 5.0 x ULN and total bilirubin > 2.0 x ULN	Discontinue patient from study treatment.
Laboratory / Metabolic disorders	
Asymptomatic amylase and/or lipase elevation (Note: not by CTCAE 4.0)	
Grade 1 (>ULN – 2.0 x ULN)	• Continue BGJ398 dosing
Grade 2 (>2.0 x ULN – 5.0 x ULN with no attributable clinical signs or symptoms)	• May continue BGJ398 dosing; consider weekly laboratory monitoring
Grade 3 (> 2.0 - 5.0 x ULN with attributable clinical signs or symptoms OR > 5.0 x ULN without clinical signs or symptoms)	• Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 2. • Consider ↓ 1 dose level of BGJ398 Note: A CT scan or other imaging study to assess the pancreas, liver, and gallbladder should be considered after the first occurrence of any CTCAE ≥ Grade 3 amylase and/or lipase.

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
Grade 4 (> 5.0 x ULN with clinical signs or symptoms)	• Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 2. • ↓ 1 dose level of BGJ398 • If recurs, discontinue patient from study treatment
Hyperphosphatemia Without Elevated Creatinine	See Table 8 for details. Note that the "Elevated creatinine" section above provides guidance when creatinine is elevated.
Hypercalcemia Serum calcium grade 2	Hold BGJ398 dose until resolved to grade 1 or baseline: • if resolved ≤ 7 days after suspending BGJ398, maintain dose level • if resolved > 7 days after suspending BGJ398, ↓ 1 dose level
Serum calcium ≥ grade 3	Discontinue patient from the study
Nervous system disorders	
Peripheral Neuropathy Grade 2	Omit dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398
Grade ≥ 3	Discontinue patient from study drug treatment
GI disorders	
Pancreatitis Grade 2	Omit dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398 If Grade 2 recurs despite dose reduction, discontinue study drug treatment
Grade ≥3	Discontinue patient from study drug treatment

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
Diarrhea	
Grade 1	Maintain dose level of BGJ398, but initiate anti-diarrheal treatment
Grade 2	• Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment, maintain dose level of BGJ398. • For reoccurrence of diarrhea CTCAE Grade 2, hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1, ↓ BGJ398 by 1 dose level
Grade 3	• Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment • ↓ BGJ398 by 1 dose level • For reoccurrence of diarrhea CTCAE Grade 3, despite optimal anti-diarrheal treatment, discontinue patient from study treatment.
Grade 4	Discontinue patient from study treatment. Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea
Vomiting Grade 2 not controlled by optimal anti-emetic therapy Grade 3 not controlled by optimal anti-emetic therapy or Grade 4	Hold BGJ398 doses until ≤ grade 1, ↓ 1 dose level Discontinue patient from study
Eye Disorders (confirmed by ophthalmologic examination)	
Retinal disorders	
Grade 2 CSR and CSR-like events	Hold BGJ398 until resolved to ≤ grade 1 but refer the patient to a retinal specialist for evaluation • If resolved in ≤ 14 days, ↓ BGJ398 by 1 dose level • If resolved in > 14 days, discontinue BGJ398
Grade 3 CSR and CSR-like events and any other grade 3 eye disorders	Hold BGJ398 until resolved to grade ≤ 1. • If resolved in ≤ 14 days, ↓ BGJ398 by 1 dose level • If resolved in > 14 days, discontinue BGJ398
≥ grade 1 retinal vein occlusion, grade 4 CSR and CSR-like events, and grade 4	

Worst Toxicity CTCAE using the current active CTCAE version	Recommended Dose Modifications any time during a cycle of therapy
other eye disorders	Discontinue BGJ398
Other ocular/visual toxicity	
≥ grade 3	Hold BGJ398 until resolution to ≤ grade 1 If resolution in ≤14 days, ↓ 1 dose level, otherwise discontinue BGJ398
General disorders	
Fatigue Grade 3	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • If resolved in ≤ 7 days, maintain dose level of BGJ398. • If resolved in > 7 days, discontinue patient from study treatment.
Other clinically significant AEs	
Grade 3	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398.
Grade 4	Discontinue patient from study treatment.
All dose modifications should be based on the worst preceding toxicity. Once a dose has been reduced it will not be increased at a later time even if there is no toxicity. Patients who require more than two dose reductions of BGJ398 will be discontinued from study drug treatment. If a patient requires a dose delay of > 14 days from the intended day of the next scheduled dose of BGJ398 then study treatment must be stopped.	

Table 8: Prophylaxis and Treatment recommendations for hyperphosphatemia without kidney injury:

Hyperphosphatemia Prophylaxis (Patients receiving treatment schedule A)	Initiate Sevelamer 800 mg with meals (up to TID) concurrent with BGJ398, unless otherwise contraindicated by patient's current medical condition. Restrict dietary phosphate intake to 600 – 800 mg/day, if BMI ≥ 21kg/m^2.
Hyperphosphatemia Treatment Without Elevated Creatinine	**INTERVENTION**
Serum Pi > 5.5 – 7.0mg/dL:	Continue sevelamer 800 mg with 2 meals per day and increase the dose of sevelamer with the largest meal to 1600mg (total daily dose = 3200 mg).
Serum Pi 7.1mg – 9.0mg/dL	Increase the dose of sevelamer up to 1600mg (2 tablets per meal) every 8 hours and continue sevelamer through Day 21 and until Serum Pi is <5.5, whichever is later. Sevelamer should be given even on days BGJ398 is not taken until serum Pi is <5.5. If serum Pi ≤ 7.0 mg/dL within 7 days, increase sevelamer to 1600 mg TID with next cycle, if not already done so. No interruption or adjustment to BGJ398 is necessary. If Serum Pi >7.0 mg/dL for longer than 7 days, **hold** BGJ398 until serum Pi is <5.5 mg/dL. Assess if patients were taking Sevelamer 1600 mg TID on Day 1 of most recent cycle.

	- If patient was NOT taking Sevelamer 1600 mg TID on Day 1 of the most recent cycle: o Increase Sevelamer to 1600 mg TID for each subsequent cycle o No dose reduction in BGJ398 is necessary - If patient WAS taking sevelamer 1600 mg TID on Day 1 of the most recent cycle: o Dose reduce BGJ398 by 1 level If serum phosphorous does not resolve to <7.0 mg/dL despite phosphorous lowering therapy within 14 days of first held dose of BGJ398, **discontinue** BGJ398 therapy. All patients will continue to be followed-up until resolution to serum phosphorus ≤ 5.5 mg/dL or baseline or stabilization.
Serum Pi 9.1 mg/dL or higher	Recheck serum Pi as soon as possible to rule out laboratory error. If confirmed, **hold** BGJ398 until Serum Pi <7.0 mg/dL. Increase the dose of sevelamer up to 1600mg (2 tablets per meal) every 8 hours and continue sevelamer through Day 21 and until Serum Pi is <5.5, whichever is later. Sevelamer should be given even on days BGJ398 is not taken until Serum Pi is <5.5. Then assess: - If patient was NOT taking Sevelamer 1600 mg TID on Day 1 of the most recent cycle: o Increase Sevelamer to 1600 mg TID for each subsequent cycle o No dose reduction in BGJ398 is necessary - If patient WAS taking sevelamer 1600 mg TID on Day 1 of the most recent cycle: o Dose reduce BGJ398 by 1 level If serum phosphorous does not resolve to <7.0 mg/dL despite phosphorous lowering therapy within 14 days of first held dose of BGJ398, **discontinue** BGJ398 therapy. All patients will continue to be followed-up until resolution to serum phosphorus ≤ 5.5 mg/dL or baseline or stabilization.

9.4 Drug Interactions

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed, provided their use is documented in the patient records and on the appropriate case report form. The administration of any other anti-cancer agents including, chemotherapy and biologic agents is not permitted. Use of erythropoietin alfa (EPO) is allowed at the discretion of the treating investigator. G-CSF or GM-CSF may not be used as a prophylactic measure but may be used as otherwise clinically indicated to support blood counts for patients in this study. The use of other concurrent investigational drugs is not allowed.

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, analgesics, short course of steroids, or bisphosphonates, when appropriate. Anti-emetics (such as prochlorperazine, lorazepam, ondansetron or other 5-HT antagonists) may be administered prophylactically in the event of nausea. Antidiarrheals, such as loperamide, may be administered as needed in the event of diarrhea. Oral contraceptive pills are permitted.

All concomitant medications taken during the study will be recorded with indication, dose information, and dates of administration. The Electronic Data Capture system, MediData RAVE, must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The MSKCC Principal Investigator should be alerted if the patient is taking any agent known to affect (or with the potential to affect) selected P450 isoenzymes.

All subjects will be asked to provide a complete list of prescription and over-the-counter medications that have been taken within the 4 weeks prior to screening. The investigator must be informed as soon as possible about any new medication(s) taken from the time of screening until the completion of the post-treatment follow-up visit. Additionally, patient nicotine history should be recorded as indicated on the eCRFs.

9.4.1 Permitted concomitant therapy with Imatinib requiring caution and/or action

Imatinib appears to be a competitive inhibitor of CYP2Cp, CYP2D6, CYP3A4/5, suggesting that imatinib could reduce the clearance of co-administered drugs whose metabolism is dependent on these P450 cytochrome isoenzymes. Because of the inherent risk of either reduced activity or enhanced toxicity of concomitant medications and/or imatinib, drugs known to be metabolized by the same P450 isoenzymes as imatinib should be used with caution (Appendix C). A non-comprehensive list of cytochrome CYP3A4 inhibitors and inducers may be found in Appendix C. FDA classification of CYP3A4 inhibitors can be found at:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#cypEnzymes

A non-comprehensive list of CYP3A4 inducers is provided in Appendix C.

Special care has to be given to the concomitant use of acetaminophen (paracetamol, Tylenol) with imatinib. Any use of this drug has to be documented in the medical records and/or captured on the appropriate case report form. Patients should be warned to avoid or restrict the use of over-the-counter and prescription medicines containing acetaminophen (paracetamol).

Since warfarin is metabolized by CYP2C9 and CYP3A4, patients who require anticoagulation should receive low-molecular weight or standard heparin, if possible.

Patients should also avoid Seville oranges or Seville oranges derivatives, grapefruit or grapefruit juice, star fruit or star fruit juice and other foods known to inhibit CYP3A4 while taking imatinib.

Drugs that may increase imatinib plasma concentrations (Appendix C): Caution is recommended when administering imatinib with inhibitors of the cytochrome P450 isoenzyme CYP3A4 family (e.g., ketoconazole, itraconazole, erythromycin, and clarithromycin). Substances that inhibit CYP3A4 activity may decrease metabolism and increase imatinib concentrations. There was a significant increase in exposure to imatinib when the compound was co-administered with ketoconazole, a CYP3A4 inhibitor.

Drugs that may decrease imatinib plasma concentrations (Appendix C): Substances that are inducers of CYP3A4 activity may increase metabolism and decrease imatinib plasma concentrations. Co-medications that induce CYP3A4 (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or St. John's Wort) may reduce exposure to imatinib.

Drugs that may have their plasma concentration altered by imatinib (Appendix C): Imatinib increases the mean C_{max} and AUC of simvastatin (a CYP3A4 substrate) 2- and 3.5-fold, respectively, indicating inhibition of CYP3A4 by imatinib. Particular caution is recommended when administering imatinib with CYP3A4/5 substrates with a narrow therapeutic window (e.g., cyclosporine or pimozide). Imatinib will increase plasma concentrations of other CYP3A4 metabolized drugs (e.g., triazolo-benzodiazepines, dihydropyridine calcium channel blockers, certain HMG-CoA reductase inhibitors, etc.).

9.4.2 Permitted concomitant therapy requiring caution and/or action with BGJ398

Drugs that alter the pH of the GI tract: BGJ398 is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of both compounds, and limit bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. Therefore, study drug(s) should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent. Note that some proton-pump inhibitors may inhibit BCRP.

Corticosteroids: Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to induce CYP3A enzymes, thereby increasing the risk of reducing drug exposure to sub-therapeutic levels. In addition BGJ398 is an in vitro inhibitor of CYP3A4 and has the potential to increase the systemic exposure of corticosteroids that are metabolized by CYP3A4. Systemic corticosteroid treatment can be used with caution and minimized to the extent possible.

Substrates and inhibitors:

CYP substrates and inhibitors:

BGJ398 was shown to inhibit the cytochrome p450 isoenzyme CYP3A4 in in-vitro assays, thus, suggesting an increased risk of drug interactions with concomitant medications that are metabolized by CYP3A4. However, such interactions have not been confirmed in patients. Therefore, investigators may administer medications that are known to be metabolized by CYP3A4. Patients must be monitored for potentiation of toxicity and may require dose titration or reduction of the CYP3A4 substrate. In particular caution is advised when substrates with a narrow therapeutic index, such as alfentanil, fentanyl, astemizole, cisapride, diergotamine, ergotamine, pimozide, quinidine, sirolimus, tacrolimus, and terfenadine need to be administered. Please refer to Appendix D for the list of medications to be used with caution.

Caution is advised when BGJ398 is co-administered with opioid analgesics. Inhibition of opioid metabolism by CYP3A4 can lead to opioid toxicity, including fatal respiratory depression, or an enhanced risk for QTc prolongation. Patients receiving BGJ398 and opioid analgesics should be carefully monitored. Synthetic opioids with clinically relevant interactions with CYP3A4 inhibitors include, but are not limited to, propoxyphene, fentanyl, alfentanyl and sufentanil. Use of alfentanyl, a sensitive CYP3A4 substrate with narrow therapeutic window, should be avoided whenever possible. The use of methadone and levomethadyl should also be avoided whenever possible. Refer to the Appendix D for the list of medications to be used with caution. Note that the list may not be comprehensive.

Hormonal contraceptives may be affected by cytochrome P450 interactions and are therefore not considered effective for this study. For allowed contraception methods please refer to section 11.4.1. Highly effective contraception should be maintained throughout the study.

BGJ398 is a reversible inhibitor of CYP2C8, CYP2C9 and CYP2C19; coadministration of medications that are substrates or inducers of CYP2C are permitted. BGJ398 is a substrate of CYP3A4. Therefore moderate inhibitors and inducers should be used with caution if no other alternative is available. Strong inhibitors and inducers are prohibited.

Please refer to Appendix D for the list of medications to be used with caution and Appendix E for drugs that are prohibited to be used with BGJ398. Please note that the list might not be comprehensive.

Transporter substrates: In vitro data show that BGJ398 is an inhibitor of BCRP. CQM157, a metabolite of BGJ398, is an inhibitor of transporters P-gp, BCRP, OATP1B1, and OATP1B3 (IC50 2-4 µM). In the absence of data confirming whether transporter interactions occurs in vivo, patients receiving medications that are substrate of these transporters must be monitored for potential toxicity and may require dose titration or reduction of the medication.

Non-enzyme Inducing Anti-epileptic drugs (non-EIAED): Non-enzyme inducing anti-epileptic medication (non-EIAED) such as valproic acid, levetiracetam and lamotrigine are allowed with caution. Patients who were previously on a non-EIAED and need to change anti-convulsants should be started on another non-EIAED if at all possible. EIAEDs are not permitted (Appendix E).

Anti-emetics: Anti-emetics are allowed for the treatment of nausea or vomiting. It is recommended to avoid using drugs that are known to cause QT prolongation. Note that some anti-emetics have a known risk for Torsade do Pointes, and therefore need to be used with caution. See Appendix D for list of drugs that need to be used with caution. Aprepitant is both a sensitive substrate and a moderate CYP3A4 inhibitor and can be used with caution if an alternative is not available.

QT/QTc interval prolongation or torsade de pointes medications: Medications that have the potential to prolong the QT/QTc interval or induce torsades de pointes are allowed with caution. Investigators at their discretion may co-administer such medications, but patients should be carefully monitored. See Appendix D for list of drugs that need to be used with caution.

9.4.3 Prohibited concomitant therapy with BGJ398

CYP inhibitors

Strong inhibitors of CYP3A4 such as the ones listed in Appendix C are prohibited because BGJ398 is a likely substrate of this isoenzyme. Caution should be used during administration of moderate inhibitors. The following food products are prohibited: Seville oranges or juice, grapefruit, grapefruit juice, grapefruit hybrids, and pummelos.

CYP inducers: Strong inducers of CYP3A4 are prohibited because their usage would likely decrease the exposure of BGJ398. Therefore, agents such as those listed in Appendix E are prohibited. Caution should be used during administration of moderate inhibitors.

Phosphorus and calcium: Medications that increase the serum levels of phosphorus and/or calcium are prohibited. These include, but are not limited to, calcium, phosphate, vitamin D, parathyroid hormone (PTH).

Herbal medications: Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug.

Enzyme Inducing Anti-epileptic drugs (EIAEDs): Enzyme inducing anti-epileptic medication is not allowed (please refer to Appendix E). Patients who were previously on a non-EIAED and need to permanently change anticonvulsants, but who cannot change to another non-EIAED must be discussed with the MSKCC PI and Novartis. These patients will be taken off-study unless it is felt that they have benefited from the therapy following discussion with the MSKCC PI and Novartis.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10. 1 Standard Evaluation

10.1.1 Study Calendar (Phase I Portion Study)

Baseline clinical evaluations are to be conducted within 2 weeks of starting protocol therapy. Radiologic evaluations and surgical biopsies must be done ≤4 weeks prior to the start of therapy.

Informed Consent can be obtained 30 days prior to the start of study therapy.

After patients have been on the combination therapy more than 4 cycles, the patient can increase the duration of the evaluation by the MD and RN to every 8 or 12 weeks at the investigator's discretion. The basic laboratory and EKG assessment between evaluations can be performed locally and will be obtained every 4 weeks for patients on the phase Ib portion of the study.

Table 9: Visit Evaluation Schedule during Phase Ib

	Pre-Study	Cycle 1				Cycle 2				Cycle 3 and beyond				Off Study[c]
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12+	
Imatinib[X]		X	X	X	X	X	X	X	X	X	X	X	X	
BGJ398[YA] Treatment Schedule A		YA	YA	YA		YA	YA	YA		YA	YA	YA		
BGJ398[YB] Treatment Schedule B		YB				YB				YB				
Informed consent	X													
Demographics	X													
Medical history	X													
Concurrent Meds	X	X	X	X	X	X				X[d]				
Physical exam	X	X	X	X	X	X				X[d]				X
Vital signs	X	X	X	X	X	X				X[d]				X
Height	X													
Weight	X	X		X		X				X[d]				X
Eye Exam [g]	X				X									
Performance status	X	X	X	X	X	X				X[d]				X
CBC w/diff, plts[j]	X	X	X	X	X	X		X		X[d]				X
Urinalysis	X													
Blood chemistry [a,j]	X	X	X	X	X	X		X		X[d]				X
Hep B	X													
TSH	X							X		X[d]				
EKG	X			X		X				X[d]				
Echo or MUGA	X				X								X[e]	X

Adverse event evaluation		X		X		X				X[d]				X
Radiologic evaluation	X									X[f]				X[f]
Tumor measurements	X									X[f]				
B-HCG	X[b]													
BGJ398 and imatinib PK Levels		X[h, i]		X[h,i]	X[h, i]									

X: Imatinib: Dose as assigned; PO once daily

YA: BGJ398: Dose as assigned; PO once daily for 3 weeks on and one week off

YB: BGJ398: Dose as assigned; PO once daily for one week on and 3 weeks off

a: Comp- Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. In addition, LDH, phosphorus, magnesium, creatine kinase (CK), amylase, lipase.

b: Blood pregnancy test (women of childbearing potential) once at baseline; further testing at the discretion of the investigator while on study.

c: Off-study evaluation performed 4 weeks after removal from study with a window of +/- 7 days

d: Day 1 of each cycle while on study. At the investigator's discretion, patients can return for RN/MD visits and get evaluated every 8 or 12weeks after cycle 4. Laboratory assessments and EKG assessments between MD/RN visits can be performed locally with results sent to the study site

e: TTE or MUGA will be performed once at week 16 as well as any time felt to be necessary by the investigator. Modalities should remain consistent whenever feasible.

f: Scans should be performed every 8 weeks x 4 starting after 2 cycles (e.g. C3D1, C5D1, C7D1, C9D1), then every 12 weeks (C12D1, C15D1, etc). Radiologic documentation must be provided for patients removed from study for progressive disease within 28 days of clinical assessment of progression if no scan was performed within 28 days of the time of that assessment.

g: At eye exams the follow tests should be completed :
- slit lamp exam
- dilated funduscopic exam with photos
- optical coherence tomography testing

A follow-up eye exam will occur at week 4 (C1W4) and/or if the patient develops new or worsening ocular symptoms

h: The timing of pharmacokinetic sample collections is dependent on the treatment schedule the patient is enrolled onto. For treatment schedule A pharmacokinetic sample collections should be drawn at the following timepoints: Cycle 1, Day 1 plasma will be drawn at 0, 1, 2, 4, 6, 8, and 24 hours after taking BGJ398; the 0 and 24 hour timepoints will be drawn before dosing BGJ398. Cycle 1, Day 21 plasma will be drawn 0, 1, 2, 4, 6, and 8 hours after dosing BGJ398. See Table 10.A. These assessments must be done on the exact dates except -3 /+1 day window for C1D21 timepoint. Other levels may be drawn as clinically indicated. For treatment schedule B pharmacokinetic sample collections should be drawn at the following timepoints: Cycle 1, Day 1 plasma will be drawn at 0, 1, 2, 4, 6, 8, and 24 hours after taking BGJ398; the 0 and 24 hour timepoints will be drawn before dosing BGJ398. Cycle 1, Day 7 will be drawn at 0, 1, 2, 4, 6, and 8 hours after dosing BGJ398; the 0 hour timepoint will be drawn before dosing BGJ398 . Cycle 1, Day 15 will be drawn at 0hr. Cycle 1, Day 21 will be drawn at 0hr. See Table 10.B. These assessments must be done on the exact dates except -2 /0 day window for C1D7 and -3 /+1 day

	window for C1D15 and C1D21 timepoint. Other levels may be drawn as clinically indicated. i: For treatment schedule A plasma for imatinib levels will be drawn concurrently with BGJ398 levels at the following two time points: C1D2 (24 hours post-first dose) and C1D21. Both time points will be drawn before dosing imatinib on that day. C1D2 must be done on the exact date, and C1D21 may be drawn within a -3/+1 day window. Other levels may be drawn as clinically indicated. For treatment schedule B plasma for imatinib levels will be drawn concurrently with BGJ398 levels at the following three timepoints: C1D2 (24 hours post-first dose), C1D7 and C1D21. All time points will be drawn before dosing imatinib on that day. C1D2 must be done on the exact date. C1D7 can be drawn within a -2/0 day window and C1D21 can be drawn within a -3/+1 day window. Other levels may be drawn as clinically indicated. j. CBC and Blood Chemistry performed on Day 1 of each cycle must be resulted prior to treatment. All assessments are to be done +/-3 days of the scheduled timepoints unless otherwise noted above. Radiologic assessments (CT, PET, TTE) are to be done +/-7 days from the scheduled appointment.

Table 10.A: Pharmacokinetic Assessments of BGJ398 on Treatment Schedule A

Treatment Cycle	Day	PK Sample # BGJ398 (Plasma)	Time Relative to Dose
1	1	1	Pre-dose[a]
1	1	2	1hr ± 5 min
1	1	3	2hr ± 5 min
1	1	4	4hr ± 10 min
1	1	5	6hr ± 10 min
1	1	6	8hr ± 15 min
1	2	7	24hr ± 60 min[a]
1	21	8	Pre-dose[a]
1	21	9	1hr ± 5 min
1	21	10	2hr ± 5 min
1	21	11	4hr ± 10

			min
1	21	12	6hr ± 10 min
1	21	13	8hr ± 15 min
Any	Any	101, 102, etc	As clinically indicated

a: These levels should be drawn just prior to administration of BGJ398 plus imatinib on that day

Note: C1D21 will have a -3 days/+1 day window, this window differs from all other PK visits

Table 10.B: Pharmacokinetic Assessments of BGJ398 on Treatment Schedule B

Treatment Cycle	Day	PK Sample # BGJ398 (Plasma)	Time Relative to Dose
1	1	1	Pre-dose[a]
1	1	2	1hr ± 5 min
1	1	3	2hr ± 5 min
1	1	4	4hr ± 10 min
1	1	5	6hr ± 10 min
1	1	6	8hr ± 15 min
1	2	7	24hr ± 60 min[a]
1	7	8	Pre-dose[a]
1	7	9	1hr ± 5 min
1	7	10	2hr ± 5 min
1	7	11	4hr ± 10 min

1	7	12	6hr ± 10 min
1	7	13	8hr ± 15 min
1	15	14	Pre-dose[b]
1	21	15	Pre-dose[b]
Any	Any	101, 102, etc	As clinically indicated

b: These levels should be drawn just prior to administration of the study drugs (BGJ398 and/or imatinib) on that day

Note: C1D7 will have a window of -2/0 day window, C1D15 and C1D21 will have a -3/+1 day window, these windows differ from all other PK visits

10.1.2 Study Calendar (Phase II Portion Study)

Baseline clinical evaluations are to be conducted within 2 weeks of starting protocol therapy including a baseline FDG-PET prior to the lead-in phase of imatinib. Radiologic evaluations and surgical biopsies must be done ≤4 weeks prior to the start of therapy. There is a 2-week lead in of imatinib alone and then BGJ398 will be added to imatinib.

Informed Consent can be obtained 30 days prior to study start.

After patients have been on the combination therapy more than 4 cycles, the patient can increase the duration of the evaluation by the MD and RN to every 8 or 12 weeks at the investigator's discretion. The basic laboratory and EKG assessment between evaluations can be performed locally.

Table 11: Visit Evaluation Schedule during Phase II

	Pre-Study	Wk -2	Cycle 1				Cycle 2				Cycle 3 and beyond				Off Study/ EOT[c]
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12+	
Imatinib[x]		X	X	X	X	X	X	X	X	X	X	X	X	X	

BGJ398[Y] Treatment schedule to be determined by the phase Ib portion of the study															
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent Meds	X		X	X	X	X	X				X[d]				
Physical exam	X		X	X	X	X	X				X[d]				X
Vital signs	X		X	X	X	X	X				X[d]				X
Height	X														
Weight	X		X		X		X				X[d]				X
Eye Exam [k]	X					X									
Performance status	X		X	X	X	X	X				X[d]				X
CBC w/diff, plts[m]	X		X	X	X	X	X		X		X[d]				X
Urinalysis	X														
Blood chemistry[a,m]	X		X	X	X	X	X		X		X[d]				X
Hep B	X														
TSH	X						X				X[d]				
EKG	X				X		X				X[d]				
Echo or MUGA	X					X								X[e]	X
Adverse event evaluation			X		X		X				X[d]				X
Radiologic evaluation	X										X[f]				
Tumor measurements	X										X[f]				X[f]
B-HCG	X[b]														

FDG PET scan	X				X[g]										
Tumor Biopsy	X			X[h]											X[h]
Research Blood Draw		X[i]	X[i]		X[i]		X[i]								X[i]
Survival Status															X[l]

Key for Table 10: Schedule of Phase 2 Evaluations	X: Imatinib: Dose as assigned; *PO once daily* Y: BGJ398: Dose as assigned; PO once daily the treatment schedule will be determined by the phase Ib portion of the study a: Comp- Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. In addition, LDH, phosphorus, magnesium, creatine kinase (CK), amylase, lipase. b: Blood pregnancy test (women of childbearing potential) once at baseline; blood or urine pregnancy test at the discretion of the investigator while on study. c: Off-study evaluation performed 4 weeks after removal from study. d: Day 1 of every cycle while on study. At the investigator's discretion, patients can return for RN/MD visits and get evaluated every 8 or 12 weeks after cycle 4. Laboratory assessments and EKG assessments between MD/RN visits can be performed locally with results sent to the study site e: TTE or MUGA will be performed once at week 16 as well as any time felt to be necessary by the investigator. Modalities should remain consistent whenever feasible. f: Scans should be performed every 8 weeks x 4 starting after 2 cycles (e.g. C3D1, C5D1, C7D1, C9D1), then every 12 weeks (C12D1, C15D1, etc). Radiologic documentation must be provided for patients removed from study for progressive disease within 28 days of clinical assessment of progression if no scan was performed within 28 days of the time of that assessment. g: FDG PET scan will be performed at baseline (pre-treatment) and during week 3 of combination therapy (C1D21). h: Tumor biopsy will be performed pre-treatment, after week 1 (C1D8) of therapy, and at disease progression for patients who have consented for research biopsies including the first twenty mandatory patients and any subsequent voluntary patients. A +/- 4 day window will be provided for the biopsies to account for scheduling. i: Four research blood 4-8mL vials will be obtained at baseline (week -2), two weeks after the single agent imatinib lead in (C1D1 of combination therapy), week 3 (C1D15), week 5 (C2D1). At least one tube at those timepoints will be used for imatinib trough levels, and two tubes will be used for correlative analyses. Imatinib levels will be prioritized. j: Two research blood 4-8mL vials for correlative analyses will be obtained at the time of progression. k: At eye exams the follow tests should be completed : - slit lamp exam - dilated funduscopic exam with photos - optical coherence tomography testing A follow-up eye exam will occur at week 4 (C1W4) and if the patient develops new or worsening ocular symptoms. l: Study personnel will attempt to contact all evaluable patients every 3 months (±2 weeks) via telephone, email, etc to assess survival status for up to 3 years. m. CBC and Blood Chemistry performed on Day 1 of each cycle must be resulted prior to treatment All assessments are to be done +/-3 days of the scheduled timepoints unless otherwise noted. Radiologic assessments (CT, PET, TTE) are to be done +/-7 days from the scheduled appointment.

10.2 PATHOLOGY/CORRELATIVE/SPECIAL STUDIES

Tumor Collection and Screening

10.2.1 Pre-treatment diagnosis confirmation:

All patients will have histological or cytological confirmation of a diagnosis at their treating institution prior to treatment. If necessary a patient may have to undergo a biopsy of their disease as per standard clinical practice to ensure that a proper diagnosis of their disease is made. Tissue will be obtained for correlative studies only after a definitive diagnosis has been made by pathology and informed consent has been obtained.

10.2.2 Biopsy specimen collection for correlative studies:

Following informed consent, the first 20 patients enrolled on the phase II portion will undergo mandatory research biopsies. All biopsies will be performed at MSKCC or other participating institutions. These patients will undergo a pre-treatment biopsy and then a post-treatment biopsy (C1D8) that will be performed after week 1 of the combination therapy. Biopsies at the time of progression will be optional but encouraged. After 20 paired biopsy specimens are obtained, the remainder are optional and encouraged if additional funding is identified. If an open incisional biopsy is performed, 1 cm^3 of tissue will be flash frozen and 0.5 to 1cm^3 will be formalin fixed and sent to pathology for correlative studies. Alternatively, a CT guided core biopsy could be performed. Core biopsy will be performed of a lesion of at least 2 cm by a study interventional radiologist with local anesthesia and through a single entrance site on the skin surface, up to five tissue cores of the GIST will be obtained. Four cores will be flash frozen and one core will be fixed in formalin for correlative pathology. We believe that both approaches will provide sufficient tissue to do the proposed studies. As mentioned in 10.2.1, we may also collect tissue from patients required to undergo a pre-treatment biopsy for confirmation of diagnosis. A patient may be excused from this requirement if tissue is not deemed accessible or for safety reasons as determined by local study investigator. In such a case, subsequent patients will be approached for a mandatory biopsy until a total of 20 paired patient biopsies are obtained. Biopsies will not be performed on the Phase I portion of the protocol.

10.2.3 Research Blood:

Research blood will be drawn on the Phase Ib portion at the time points noted in Tables 10.A and 10.B for BJG398 and imatinib plasma levels. Research blood will be obtained on the Phase II portion at baseline, 2 weeks after single agent imatinib lead in (+/-3 days) prior to Cycle 1 Day 1, and at C1D15 and C2D1 after the combination therapy started from all patients. All blood samples should be obtained **prior** to the daily dose of imatinib +/- BGJ398; i.e. a trough level. Research blood will be used to evaluate the steady-state imatinib trough level.

10.2.4 Collection of Specimen(s):

Tumor samples will be collected pre-treatment from the first 20 patients enrolled on the Phase II portion of the trial who have accessible tumor for biopsy and will start imatinib de novo for this trial. Also, tissue will be collected from any subsequent patients who require standard of care biopsies prior to systemic treatment, or those patients who volunteer for research biopsies if funding is available.

10.2.4 Handling of Specimens(s):

For each sample indicate the unique patient study identification number, histology diagnosis, and the date of the specimen.

10.2.5 Shipping of Specimen(s)

Flash frozen tumor for extraction of RNA and DNA and for protein extraction:
Ping Chi, Sarcoma Biology Lab
Human Oncology and Pathogenesis Program
Memorial Sloan-Kettering Cancer Center
Zuckerman Research Building
Attn: Ping Chi MD, PhD
417 E 68th St., Rm Z527
New York, NY 10065
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Fresh tumor fixed in formalin:
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Plasma for imatinib levels and Plasma for BGJ398 will be shipped to MSK. MSK will batch ship the samples to WuXi AppTec Co. Ltd.

All participating sites will notify the Multicenter Trial Research Staff at MSKCC (Email: medmctcore@mskcc.org) when samples are shipped by completing and emailing the sample requisition form.

Correlative studies will be performed on all obtained biopsy specimens detailed as the following.

1. **Molecular based correlative studies**
   1a. Phenotypic characterizations by immunohistochemistry (IHC)
   For pathway response studies, we will assess the baseline characteristics of the MAP kinase, FGF, and KIT pathway members in FFPE samples collected from all patients. Previous studies have demonstrated the reliability of pathway members KIT, pKIT, pERK1/2, pAKT, PTEN, p-S6, p4E-BP1, pFRS2, FRS2, pPRAS40, pSTAT3, and STAT3, which will be evaluated by IHC. Baseline tissue characteristics will be derived from histological characterization for KIT, CD34 and DOG1. FGF2 and FGFR will also be screened by IHC on all tumor samples.

1b. Genetic characterization of tumors

All tumor specimens will be genotyped via standard sequenom assay for hotspot mutations in KIT, PDGFRA and BRAF that are commonly mutated in GIST. In addition, we will perform multiplex custom exome capture coupled with deep-sequencing for genes that are frequently implicated in GIST pathogenesis, including KIT, PDGFRA, BRAF, NF1, ETV1, PTEN, NRAS, HRAS, KRAS and p53 mutational status.

1c. Transcriptome characterization of tumors

As an exploratory study, we will perform custom transcriptome analysis of a custom ETV1-dependent gene signature in GIST[25] in FFPE samples from all patients using nanostring, because ETV1protein level is very unstable.

1d. Pharmacodynamic studies by IHC, WB and immunofluorescence

FFPE tumor tissue and pre-and post-treatment tumor frozen samples from the first 20 patients will be evaluated for inhibition of ETV1 and target pathway inhibition (MAP kinase, FGF, and KIT pathways). A variety of pathway markers of the MAP kinase and KIT pathways, including KIT, pKIT, pERK1/2, pAKT, PTEN, p-S6, p4E-BP1, pFRS2, FRS2, pPRAS40, pSTAT3 and STAT3 will be evaluated by IHC. ETV1 protein levels will also be evaluated by both western blot and immunofluorescence of frozen tissues, since there is no IHC grade ETV1 antibody.

1e. Pharmacodynamic studies by transcriptome

We will perform custom transcriptome analyses of the ETV1-dependent gene signature in GIST in pre- and post-treatment biopsies to assess the inhibition of the ETV1 transcriptional activity and correlate with response.

1f. Phenotypic changes in pre- and post-treatment tumors by IHC

In addition to the IHC of pKIT, pAKT,pERK1/2, etc as outlined in **1d** in pre- and post-treatment biopsies, we will explore the relationship between the immunostains with the effects on tumor growth as assayed by the proliferation marker, Ki-67, and the apoptosis/cell death marker, cleaved caspase 3.

1g. Steady state plasma imatinib trough levels

The acute and steady state imatinib level will be assessed in all Phase Ib patients (one sample/timepoint). Patients enrolled onto treatment schedule A will have a plasma sample for imatinib levels drawn at C1D2 and C1D21 before imatinib is dosed on those days. Patients enrolled onto treatment schedule B will have a plasma sample for imatinib level drawn at C1D2, C1D7 and C1D21 before imatinib is dose on those days. The steady state imatinib trough levels will be obtained and evaluated in the two-week imatinib lead in phase (one sample/patient) and in the combination therapy phase (one sample/patient) from all patients in the Phase II portion of the trial. We will evaluate the effects of BGJ398 on imatinib steady state trough levels by comparing these two phases.

1i. BGJ398 pharmacokinetic assessment

BGJ398 levels will be assessed in all Phase Ib patients (1 sample per timepoint). Patients enrolled onto treatment schedule A will have plasma samples for BGJ398 levels collected at

C1D1 at 0, 1, 2, 4, 6, 8 hours; C1D2 24 hr time point; and C1D21 at 0, 1, 2, 4, 6, 8 hours. Patients enrolled onto treatment schedule B will have plasma samples for BGJ398 levels collected at C1D1 at 0, 1, 2, 4, 6, 8 hours; C1D2 24 hr time point after the first dose of BGJ398&imatinib; C1D7 at 0, 1, 2, 4, 6, 8 hours; C1D15 at 0 hours and C1D21 at 0 hours.

1i. FGF2 serum/plasma levels by ELISA
A commercially available ELISA kit for serum/plasma FGF2 (Bioagilytix) will be evaluated in all patients at baseline, with the initiation of imatinib, after imatinib lead in and serially, after the initiation of combination therapy. FGF2 levels will be correlated to primary and secondary outcomes.

2. **Sample collections pre- and during treatment**
   2a. Archival biopsy FFPE samples (as available, ~25 unstained FFPE sections of standard 5 µm slides, OR 10-20 unstained FFPE sections of 10 µm slides)
   2b. Frozen pre-treatment core biopsy samples (up to five cores)
   2c. Frozen 1 week post-combination treatment biopsy samples (up to five cores)
   2d. Frozen post-treatment biopsy or surgical samples at disease progression (if possible)
   2e. Whole blood for research purposes. These samples will possibly be used for serum FGF2 levels and screening for other potential soluble protein biomarkers, etc. pre-treatment and 1 or 2 weeks after treatment and periodically, day 1 of each cycle.

3. **Imaging based correlative studies:**
   FDG PET per standard of care will be obtained pre-treatment and three weeks (C1D21) after initiation of the combined imatinib and BGJ398 treatment in the Phase II portion. These images will be evaluated to determine whether the FDG PET studies can be used to determine and predict treatment response.

4. **Imatinib Levels:**
   As imatinib is standard of care for patients with untreated inoperable locally advanced or metastatic GIST, imatinib levels will be tested to ensure that BGJ398 does not affect imatinib serum levels. In Phase Ib, imatinib levels will be tested on C1D2 (24 hour timepoint after the first dose of imatinib&BGJ398) and C1D21 (prior to dosing on that day) on both treatment schedules (A and B). In phase Ib, on schedule B, imatinib level will also be tested on C1D7 (prior to dosing on that day). All participants on the Phase II portion will undergo a 2-week lead in of single agent imatinib in order to establish a steady-state serum imatinib trough level. Imatinib levels will be rechecked during week 3 and week 5 of the combination therapy. We will correlate imatinib levels to primary and secondary outcome measures. Imatinib levels will be stratified into quartiles as done previously [31].
5. **FGF2 Serum Levels:**
   Preclinical data suggests that FGF2 levels may correlate with the development of imatinib resistance and may predict response to inhibition with BGJ398. Blood will be collected at baseline (if not on imatinib), after the imatinib lead-in, and during week 3 and 5 of the combination therapy. We will correlate FGF2 levels to our primary and secondary endpoints with the hope of establishing an integral biomarker for BGJ398 and evaluating the penetrance of the FGF pathway in GIST. If collected blood specimen is only adequate for 1 assay, imatinib levels should be prioritized.

Please reference the laboratory manual for instructions on sample labeling and shipping.

11.0 TOXICITIES/SIDE EFFECTS

Toxicity grading will be performed in accordance with NCI CTC version 4.03, (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 11.1) and the characteristics of an observed AE (Section 11.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

11.1 Adverse Events

11.1.1 Imatinib Mesylate

See the package insert for complete list of possible adverse events related to imatinib:

The majority of imatinib-treated patients experienced AEs at some time. Approximately 60% of patients reported at least one grade 3/4 AE at some time during the study, and imatinib was discontinued due to AEs in 18 patients. The most frequently reported AEs were edema, nausea, diarrhea, abdominal pain, muscle cramps, fatigue, and rash, most of which were of mild-to-moderate severity. Imatinib was discontinued for AEs in 7 patients (5%) in both dose levels (400 and 800 mg/d) studied. Superficial edema, most frequently periorbital or lower extremity, was managed with diuretics, other supportive measures, or by reducing the dose of imatinib. Severe (NCI-CTCAE Grade 3/4) superficial edema was observed in 3 patients (2%), including facial edema in 1 patient. Grade 3/4 pleural effusion or ascites was observed in 3 patients (2%). Nine (6%) patients (600 mg/d (n=6); 400 mg/d (n=3)) were reported to have grade 3/4 GI or intra-tumoral hemorrhage during the study (GI bleeding (n=5); intratumoral bleeding (n=3); both GI and intratumoral bleeding (n=1). The GI localization of the tumor likely contributed to this AE in this patient population. None of these patients had thrombocytopenia at the time of hemorrhage. The small number of events and the variability in baseline clinical profiles preclude conclusions to aid the identification of patients at increased risk of hemorrhage during therapy with imatinib.

Table 12: Adverse events greater than or equal to 10% of patients with imatinib treatment in GIST

	All CTC Grades			CTC Grades 3 / 4
	400 mg (N=73)	600 mg (N=74)	400 mg (N=73)	600 mg (N=74)
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Fluid retention	81	80(93.2)	7	12
Superficial edema	81	77	6	5
Pleural effusion or Ascites	15	12	3	8
Diarrhea	59	70	3	7
Nausea	63	74	6	4

	All CTC Grades			CTC Grades 3 / 4
Fatigue	48	53	1	1
Muscle Cramps	47	58	0	0
abdominal Pain	40	37	11	4
Rash and related term	38	53	4	3
Vomiting	38	35	3	5
Musculoskeletal Pain	37	30	6	1
Headache	33	39	0	0
Flatulence	30	34	0	0
Any Hemorrhage	26	34	6	11
Pyrexia	25	16	3	0
Back Pain	23	36	6	0
Nasopharyngitis	21	27	0	0
Insomnia	19	18	1	0
Lacrimation Increased	16	18	0	0
Dyspepsia	15	15	0	0
Upper respiratory tract infection	14	18	0	0
Liver Toxicity	12	12	6	8
Dizziness	12	11	0	0

*All adverse events occurring in ≥ 10% of patients regardless of suspected relationship to treatment

Also reported on Imatinib Mesylate (STI571) trials but with the relationship to Imatinib Mesylate (STI571 still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Disseminated intravascular coagulation; Febrile neutropenia

CARDIAC DISORDERS - Cardiac arrest; Heart failure; Myocardial infarction; Ventricular arrhythmia

ENDOCRINE DISORDERS - Hypothyroidism

EYE DISORDERS - Blurred vision; Conjunctivitis; Papilledema; Photophobia; Watering eyes

GASTROINTESTINAL DISORDERS - Abdominal distension; Duodenal perforation; Esophageal fistula; Esophagitis; Gastritis; Gastrointestinal ulcer[4]; Ileus; Pancreatitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; General disorders and administration site conditions - Other (Guillain-Barre syndrome); Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Hepatic failure

IMMUNE SYSTEM DISORDERS - Allergic reaction; Autoimmune disorder

INVESTIGATIONS - CPK increased; GGT increased; Lipase increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypomagnesemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Back pain; Bone pain; Generalized muscle weakness; Pain in extremity

NERVOUS SYSTEM DISORDERS - Depressed level of consciousness; Dysgeusia; Encephalopathy; Hydrocephalus; Intracranial hemorrhage; Ischemia cerebrovascular; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Tremor

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria; Renal and urinary disorders - Other (kidney stones)

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Hypoxia; Pharyngolaryngeal pain; Pneumonitis; Pulmonary hypertension; Respiratory hemorrhage[5]; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Purpura

VASCULAR DISORDERS - Hypotension; Thromboembolic event; Vasculitis

Note: Imatinib Mesylate (STI571) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

11.1.2 BGJ398

11.1.2.1Adverse Events, Dose Limiting Toxicities, and Reasons for Discontinuation of BGJ398

From 21 December 2009 to 24 September 2013 (data cutoff date), 94 patients received at least one dose of BGJ398 in the clinical study CBGJ398X2101 and are included in the current safety set. The most common adverse events of all severity grades (CTCAE v.3.0.) suspected to be related to BGJ398 (Table 13, below), were hyperphosphatemia (71%), decreased appetite (27%), fatigue (26%), stomatitis (25%), and alopecia (21%). All other adverse events were reported in less than 20% of patients. Overall, most adverse events reported have been mild to moderate in severity. Twenty-six (27.7%) patients experienced at least one grade 3 or 4 event suspected to be related to BGJ398.

As of 23 September 2013, four DLTs have been reported in Cycle 1 during dose escalation. One grade 3 event of AST/ALT elevation was reported in the 100mg cohort. In the 125mg cohort, one patient experienced hyperphosphatemia for greater than 14 days despite adequate therapy that resulted in study drug interruption. In the 150mg cohort, one patient each experienced grade 1 corneal toxicity and grade 3 AST/ALT elevations, the latter leading to study treatment interruption and dose reduction. Eleven other DLTs occurred in 6 patients enrolled in the first of two dose expansion cohorts receiving BGJ398 125 mg daily, continuous schedule. Five patients experienced

hyperphosphatemia that required discontinuation of study drug despite optimal prophylactic treatment with phosphate binders and dietary phosphate restrictions. The sixth patient experienced Grade 3 increases in AST and ALT.

At the time of data cutoff, 0 of 18 patients receiving 125 mg daily 3 weeks on, 1 week off had experienced a DLT.

As of 23 September 2013, among the 94 patients enrolled on the study and available for analysis, 12 patients are still receiving study medication. Of the 82 patients who discontinued treatment, 56 (68%) did so for progression of disease. Ten patients (10.6%) discontinued treatment due to adverse events, including peripheral neuropathy (5mg dose level), pulmonary embolism (10mg dose level), gallbladder removal (20mg), punctate corneal epitheliopathy (60mg dose level), cutaneous lesion growth (100mg dose level) and bilateral retinal detachment (100mg dose level). Neither the retinal detachment nor the punctate corneal epitheliopathy was considered a DLT since they occurred after the first cycle of therapy. Two patients died while on study, both due to disease progression. Twelve patients discontinued due to withdrawal of consent, one patient due to administrative problems, and one patient due to protocol deviation.

As of the data cutoff date, 67 events of hyperphosphatemia among 25 patients were reported at dose levels greater than 60 mg. Twenty of these events led to study drug interruption/dose reduction. Phosphate binding therapy was administered for 38 of these events. The events of hyperphosphatemia were reversible following study treatment interruption and institution of phosphate binding therapy. Most of these events were suspected to be related to study treatment. No clinical adverse events were associated with these events.

Although occasional non-dose-related increases from baseline were observed in ECG interval parameters, including QTc, no adverse events were associated with these ECG findings. No clinically significant findings of QT prolongation have been observed to date. Monitoring of both potential QT-prolongation and left ventricular function are ongoing among the patients enrolled in the expansion cohorts of CBGJ398X2101.

11.1.2.2 Serious Adverse Events

As of 23 September 2013, 46 serious adverse events have been reported (Table 14, below), in 28 patients on study CBGJ398X2101. Seventeen serious adverse events in 9 patients were reported to be suspected to BGJ398 (Table 15, below).

Six events were reported as suspected, unexpected, serious adverse reactions (SUSARs) and resulted in the distribution of Investigator Notifications. These events include two events of cardiac dysfunction with left ventricular ejection fraction (LVEF) decreases, and one event each of grade 1 reversible acute renal injury, grade 4 hepatic failure 6 months after last dose of drug, grade 3 hypercalcemia, and grade 4 hypophosphatemia and hypocalcaemia.

The events of cardiac dysfunction with LVEF decrease occurred in two different male patients with advanced lung SCC. The first patient, who received 100 mg qd of BGJ398, experienced a > 20% decrease in LVEF (66% to 42%) after receiving BGJ398 for approximately 10 months. Associated with this decrease were left ventricular thrombus and bilateral pleural effusions. The patient discontinued study treatment six days later due to progressive disease. The second patient, enrolled to the 125 mg qd dose expansion cohort, experienced a grade 3 decrease in LVEF (> 20% decrease from baseline; 73% to 53%) after approximately 3 months of study drug. Drug administration was interrupted for 14

days following this event. Due to improvement in LVEF to 58%, BGJ398 was restarted at 100 mg qd and LVEF returned to baseline (71%) approximately 2 months later. The patient discontinued study three weeks later due to progressive disease.

More recently, the first patient enrolled on this clinical trial developed a serious unexpected SAE, a Grade 3 Non-ST Elevation MI (NSTEMI) on Day 7 with concomitant Grade 4 CPK elevation on Day 6. The patient is a 64 year old gentleman, former smoker with HTN and diabetes mellitus Type II, with progressive GIST who had progressed on imatinib and sunitinib and was receiving imatinib 400 mg daily plus BGJ398 75mg daily, 3 weeks on / 1 week off. Hemoglobin at screening was 12.8 g/dL and had decreased to 9.5 on Day 1 (pre-treatment) and 9.0 g/dL on Day 2. There was no hematochezia or other signs of bleeding. By Day 5, the patient had worsening fatigue and dyspnea on exertion; in retrospect, the patient had experienced similar symptoms while on sunitinib. On Day 6, November 18, 2014, the hemoglobin was 8.6 and the patient was transfused 2 units of PRBCs. CPK was 2011 U/L (38-174). EKG showed normal sinus rhythm, new T wave inversion in V1-V4, T wave flattening in V5. Calcium was normal and phosphorus grade 1 (4.9 mg/dl (2.5-4.2 mg/dl)).

The patient was hospitalized on Day 7, November 19, 2014 and was diagnosed with grade 3 NSTEMI. Cardiac enzymes were elevated (Troponin I 1.67 ng/ml (0-0.64 ng/ml)), ECG showed flattening in V4, continued TWI in V1-V3; unstable baseline in III leading to isolated 1 mm ST elevation. He was treated medically with heparin ASA, Plavix, beta blocker, statins and was transfused with 2 units PRBC. Echocardiogram showed a stable ejection fraction without wall motion abnormalities, and stable appearance of concentric left ventricular hypertrophy and mild diastolic dysfunction.

The patient was taken off study for SAE on Day 7; last dose of imatinib was on the evening of Day 6 and last dose of BGJ398 was morning of Day 7. The patient was discharged on November 22, 2014. The event was considered possibly related to imatinib and BGJ398 due to the temporal association between symptoms and administration of study drugs balanced against the history of stable angina on sunitinib.

11.1.2.3 Deaths on Study CBGJ398X2101

Two patients, both with advanced lung SCC, died while taking BGJ398. One patient who was enrolled to the 50 mg bid dose escalation cohort died at home on C2D5. The death was assessed by the investigator as due to underlying disease and not related to study medication. The second patient, enrolled to the 125 mg dose expansion cohort, was diagnosed with pneumogenic sepsis on C1D27 and was hospitalized on the same day. Study medication was interrupted on C1D28 and the patient died on C2D1. The event was assessed as not related to BGJ398.

Two patients died within 28 days of their last dose of BGJ398. One patient with squamous carcinoma of unknown origin was enrolled to the dose expansion part of the study (125 mg qd, continuously) and received study medication for 15 weeks before discontinuing treatment due to progressive disease. The patient died four days later due to progression of disease. The death was assessed as not related to study medication. The second patient with lung SCC was enrolled to the 125 mg dose escalation cohort. Administration of BGJ398 was discontinued on week 13 due to progressive disease. Eighteen days after study drug was discontinued, the patient died due to disease progression. The death was assessed as not related to study medication.

Table 13: Treatment emergent adverse events suspected to be drug related, by preferred term and treatment group

Preferred term	5 mg N=3		10 mg N=3		20 mg N=4		40 mg N=6		60 mg N=3	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
- Total	3 (100.0)	1 (33.3)	3 (100.0)	0 (0.0)	3 (75.0)	0 (0.0)	6 (100.0)	1 (16.7)	3 (100.0)	1 (33.3)
Hyperphosphataemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alopecia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Dry eye	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood phosphorus increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)
Lipase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	1 (33.3)	1 (33.3)
Hypercalcaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oral pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Amylase increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)
Myalgia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dehydration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy peripheral	1 (33.3)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Onycholysis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Visual impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 13, cont.: Treatment emergent adverse events suspected to be drug related, by preferred term and treatment group

	100 mg N=6		125 mg N=41		150 mg N=6		50mg BID N=4		3 wks on 1 wk off N=18		All patients N=94	
Preferred term	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
- Total	6 (100.0)	3(50.0)	40 (97.6)	13 (31.7)	6 (100.0)	2 (33.3)	4 (100.0)	1 (25.0)	16 (88.9)	4 (22.2)	90 (95.7)	26 (27.7)
Hyperphosphataemia	5 (83.3)	0 (0.0)	32 (78.0)	2 (4.9)	4 (66.7)	0 (0.0)	4 (100.0)	1 (25.0)	13 (72.2)	1 (5.6)	58 (61.7)	4 (4.3)
Decreased appetite	3 (50.0)	0 (0.0)	13 (31.7)	1 (2.4)	2 (33.3)	1 (16.7)	2 (50.0)	0(0.0)	3 (16.7)	0(0.0)	25 (26.6)	2 (2.1)
Fatigue	0 (0.0)	0 (0.0)	9 (22.0)	1 (2.4)	1 (16.7)	0(0.0)	2 (50.0)	0(0.0)	7 (38.9)	0(0.0)	24 (25.5)	1 (1.1)
Stomatitis	2 33.3)	0 (0.0)	15 (36.6)	3 (7.3)	1 (16.7)	0(0.0)	1 (25.0)	0(0.0)	4 (22.2)	0(0.0)	23 (24.5)	3 (3.2)
Alopecia	1 (16.7)	0 (0.0)	13 (31.7)	0(0.0)	1 (16.7)	0(0.0)	0(0.0)	0(0.0)	5 (27.8)	1 (5.6)	20 (21.3)	1 (1.1)
Asthenia	2 33.3)	0 (0.0)	7 (17.1)	1 (2.4)	1 (16.7)	0(0.0)	2 (50.0)	0(0.0)	2 (11.1)	0(0.0)	15 (16.0)	1 (1.1)
Alanine aminotransferase increased	1 (16.7)	1(16.7)	6 (14.6)	2 (4.9)	1 (16.7)	1 (16.7)	0 (0.0)	0(0.0)	2 (11.1)	2 (11.1)	11 (11.7)	6 (6.4)
Aspartate aminotransferase increased	1 (16.7)	1(16.7)	6 (14.6)	2 (4.9)	1 (16.7)	1 (16.7)	0 (0.0)	0(0.0)	2 (11.1)	0(0.0)	11 (11.7)	4 (4.3)
Dry eye	1 (16.7)	1(16.7)	5 (12.2)	0(0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0(0.0)	3 (16.7)	0(0.0)	10 (10.6)	1 (1.1)
Blood phosphorus increased	1 (16.7)	0 (0.0)	5 (12.2)	1 (2.4)	1 (16.7)	1 (16.7)	0 (0.0)	0(0.0)	0 (0.0)	0(0.0)	9 (9.6)	2 (2.1)
Lipase increased	0 0.0)	0 (0.0)	4 (9.8)	2 4.9)	0(0.0)	0(0.0)	1 (25.0)	0(0.0)	1 (5.6)	1 (5.6)	8 (8.5)	5 (5.3)
Hypercalcaemia	0 0.0)	0 (0.0)	2 (4.9)	0(0.0)	0(0.0)	0(0.0)	1 (25.0)	0(0.0)	1 (5.6)	1 (5.6)	5 (5.3)	1 (1.1)
Gamma-glutamyltransferase increased	1 (16.7)	0 (0.0)	2 (4.9)	1 (2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1 (5.6)	0(0.0)	4 (4.3)	1 (1.1)
Oral pain	1 (16.7)	0 (0.0)	3 (7.3)	1 (2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4 (4.3)	1 (1.1)
Palmar-plantar erythrodysaesthesia syndrome	0 (0.0)	0 (0.0)	4 (9.8)	2 (4.9)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	4 (4.3)	2 (2.1)
Amylase increased	0 (0.0)	0 (0.0)	1 (2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	3 (3.2)	1 (1.1)
Myalgia	1 (16.7)	0 (0.0)	1 (2.4)	1 (2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1 (5.6)	0 (0.0)	3 (3.2)	1 (1.1)
Dehydration	0 (0.0)	0 (0.0)	2 (4.9)	1 (2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2 (2.1)	1 (1.1)
Hyponatraemia	0 (0.0)	0 (0.0)	2 (4.9)	1 (2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	2 (2.1)	1 (1.1)
Cardiac failure	1 (16.7)	1 (16.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1 (1.1)	1 (1.1)
Hyperkalaemia	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1 (1.1)	1 (1.1)
Neuropathy peripheral	0 (0.0)	0 (0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1 (1.1)	1 (1.1)
Onycholysis	0 (0.0)	0 (0.0)	1 (2.4)	1 (2.4)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1 (1.1)	1 (1.1)
Visual impairment	1 (16.7)	1 (16.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1 (1.1)	1 (1.1)

Table 14: Serious adverse events by preferred term and treatment group, regardless of relationship to BGJ398

Preferred term	10 mg N=3 n (%)	40 mg N=6 n (%)	100 mg N=6 n (%)	125 mg N=4 1 n	150 mg N=6 n (%)	50mg BID N=4 n (%)	3 wks on 1 wk off	All patients N=94 n (%)
Patients with at least one AE	1(33.3)	1(16.7)	2(33.3)	16(39.0)	3(50.0)	1(25.0)	4(22.2)	28(29.8)

General physical health deterioration	0(0.0)	0(0.0)	0(0.0)	3(7.3)	0(0.0)	0(0.0)	0(0.0)	3(3.2)
Pneumonia	0(0.0)	0(0.0)	0(0.0)	2(4.9)	1(16.7)	0(0.0)	0(0.0)	3(3.2)
Dyspnoea	0(0.0)	0(0.0)	0(0.0)	1(2.4)	1(16.7)	0(0.0)	0(0.0)	2(2.1)
Fatigue	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	1(25.0)	0(0.0)	2(2.1)
Infection	0(0.0)	0(0.0)	0(0.0)	2(4.9)	0(0.0)	0(0.0)	0(0.0)	2(2.1)
Accidental overdose	0(0.0)	1(16.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Adrenal insufficiency	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Anxiety	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(25.0)	0(0.0)	1(1.1)
Asthenia	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Preferred term	**10 mg N=3 n (%)**	**40 mg N=6 n (%)**	**100 mg N=6 n (%)**	**125 mg N=41 n (%)**	**150 mg N=6 n (%)**	**50mg BID N=4 n (%)**	**3 wks on 1 wk off N=18 n (%)**	**All patients N=94 n (%)**
Bronchitis	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(5.6)	1(1.1)
Cardiac failure	0(0.0)	0(0.0)	1(16.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Cervical root pain	0(0.0)	0(0.0)	1(16.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Confusional state	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Constipation	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Decreased appetite	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Dehydration	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Disease progression	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Dysphagia	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Ejection fraction	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Grand mal convulsion	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(16.7)	0(0.0)	0(0.0)	1(1.1)
Haemoptysis	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Headache	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(25.0)	0(0.0)	1(1.1)
Hypercalcaemia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(5.6)	1(1.1)
Keratitis	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Muscular weakness	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Musculoskeletal pain	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Non-cardiac chest pain	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Pain	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(5.6)	1(1.1)
Pneumonitis	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Pneumothorax	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Pulmonary embolism	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Renal failure acute	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Respiratory distress	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Respiratory failure	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Sepsis	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Stomatitis	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Superior vena cava	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Tibia fracture	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(5.6)	1(1.1)
Vomiting	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)

Table 15: Serious adverse events by preferred term and treatment group, at least possibly related to BGJ398

Preferred term	10 mg N=3 n (%)	40 mg N=6 n (%)	100 mg N=6 n (%)	125 mg N=41 n (%)	150 mg N=6 n (%)	50mg BID N=4 n (%)	on 1 wk off N=18 n (%)	All patients N=94 n (%)
Patients with at least one AE	1(33.3)	1(16.7)	2(33.3)	16(39.0)	3(50.0)	1(25.0)	4(22.2)	28(29.8)
Fatigue	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	1(25.0)	0(0.0)	2(2.1)
Infection	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Adrenal insufficiency	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Anxiety	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(25.0)	0(0.0)	1(1.1)
Cardiac failure	0(0.0)	0(0.0)	1(16.7)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Confusional state	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Constipation	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Decreased appetite	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(25.0)	0(0.0)	1(1.1)
Dehydration	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Ejection fraction decreased	0(0.0)	0(0.0)	0(0.0)	12.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Headache	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(25.0)	0(0.0)	1(1.1)
Hypercalcaemia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(5.6)	1(1.1)
Keratitis	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Muscular weakness	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(25.0)	0(0.0)	1(1.1)
Renal failure acute	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)
Stomatitis	0(0.0)	0(0.0)	0(0.0)	1(2.4)	0(0.0)	0(0.0)	0(0.0)	1(1.1)

Adverse Events Considered to be Expected for Reporting Purposes

Tables 13 and 15 above present the most common suspected AEs and SAEs reported in the 94 patients cumulatively treated with BGJ398 as of 23 September 2013. The suspected Grade 3 and 4 adverse events will be considered to be expected for reporting purposes and are presented in Table 16. Due to the limited clinical experience available to date with BGJ398, it is still difficult to identify events potentially due to the drug. Therefore, any event previously reported should be considered to be expected regardless of event grade, unless the reported diagnosis upon medical review is assessed to be of unexpected severity or of significantly greater specificity. It should be stressed that many of the listed AEs have been reported only on a single occasion making an accurate assessment of causality very difficult. Due to the imprecision of causality assessments it should not be assumed that all of these events are indeed the result of therapy with BGJ398. Moreover, the assessment of causality is particularly difficult in critically ill patients where confounding factors are present relating mainly to complications of the underlying disease and to the use of concomitant medications.

Table 16: Suspected grade 3 and 4 BGJ398 Adverse Events considered to be expected for reporting purposes

MedDRA system organ class	Preferred term (PT)
Cardiac disorders	**Cardiac failure**, Left ventricular dysfunction
Endocrine disorders	**Adrenal insufficiency**
Eye disorders	Dry eye, **Keratitis**, Visual impairment
Gastrointestinal disorders	Stomatitis, **Oral pain**
General disorders and administration site conditions	Asthenia, **Fatigue**
Hepatobiliary disorders	**Hepatic failure (fatal)**
Investigations	Alanine aminotransferase increased, Amylase increased, Aspartate aminotransferase increased, **Blood phosphorus increased, Ejection fraction decreased, Gamma-glutamyltransferase increased**, Lipase increased
Metabolism and nutrition disorders	Decreased appetite, **Dehydration, Hypercalcaemia, Hyperkalaemia, Hyponatraemia**, Hyperphosphataemia,
Musculoskeletal and connective tissue disorders	**Myalgia**
Nervous system disorders	**Headache**, Neuropathy peripheral
Psychiatric disorders	**Anxiety**
urinary disorders	**Renal injury**
Respiratory, thoracic and mediastinal disorders	**Pulmonary oedema**
Skin and subcutaneous tissue disorders	**Alopecia, Onycholysis, Palmar-plantar erythrodysaesthesia syndrome**

Events in bold indicate an event that is newly included since the previous edition of the Investigator's Brochure

Please refer to the Investigator's Brochure for details of all AEs.

11.2 Adverse Event Characteristics

11.2.1 Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

• Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition

• New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study Signs, symptoms, or the clinical sequelae of a suspected interaction

• Signs, symptoms, or the clinical sequelae of a suspected interaction

• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE).

"Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events that **do not** meet the definition of an AE include:

• Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.

• Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

• The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

11.2.2 Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.

d. Results in disability/incapacity

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

f. All grade 4 laboratory abnormalities

SAEs will be recorded and reported as detailed in section 17.2.

11.2.3 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

Refer to Section 17.2 on criteria, time frame and process on reporting abnormalities that are qualified as SAEs.

11.2.4 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event that is part of the natural course of the disease under study (i.e., disease progression or hospitalization due to disease progression) does not need to be reported as an SAE. Death due to disease under study is to be recorded in the EDC system. However, if the underlying disease (i.e., progression) is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study treatment(s) or protocol design/procedures and the disease progression, then this must be reported as an SAE.

11.2.5 Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the time the first dose of study treatment is administered until 28 days following discontinuation of study treatment regardless of initiation of a new cancer therapy or transfer to hospice.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after treatment discontinuation the investigator may report any adverse event that they believe possibly related to study treatment.

Refer to Section 17.2 on criteria, time frame and process on reporting abnormalities that are qualified as SAEs.

11.2.6 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 4.03. 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.

11.2.7 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.

11.3 Pregnancy Testing, Prevention and Reporting

11.3.1 Pregnancy Testing and Prevention

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

A female of non-childbearing potential (i.e., physiologically incapable of becoming pregnant) is defined as any female who has had a hysterectomy, bilateral oophorectomy (ovariectomy) or bilateral tubal ligation, or is post-menopausal.

A practical definition accepts menopause after 1 year without menses with an appropriate clinical profile, e.g., age appropriate, >45 years in the absence of hormone replacement therapy (HRT). In questionable cases, the subject must have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value < 40pg/mL (<140 pmol/L).

A female of child-bearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

If a female subject is of childbearing potential, she must have a blood β-HCG pregnancy test performed within 14 days of the first dose of study treatment. Subjects with positive pregnancy test result must be excluded from the study. Subjects with negative pregnancy test result must agree to use an effective contraception method as described below from 14 days prior to the first dose of study treatment until 3 monthsfollowing the last dose of study treatment.

Acceptable contraceptive methods, when used consistently and in accordance with both the product label and the instructions of the physician, are as follow:

- An intrauterine device with a documented failure rate of less than 1% per year.
- Vasectomized partner who is sterile prior to the female subject's entry and is the sole sexual partner for that female.
- Complete abstinence from sexual intercourse for 14 days before exposure to investigational product, through the dosing period, and for at least 21 days after the last dose of investigational product.
- Double-barrier contraception: condom and occlusive cap (diaphragm or cervical/vault caps) with a vaginal spermicidal agent (foam/gel/cream/suppository).
- Implants of levonorgestrel where not contraindicated for this patient population or per local practice
- Injectable progesterone where not contraindicated for this patient population or per local practice.
- Estrogenic vaginal ring
- Percutaneous contraceptive patches

If a female subject is suspected to be pregnant during the study, a blood pregnancy test must be performed. If pregnancy is confirmed, subject must stop study treatment immediately and the pregnancy must be reported according to procedures described in Section 12.0

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

12.1 Antitumor Effect – Solid Tumors

During the treatment period, patients will be evaluated prior to treatment and re-evaluated for response every 8 weeks for four scans. Patients will then be imaged approximately every 12 weeks until disease progression is noted. If a patient has a durable response of > 2 year, patients can be imaged every 6 months. 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) [32]. 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. CHOI response criteria as outlined in GIST will be used as a secondary response [33]. In addition, patients will be evaluated by FDG-PET prior to treatment and re-evaluated for response 3 weeks after the combination treatment based on the EORTC criteria[34]. This will also be used as secondary response.

12.1.1 Definitions

Evaluable for toxicity. All Phase Ib patients will be evaluable for toxicity from the time of their first treatment with imatinib plus BGJ398. All Phase II patients will be evaluable for toxicity from the time of their first treatment with imatinib alone.

Evaluable for efficacy. Only those patients who have measurable disease present at baseline and have received at least one dose of imatinib plus BGJ398 therapy will be considered evaluable for efficacy. These patients will have their response classified according to the definitions stated below. Patients on the Phase II portion who are taken off study prior to receiving their first dose of BGJ398 for reasons other than progressive disease are considered replaceable for the purposes of evaluating primary and secondary endpoints.

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.

12.1.2 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 for non-nodal lesions and short axis for nodal lesions) as >20 mm by chest x-ray, as >10 mm with CT scan or MRI, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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.

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.

12.1.3 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 portion of study. 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.

12.1.4 Primary Response Criteria (RECIST 1.1)

12.1.4.1 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.

12.1.4.2 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 MSKCC Principal Investigator).

12.1.5 Secondary Response Criteria (CHOI for CT and EORTC for [^{18}F]-FDG-PET)

CHOI criteria determines response based on changes in size and tumor density (Table 17) [33]. This is of particular importance in GIST, as tumors often initially respond to selective KIT inhibition with inflammation and a paradoxical increase in size with a decrease in density prior to decreasing in size.

Table 17: CHOI Criteria:

Modified CT Response Evaluation Criteria	
Response	Definition
CR	Disappearance of all lesions No new lesions
PR	A decrease in size* of ≥ 10% or a decrease in tumor density (HU) ≥ 15% on CT No new lesions No obvious progression of nonmeasurable disease
SD	Does not meet the criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression
PD	An increase in tumor size of ≥ 10% and does not meet criteria of PR by tumor density (HU) on CT New lesions New intratumoral nodules or increase in the size of the existing intratumoral nodules

Abbreviations: CR, complete response; PR, partial response; HU, Hounsfield unit; CT, computed tomography; SD, stable disease; PD, progression of disease; RECIST, Response Evaluation Criteria in Solid Tumors.
*The sum of longest diameters of target lesions as defined in RECIST.

To evaluate for early tumor response based on FDG-PET, the EORTC criteria [34]. The EORTC FDG-PET response criteria is defined as the following:

Progressive metabolic disease (PMD) is classified as an increase in [^{18}F]-FDG tumor SUV of greater than 25% within the tumor region defined on the baseline scan, visible increase in the extent of [^{18}F]-FDG tumor uptake (>20% in the longest dimension) or the appearance of new [^{18}F]-FDG uptake in metastatic lesions.

Stable metabolic disease (SMD) is classified as an increase in tumor [^{18}F]-FDG SUV of less than 25% or a decrease of less than 15% and no visible increase in extent of [^{18}F]-FDG tumor uptake (>20% in the longest dimension).

Partial metabolic response (PMR) is defined as a reduction of a minimum of 25% in tumor [^{18}F]-FDG SUV after 4 weeks of treatment.

Complete metabolic response (CMR) is defined as complete resolution of [^{18}F]-FDG uptake within the tumor volume so that it was indistinguishable from surrounding normal tissue.

12.1.6 Not evaluable (NE)

When no imaging/measurement is done at all at a particular time point, the patient is considered not evaluable (NE) at that time point.

12.1.7 Early death

If the patient has NO repeat tumor assessments following initiation of study therapy resulting from the death of the patient due to disease or treatment, it is considered early death.

12.1.8 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time will be recorded as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment.

12.1.9 Confirmation of response

Complete or partial response may only be claimed if the criteria for each are met at a subsequent time point (≥ 4 weeks later) in studies with a primary endpoint that include response rate. When response rate is a secondary endpoint, confirmation is NOT required.

12.1.10 Special note on target lesions that become "too small to measure"

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes, lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded on the D2M form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a **default value** of 5 mm should be assigned.

12.1.11 Evaluation of best overall response within 32 weeks of combination treatment based on Table 18:

Table 18:

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

* If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have appeared after CR). However, sometimes "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first

time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

12.1.12 Duration of response

Defined as the time measurement criteria are first met for CR/PR until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study).

12.1.13 Duration of stable disease

Measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). For the Phase II portion, start of treatment is defined as the start of the imatinib lead-in period.

12.1.14 Progression-Free Survival (PFS)

PFS is defined as the period from start of study treatment until recurrent or progressive of disease (POD) is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study), death, or date of last contact. For the Phase II portion, start of treatment is defined as the start of the imatinib lead-in period.

12.1.15 Overall Survival (OS)

OS is defined as the observed length of life from study entry to death or the date of last contact.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from study when any of the criteria listed below applies. The reason for study removal and the date the patient was removed must be documented in the EDC system. Patients on the Phase II study may be replaced if they come off study for reasons other than progressive disease prior to receiving their first dose of BGJ398. Unless otherwise stated, patients will be included in the safety and/or efficacy analysis as described in Section 14.

A dose interruption of ≥ 28 days will require the patient to be discontinued from the study (with the exception of patients who undergo surgery). Local procedures (e.g. surgery, embolization) are permitted on this trial a) if clinically indicated or b) if response to therapy converts the patient into a surgical candidate. All drugs will be held for at least one week prior to the local procedure. Patients will resume therapy when deemed clinically safe, but no sooner than 1 week and no later than 5 weeks after the procedure. If a patient falls out of this window, consideration should be had for withdrawal from the study based on clinical reasons for the delay. Patients who have had a local procedure will be allowed to remain on the study if they have measurable disease (RECIST 1.1) after the procedure. Patients who are rendered disease free will be taken off the study and can be considered for adjuvant imatinib per standard of care. Conversion to resectability rate will be a secondary endpoint.

Duration of Therapy: In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse events(s),
- 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.
- Inability of the patient to comply with the requirement of the protocol for treatment or evaluation.

Duration of Follow Up: Patients will be followed for toxicities 4 weeks after last dose or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For Phase II, study personnel will attempt to collect survival status for all patients after the end-of-study visit every 3 months via telephone, email, or other method for up to 3 years.

14.0 BIOSTATISTICS

This is a multi institution single arm phase Ib/II trial to evaluate the clinical safety and efficacy of imatinib and BGJ398 in patients with advanced Gastrointestinal Stromal Tumors. Patients in the Phase Ib portion of the trial are required to have metastatic and or locally advanced GIST that has been treated with imatinib. Patients on the Phase II portion of the study are required to have advanced GIST and not have received any prior systemic therapy (untreated/treatment naïve).

Phase 1b Portion Study Design and Endpoint Assessment

The primary endpoint of the phase 1b portion of this study is to determine the maximum tolerated dose (MTD) and treatment schedule of BGJ398 administered in combination with imatinib in patients with GIST. The phase Ib will be pursued in standard 3+3 format, based on toxicities encountered during the first cycle of therapy.

The dose escalation schema is listed in Table 1. Dose escalation will proceed within each cohort according to Table 2. The first three patients will be enrolled at Dose Level 1. If dose level 1 is not found to be tolerable, then the next cohort will be enrolled at dose level -1. If dose level -1 is not found to be tolerable, then the next cohort will be enrolled at dose level -2. If dose level -2 is not found to be tolerable, then the study may be terminated based on discussions with the MSKCC Principal Investigator. If 0 or 1 of 6 patients experience a DLT on dose level 3, this will be the RP2D unless a lower dose is selected based on chronic tolerance of the combination and pharmacokinetic data. Lower dose levels may be expanded and an RP2D lower than the MTD may be selected based on safety and chronic tolerance considerations by the MSKCC Principal Investigator. If dose level 1 to -2 is identified as the MTD and concern exists regarding therapeutic activity of BGJ398 at this dose level, expansions with higher dose levels (1 to 3) may be considered at the MSKCC PI's discretion, with modification of the treatment schedule. When the RP2D is found, any patients from the Phase Ib portion of the study who remain on therapy below the MTD may have their BGJ398 dose increased to the MTD at the treating physician's discretion.

The secondary endpoints of the phase 1b portion are (1) Response Rate (RR) defined by RECIST 1.1 criteria and by CHOI criteria, (2) Progression Free Survival (PFS), (3) Clinical Benefit Rate (CBR) at 32 weeks, and (4) BGJ398 pharmacokinetic parameters, such as area under the curve (AUC) and maximum concentration (Cmax). RR will be estimated as the proportion of patients who have complete response or partial response for each criterion. PFS will be calculated using Kaplan-Meier estimate among all patients enrolled at each dose level. Patients who have not experienced the event of interest by the end of the study will be censored at the time of the last follow-up. Plasma concentrations of BGJ398 will be analyzed at multiple time points and expressed as a mean +/- SE.

The phase Ib portion of the study will have a minimum sample size of 6 patients and a maximum of 30. We expect to accrue approximately 2 patients each month, and hence expect to finish the phase 1b portion of the study in approximately 9-15 months.

Evaluable patients for safety analysis include all patients who have received one dose of imatinib plus BGJ398. Patients who stop therapy before Cycle 2, Day 1 for reasons other than toxicity will be replaced in the Phase I study for the purposes of evaluating the DLT. Evaluable patients for efficacy include all patients who have received one dose of imatinib plus BGJ398. Patients who are missing an assessment of response post baseline will be considered non-responders for that time point.

Patients on the Phase I portion of the study will not be included in the final efficacy analysis due to differences in the eligibility criteria in the two phases.

Phase 2 Portion Study Design and Endpoint Assessment

The primary endpoint of the phase II portion of the study is to assess Response Rate (CR+PR, RECIST 1.1) after 32 weeks of combination therapy. In order to detect a 20% improvement in the RR over imatinib alone (unacceptable rate of 45%; acceptable rate of 65%), 44 Phase II patients will be enrolled. At the end of the study, if > 24 patients have had a documented response by RECIST 1.1, the study will be considered positive and the treatment regimen will be considered worthy of further investigation. The study design is based on an exact Binomial test and has a one-sided type I error of 0.08 and a type II error of 0.1.

We expect to accrue 2 patients each month, and hence expect to finish the phase 2 portion of the study in 24 months.

Response rate (RECIST 1.1) will be determined as the proportion of patients evaluable for efficacy (defined as patients who receive at least one dose of the combination regimen) who have complete response or partial response defined by the RECIST 1.1 with a one-sided 90% confidence interval (CI) provided. Patients missing post baseline assessment of response will be considered non-responders for the primary endpoint at that time point.

The steady state serum imatinib trough levels will be obtained and evaluated in the two-week imatinib lead in phase (two samples/patient) and in the combination therapy phase (2 samples/patient) from all patients in the Phase II portion of the trial. We will evaluate the effects of BGJ398 on imatinib steady state trough levels by comparing the values at these two time points (before and after lead in period). We will compare the ranges we obtain with the ranges reported by Demetri et al JCO 2009 and assess whether the effects are considered subtherapeutic, therapeutic, or

supra-therapeutic. This analysis may inform future trials with this combination and will not change the dose that will be given in the combination regimen.

The secondary endpoints of the phase 2 portion include:

(1) RR by CHOI criteria. It will be determined as the proportion of patients evaluable for efficacy who have complete response or partial response defined by the CHOI criteria with a two-sided 95% CI provided.
(2) RR by EORTC criteria. It will be determined as the proportion of patients evaluable for efficacy who have complete response or partial response defined by the EORTC criteria with a two-sided 95% CI provided.
(3) Progression free survival and Overall Survival. PFS and OS will be calculated using a Kaplan-Meier estimate among all patients enrolled. They are defined from the start of imatinib treatment, i.e. the lead in period is included in this endpoint. Patients on the Phase II portion who stop study prior to receiving a dose of BGJ398 for reasons unrelated to progression (e.g. intolerance to imatinib) will be censored at the time of withdrawal. Patients who have not had the event of interest by the end of the study will be censored at the time of last follow-up.
(4) Resectability rate. It will be calculated by the proportion of Phase II patients who have completed 1 cycle of treatment who have resection of their disease with a two-sided 95% CI provided.

For the purpose of exploratory studies, the phase 2 portion includes the phenotypic (by IHC), genetic, transcriptomic, epigenetic, and pharmacodynamic characterization of the tumors as correlative endpoints. Twenty patients are planned to have mandatory paired biopsies (pre and post treatment), and the remaining patients will provide optional biopsies if funding is identified. This sample size provides 80% power to detect a standardized difference of 0.55 assuming 2 sided one sample paired t test at 10% significance level. The variable of interest will be change in protein levels.

The analysis of the exploratory studies is planned as follows.

1) ETV1 protein level by western blot (WB) as a continuous variable. The change of ETV1 protein level (before vs. after the combination therapy) will be recorded as up, down, and no-change (categorical response). It will be tabulated with the percentages provided. It will be correlated with response using the Fisher's exact test.

2) ETV1-dependent transcriptome (expression profile of ETV1-dependent gene targets) by nanostring. The expression change of ETV1 target genes (before vs. after the combination therapy) will be correlated with clinical response using the Wilcoxon rank test. The outcome will be a composite score (based on gene expression level and directionality of the changes), and it is continuous variable.

3) Cell proliferation (Ki-67) and apoptosis (cleaved caspase-3) by IHC. Descriptive statistics will be provided. These variables are continuous.

4) MAP kinase pathway and other pathways downstream of KIT and FGF signaling using standard antibodies (phospho-ERK, phospho-KIT, phospho-MEK, phospho-AKT, etc) by IHC. Descriptive statistics will be provided.

5) KIT/PDGFRA mutational status in matched tumor biopsy specimens collected prior to therapy, after combination therapy and upon disease progression. FGFR and FGF2 expression on tumor

samples by IHC analyzed as a binary covariate and FGF2 ligand levels in collected serum by ELISA analyzed as a continuous covariate.

6) Protein expression of FGF2, sVEGFR1, sVEGFR2, VEGF-A, -C, -D, cKIT, PLGF, and Tie2 in tumor tissues utilizing commercially available immunoassay kits. This will be a continuous variable.

7) Expression of genes implicated in GIST pathogenesis and signaling, including KIT, ETV1, FGFR1, -2, -3, and -4; DUSP6, SPRY2, and SPRY4 will be analyzed as a continuous covariate. Changes before and after treatment will be assessed and correlated with clinical response.

In most of the above studies, we are interested in looking at changes in expression levels, protein measurements, or mutation status before and after treatment. The correlative endpoints described above will be correlated with response (binary outcome defined as CR+PR using RECIST 1.1). These analyses are exploratory in nature and no adjustment for multiple comparisons will be made.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.1.1 Registration for Participating Sites

Central registration for this study will take place at Memorial Sloan-Kettering Cancer Center (MSKCC).

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to email registration/eligibility documents to the Multicenter Trial Core at MSKCC at medmctcore@mskcc.org.

The following documents must be sent for each enrollment within **24 hours** of the informed consent form being signed:

- The completed or partially completed MSKCC eligibility checklist

- The signed informed consent and HIPAA Authorization form
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report)

Upon receipt, the research staff at MSK will conduct an interim review of all documents. If the eligibility checklist is not complete or source documentation is missing, the participant will be registered PENDING and the site will be responsible for sending the completed registration documents within 30 days of the consent.

If the external registration submission is complete, the participating site IRB has granted approval for the protocol, and the site is in good standing, the MSK research staff will send the completed registration documents to the MSK PPR Office for participant enrollment as stated in section 15.1.

Once the participant is registered, the participant will be assigned a number in the MSK Clinical Research Database (CRDB). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

15.2 Randomization

NOT APPLICABLE

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database (MediData RAVE). Source documentation will be available to support the computerized patient record.

16.0.1 Data and Source Documentation for Participating Sites

Data
The participating site(s) will enter data remotely into an internet-based Electronic Data Capture system, termed MediData RAVE. Standardized Electronic Case Report Forms (eCRFs) and data entry guidelines have been generated for this study. The site staff will receive MediData RAVE training prior to enrolling its first patient through a series of e-Modules. The participating Site PI is responsible for ensuring these forms are completed accurately and in a timely manner. Participating sites will be responsible for filling out these eCRFs and submitting them to MSKCC per the designated timelines.

Source Documentation
Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into eCRFs. Relevant source documentation to be reviewed by the study monitor throughout the study includes:

- Baseline measures to assess pre–protocol disease status (ex. CT,PET Scan, EKG, ECHO, MUGA, etc.)
- Treatment records
- Grade 3-5 toxicities/adverse events not previously submitted with SAE Reports
- Response designation

Source documentation should include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should enter data directly into MediData RAVE. Source documentation should be sent to MSKCC at the contact provided below. Submissions should include a cover page listing relevant records enclosed per participant.

Contact for submission of Source Documentation
EMAIL: medmctcore@mskcc.org to the attention of the Multicenter Trial Core Research Staff

16.0.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSKCC according to the following chart:

Data and Source Submission Requirements and Timelines for Therapeutic Studies

	Baseline	*Every Cycle*	*SAE*	*Off Study*
SUBMISSION SCHEDULE				
Source Documentation	Within 24 hours (see section 15.1.1)	Within 14 days of visit	Within 48 hours of event (see section 17.3); updates to be submitted as available	Within 14 days of visit
eCRFs	Within 7 days of visit			
Required Forms				
Baseline Forms	X			
Cycle Forms		X		
Off Study Forms				X
Concomitant Medications Form	X	X	X	X
Adverse Event Form		X	X	
Serious Adverse Event Form			X	

16.0.3 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSK Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.1.1 Quality Assurance for Participating Sites

Monitoring

Each data collection site will be monitored periodically by MSKCC or a designated contract research organization (CRO). Monitoring visits will be conducted every 4-8 weeks, dependent upon the protocol and patient accrual and activity. The monitor and the participating site will identify a mutually agreeable time for each monitoring visit. At least 10 business days ahead of the visit, the monitor will send the site a notification letter that details the date and expectations of the visit. Monitoring may be conducted remotely or in-person. The monitor must be allowed access to all protocol regulatory and source documents to assess compliance with the protocol, federal regulations and GCPs. The monitor will assess all data for completeness of source documents and to confirm data being recorded in the eCRFs is accurate. If monitoring will be done remotely, sites must agree in advance to provide source documents as required. During onsite visits, the monitor will also inspect and review the facilities and investigational product storage area. The participating site will maintain accurate records of dispensing of study drugs for drug accountability. Drug accountability will be reviewed at monitoring visits. Study drug and bottles must be retained until the monitor performs drug accountability of the study drug(s).

The site Investigator(s) and/or an authorized member of the Investigator's staff should allow sufficient time during monitoring visits to discuss findings. The Investigator(s) or an authorized member of the Investigator's staff will make any necessary corrections during and between monitoring visits.

Auditing

Each participating site accruing participants to this protocol will be audited by MSK for protocol and regulatory compliance, data verification and source documentation. Audits of selected participant records may be conducted on-site or remotely.

Audits will be conducted annually at minimum, and more often if significant and/or repeated findings are identified during monitoring visits. The number of participants audited will be determined by the outcome of monitoring visits and complexity of the protocol.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant-specific case review, recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of the audit report with their corrective action plan.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective for the Phase II portion of this study, all sites Phase II participants' responses are subject to review by MSK's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the participating sites for MSK TRRC review and confirmation of response assessment. These materials must be sent to MSK promptly upon request.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf.

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site 1572
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Good Clinical Practice Training for the Principal Investigator and Co-Investigator
- Conflict of Interest forms for Participating Site Investigators on the 1572
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

Participating sites that are consulting and/or conducting specimen or data analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSKCC. Participating sites that are conducting specimen analysis must provide a 1572 to MSKCC.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non-expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 45 calendar days of MSKCC IRB/PB releasing the protocol. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2 Additional IRB Correspondence

Continuing Review Approval
The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of new participant enrollment.

Deviations and Violations
A protocol deviation on this study is defined as a request to treat a research participant who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB. Deviation requests from eligibility criteria will not be permitted for research participants.

A protocol violation is any change or departure from the research protocol that occurred without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC within 14 days of learning of the event. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence
Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.3.3 Regulatory Documentation Submission for Participating Sites

Participating sites should submit all aforementioned regulatory documentation to MSK via the Multicenter Office at the e-mail provided below. Submissions should include the provided Participating Site Submission Form as a cover page listing all enclosed documents.

Regulatory Contact:
Email: Multicntrproc@mskcc.org to the attention of 14-140 Document Submission

For questions regarding regulatory documentation submissions, please call 646-888-0924.

For protocol related questions, please contact your MSK Study Coordinator.

16.4 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC. The regulatory binder on site will be reviewed by the MSKCC designated study monitor at monitoring visits.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents and study related documents for 7 years.

16.5 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld, until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. The patients will be explained the extent of the risks, benefits, toxicities/side effects, alternatives/options for treatment, financial costs/burdens, and the voluntary nature of the study. All patients will be required to sign a statement of informed consent, which must conform to IRB guidelines.

Inclusion of Women and Minorities: Memorial Sloan-Kettering Cancer Center has filed forms: HHS 441 (civil rights), HHS (handicapped individual), 639-A (sex discrimination), and 680 (age discrimination); we also take due notice of the NIH policy concerning inclusion of women and minorities in clinical research populations. Patients of all races, both male and female, will be accepted into the protocol. The proposed study population is as described in section 6.0 and 7.0.

Exclusion of Lactating or Pregnant Women: Lactating and pregnant women are also excluded because of potential anti-proliferative effects of BGJ398 and/or imatinib that may be harmful to the developing fetus or nursing infant.

Inclusion of Children in Research: This protocol/project does not include patients younger than the age of 18. Although sarcomas are the most common solid tumor in children, pediatric GISTs are relatively rare. In addition, pediatric GISTs often do not respond to imatinib as they tend to not have

mutations in cKIT. Pediatric GIST patients would be better served enrolling on clinical trials specifically designed for the genetic abnormalities of their tumor.

Benefits: It is possible that this treatment will result in shrinkage of the tumor or in a stabilization of an otherwise progressing disease. It is not known, of course, whether these or any other favorable events will occur. It is not known whether this treatment will affect the overall survival of the patients.

Costs: The patient will be responsible for the costs of standard medical care, including all drug administration fees and all hospitalizations, even for complications of treatment. BGJ398 and Imatinib will be provided to the patient without charge. Research-only biopsies and laboratory tests will not be charged to the patient. Research testing performed on tissue will not be charged to the patient.

Incentives: No incentives will be offered to patients/subjects for participation in the study.

Alternatives: For patients with locally advanced and/or metastatic GIST alternative treatments may include imatinib off study per standard of care or other clinical trials.

Confidentiality: Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patient's name or any other personally identifying information will not be used in reports or publications resulting from this study. The Food and Drug Administration or other authorized agencies (e.g., qualified monitors from MSKCC or collaborating institutions) may review patients' records and pathology slides, as required.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment,

they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form

- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.2.1 Reporting to Novartis by MSKCC

Reporting Responsibility:

Any serious adverse events that occur from the first dose of study treatment until 30 days after receiving the last dose of study medication, whether or not related to the study drug, must be reported by the investigator at MSKCC to Novartis. In addition, any SAEs that occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

Each serious adverse event (but not pregnancies) must be reported by the investigator at MSKCC to Novartis within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported to Novartis within 24 hours of receiving it. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to study drug (or therapy), the Medical Safety Expert of the Clinical Safety & Epidemiology (CS&E) Department may contact the investigator to obtain further information. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug (or therapy) that this serious adverse event has been reported.

Reporting Procedures:

The MSKCC principal investigator has the obligation to report all serious adverse events to the MSKCC IRB, FDA (all correspondence with the FDA must go through the MSKCC IND Office) and Novartis Pharmaceuticals Clinical Safety & Epidemiology (CS&E) Department.

SAEs will be reported to Novartis once reported to the MSKCC IRB using the MSKCC CRDB SAE Report Form.

All serious adverse events must be reported by facsimile within 24 hours of learning of the occurrence to the local Novartis Clinical Safety & Epidemiology (CS&E) Department. Fax: 1-877-778-9739.

The investigator must then ensure that the form and coversheet are accurately and fully completed with follow-up information and fax those to Novartis CS&E Department within 5 calendar days of receiving it. The original and the duplicate copies of the CRDB SAE Report Form, Novartis SAE coversheet, and the fax confirmation sheet must be retained at MSKCC.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation.

17.3 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approvals/acknowledgments must be sent to MSK upon receipt.
- Participating sites are responsible for submitting the SAE Report Form to MSK within 48 hours of learning of the event.
- When a death is unforeseen and indicates participants or others are at increased risk of harm, participating sites should notify the MSK PI as soon as possible but within 24 hours of the time the site becomes aware of the event.

SAE contact information for the Coordinating Center is listed below:

Multicenter Trials Core Staff
MSKCC Clinical Trials Office
1114 First Avenue 7th Floor
New York, NY 10065
(F) 646-227-2482
Email: medmctcore@mskcc.org

William Tap, MD
Memorial Sloan Kettering Cancer Center
300 E66th Street
New York, NY 10065
(O) 646-888-4163 (F) 646-888-4252
Email: tapw@mskcc.org

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.2 and to Novartis as described in 17.2.1
- The MSKCC PI is responsible for informing all participating sites about all deaths and unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.4 Safety Reports

MSK must submit external safety reports to the MSK IRB/PB according to institutional guidelines. All external safety reports will be made available to the participating sites. For those safety reports that require an amendment, the participating sites will receive a special alert.

Participating sites are responsible for submitting safety reports to their local IRB per their local IRB guidelines. All local IRB approvals/acknowledgments of safety reports must be sent to MSK upon receipt.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 Informed Consent Procedures for Participating Sites

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.0 REFERENCES

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20.0 APPENDICES

Appendix A: KPS-ECOG Conversion Chart

Appendix B: Patient Oral Medication Diary

Appendix C: LIST OF CYP3A4 and CYP2B6 INHIBITORS AND INDUCERS (Imatinib)

Appendix D: List of concomitant medications to be used with caution with BGJ398

Appendix E: List of prohibited medications with BGJ398

Appendix F: List of select High-phosphorous foods and suggested alternatives

Appendix G: Ophthalmology Exam Forms

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: Pill Diary for IRB #14-140: SCHEDULE A

Name:_____

MRN:_____

A phase Ib/II study of BGJ398 in combination with imatinib mesylate in patients with untreated advanced gastrointestinal stromal tumor (GIST)

	Total Daily Dose	Capsule Strength (mg)	Number of Capsule Given	Pill Bottles Returned?	Number of Capsule Returned
Imatinib				Y or N	
BGJ398				Y or N	

(Above to be Completed by RN)

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT.

SPECIAL INSTRUCTIONS

- Imatinib should be taken orally with food. BGJ398 should be taken in the morning 2 hours after a light breakfast. No food should be consumed for 1 hour after taking the capsule. Both should be taken with a large glass of water (8oz).
- Do not chew or crush the capsule .
- Do not drink grapefruit juice or take herbal supplements such as St. John's Wort while taking these medications.
- Take imatinib once a day, no less than twelve hours between each dose. If a dose of imatinib is missed, please take the dose as soon as possible, but **only** if there are **12 or more** hours remaining before the next dose.
  a. If the dose is due in less than 12 hours, **skip** the missed dose and take the next dose as scheduled.

- Take BGJ398 once a day in the morning. If a dose of BGJ398 is missed, take as soon as possible **within 2 hours** of the missed dose. If 2 hours passes, **skip** the missed dose and take the next dose as scheduled.

- If vomiting occurs after taking either imatinib or BGJ398, even if it appears the whole capsulehas been regurgitated, do not take a replacement dose. Resume at the next scheduled dose.
  a. If consistent vomiting occurs please notify the study investigator

  All missed doses should be recorded in this pill diary.

DAY	MEDICATION	DATE	TIME	NUMBER of ____mg capsules taken	NUMBER of ___ mg capsules taken
Example	Imatinib	01/01/2010	9:00 AM or PM	1	
	BGJ398		9:00 AM		1
Day 1	Imatinib				
	BGJ398				
Day 2	Imatinib				
	BGJ398				
Day 3	Imatinib				
	BGJ398				
Day 4	Imatinib				
	BGJ398				
Day 5	Imatinib				
	BGJ398				
Day 6	Imatinib				
	BGJ398				
Day 7	Imatinib				
	BGJ398				
Day 8	Imatinib				
	BGJ398				
Day 9	Imatinib				
	BGJ398				
Day 10	Imatinib				
	BGJ398				
Day	Imatinib				

11	**BGJ398**				
Day 12	**Imatinib**				
	BGJ398				
Day 13	**Imatinib**				
	BGJ398				
Day 14	**Imatinib**				
	BGJ398				
Day 15	**Imatinib**				
	BGJ398				
Day 16	**Imatinib**				
	BGJ398				
Day 17	**Imatinib**				
	BGJ398				
Day 18	**Imatinib**				
	BGJ398				
Day 19	**Imatinib**				
	BGJ398				
Day 20	**Imatinib**				
	BGJ398				
Day 21	**Imatinib**				
	BGJ398				
Day 22	**Imatinib**				
	BGJ398			[redacted]	
Day 23	**Imatinib**				
	BGJ398			[redacted]	
Day 24	**Imatinib**				
	BGJ398			[redacted]	
Day	**Imatinib**				

25	**BGJ398**			[redacted]	
Day 26	**Imatinib**				☒
	BGJ398			[redacted]	
Day 27	**Imatinib**				☒
	BGJ398			[redacted]	
Day 28	**Imatinib**				☒
	BGJ398			[redacted]	

Patient Signature:_____
Date:_____

Consenting Professional/Research RN Signature: _____
Date:_____

Consenting Professional/Research RN Comments:

_____
_____
_____
_____

Appendix C: Pill Diary for IRB #14-140: SCHEDULE B

Name:_____

MRN:_____

A phase Ib/II study of BGJ398 in combination with imatinib mesylate in patients with untreated advanced gastrointestinal stromal tumor (GIST)

	Total Daily Dose	Capsule Strength (mg)	Number of Capsule Given	Pill Bottles Returned?	Number of Capsule Returned
Imatinib				Y or N	
BGJ398				Y or N	

(Above to be Completed by RN)

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT.

SPECIAL INSTRUCTIONS

- Imatinib should be taken orally with food. BGJ398 should be taken in the morning 2 hours after a light breakfast. No food should be consumed for 1 hour after taking the capsule. Both should be taken with a large glass of water (8oz).
- Do not chew or crush the capsule .
- Do not drink grapefruit juice or take herbal supplements such as St. John's Wort while taking these medications.
- Take imatinib once a day, no less than twelve hours between each dose. If a dose of imatinib is missed, please take the dose as soon as possible, but **only** if there are **12 or more** hours remaining before the next dose.
  b. If the dose is due in less than 12 hours, **skip** the missed dose and take the next dose as scheduled.

- Take BGJ398 once a day in the morning. If a dose of BGJ398 is missed, take as soon as possible **within 2 hours** of the missed dose. If 2 hours passes, **skip** the missed dose and take the next dose as scheduled.

- If vomiting occurs after taking either imatinib or BGJ398, even if it appears the whole capsule has been regurgitated, do not take a replacement dose. Resume at the next scheduled dose.
  b. If consistent vomiting occurs please notify the study investigator

  All missed doses should be recorded in this pill diary.

DAY	MEDICATION	DATE	TIME	NUMBER of ____mg capsules taken	NUMBER of ___ mg capsules taken
Example	Imatinib	01/01/2010	9:00 AM or PM	1	
	BGJ398		9:00 AM		1
Day 1	Imatinib				
	BGJ398				
Day 2	Imatinib				
	BGJ398				
Day 3	Imatinib				
	BGJ398				
Day 4	Imatinib				
	BGJ398				
Day 5	Imatinib				
	BGJ398				
Day 6	Imatinib				
	BGJ398				
Day 7	Imatinib				
	BGJ398				
Day 8	Imatinib				
	BGJ398				
Day 9	Imatinib				
	BGJ398				
Day 10	Imatinib				
	BGJ398				
Day	Imatinib				

11	**BGJ398**				
Day 12	**Imatinib**				
	BGJ398				
Day 13	**Imatinib**				
	BGJ398				
Day 14	**Imatinib**				
	BGJ398				
Day 15	**Imatinib**				
	BGJ398				
Day 16	**Imatinib**				
	BGJ398				
Day 17	**Imatinib**				
	BGJ398				
Day 18	**Imatinib**				
	BGJ398				
Day 19	**Imatinib**				
	BGJ398				
Day 20	**Imatinib**				
	BGJ398				
Day 21	**Imatinib**				
	BGJ398				
Day 22	**Imatinib**				
	BGJ398				
Day 23	**Imatinib**				
	BGJ398				
Day 24	**Imatinib**				
	BGJ398				
Day	**Imatinib**				

25	**BGJ398**			[redacted]
Day 26	**Imatinib**			
	BGJ398			[redacted]
Day 27	**Imatinib**			
	BGJ398			[redacted]
Day 28	**Imatinib**			
	BGJ398			[redacted]

Patient Signature:_____
Date:_____

Consenting Professional/Research RN Signature: _____
Date:_____

Consenting Professional/Research RN Comments:

_____
_____
_____
_____

Appendix D: LIST OF CYP3A4 INHIBITORS AND INDUCERS (Reference for Imatinib)

CYP3A4 Inhibitors

Acetaminophen	Diclofenac	Lomustine	Primaquine
Acetazolamide	Dihydroergotamine	Losartan Lovastatin	Progesterone
Amiodarone	Diltiazem	Mefloquine	Propofol
Amlodipine	Disulfiram	Mestranol	Propoxyphene
Amprenavir	Docetaxel	Methadone	Quinidine
Anastrozole	Doxorubicin	Methimazole	Quinine
Aprepitant	Doxycycline	Methoxsalen	Quinupristin
Atazanavir	Drospirenone	Methylprednisolone	Rabeprazole
Atorvastatin	Efavirenz	Metronidazole	Ranolazine
Azelastine	Enoxacin	Miconazole	Risperidone
Azithromycin	Entacapone	Midazolam	Ritonavir
Betamethasone	Ergotamine	Mifepristone	Saquinavir
Bortezomib	Erythromycin	Mirtazapine	Selegiline
Bromocriptine	Ethinyl estradiol	Mitoxantrone	Sertraline
Caffeine	Etoposide	Modafinil	Sildenafil
Cerivastatin	Felodipine	Nefazodone	Sirolimus
Chloramphenicol	Fentanyl	Nelfinavir	Sulconazole
Chlorzoxazone	Fluconazole	Nevirapine	Tacrolimus
Cimetidine	Fluoxetine	Nicardipine	Tamoxifen
Ciprofloxacin	Fluvastatin	Nifedipine	Telithromycin
Cisapride	Fluvoxamine	Nisoldipine	Teniposide
Clarithromycin	Fosamprenavir	Nizatidine	Testosterone
Clemastine	Glyburide	Norfloxacin	Tetracycline
Clofazimine	Grapefruit juice (2)	Olanzapine	Ticlopidine
Clotrimazole	Haloperidol	Omeprazole	Tranylcypromine
Clozapine	Hydralazine	Orphenadrine	Trazodone
Cocaine	Ifosfamide	Oxybutynin	Troleandomycin
Conivaptan	Imatinib	Paroxetine	Valproic acid
Cyclophosphamide	Indinavir	Pentamidine	Venlafaxine
Cyclosporine	Irbesartan	Pergolide	Verapamil
Danazol	Isoniazid	Phencyclidine	Vinblastine
Dasatinib (1)	Isradipine	Pilocarpine	Vincristine
Delavirdine	Itraconazole	Pimozide	Vinorelbine
Desipramine	Ketoconazole	Pravastatin	Voriconazole
Dexmedetomidine	Lansoprazole	Prednisolone	Zafirlukast
Diazepam	Lidocaine		Ziprasidone

CYP3A4 Inducers

Aminoglutethimide	Nevirapine	Phenytoin	Rifapentine
Carbamazepine	Oxcarbazepine	Primidone	St. John's wort (3)
Fosphenytoin	Pentobarbital	Rifabutin	
Nafcillin	Phenobarbital	Rifampin	

Note: Adapted from Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 15th ed. Hudson, OH; LexiComp Inc. 2007: 1899-1912.

Only major substrates and effective inducers are listed. Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.uupui.edu/flockhart/.

List of CYP3A4 and CYP2B6 substrates.

Cytochrome	Category	Substrate
CYP3A4,5,7	Antiarrhythmics	quinidine→3-OH (not CYP3A5)[2], dronedarone1
	Antihistamines	astemizole[2], ebastine[1], [terfenadine][1,2]
	Benzodiazepines (CNS agents)	alprazolam, brotizolam[1], diazepam→3OH, midazolam[1], triazolam[1]
	Calcium Channel Blockers	amlodipine, diltiazem, felodipine[1], nifedipine, nisoldipine[1], nitrendipine, verapamil
	Protease Inhibitors	boceprevir, brecanavir[1], capravirine[1], darunavir[1], indinavir[1], lopinavir[1], ritonavir, saquinavir[1], telaprevir, tipranavir[1]
	HMG CoA Reductase Inhibitors	atorvastatin[1], lovastatin[1], simvastatin[1]
	Immune Modulators	cyclosporine[2], everolimus[1], sirolimus[1,2], tacrolimus[2]
	Antibiotics	clarithromycin, erythromycin (not CYP3A5), telithromycin
	Antipsychotics	aripiprazole, haloperidol, lurasidone[1], perospirone[1], pimozide[2], quetiapine[1]
	Tyrosine Kinase Inhibitors (anticancer)	dasatinib[1], imatinib, neratinib[1] nilotinib
	Opioids	alfentanil[1,2], fentanyl[2], methadone, levomethadyl[1]
	Ergot derivatives (for migraines)	diergotamine (dihydroergotamine)[2], ergotamine[2]
	Corticosteroids	budesonide[1], fluticasone[1]
	Erectile Dysfunction Agents	sildenafil[1], vardenafil[1]
	Antiemetics	aprepitant[1], casopitant[1]
	Others	alpha-dihydroergocryptine[1], aplaviroc[1], buspirone[1], cisapride[2], conivaptan[1], darifenacin[1], eletriptan[1], eplerenone[1], lumefantrine[1], maraviroc[1], quinine, ridaforolimus[1], tamoxifen, ticagrelor[1], tolvaptan[1], trazodone, vicriviroc[1], vincristine
CYP2B6	Alkylating Agents (anticancer):	cyclophosphamide, ifosfamide, thiotepa
	Others	Bupropion[1], efavirenz[1], methadone

Cytochrome	Category	Substrate

[1] Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor.

[2] Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

This list of CYP substrates was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table; from the FDA's "Guidance for Industry, Drug Interaction Studies" and from the University of Washington's Drug Interaction Database. The following website may be further useful as a reference to avoid potential drug-drug interactions: http://medicine.iupui.edu/clinpharm/ddis/table.asp.

Appendix E: List of concomitant medications to be used with caution with BGJ398

List of CYP450 substrates and other medications to be used with caution

Table 14-1 Drugs to be used with caution while on study

Category	Drug Names
Sensitive CYP3A Substrates	Alpha-dihydroergocryptine, aplaviroc, aprepitant, atorvastatin, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, indinavir, levomethadyl, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simvastatin, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil, vicriviroc
Narrow Therapeutic index substrates of CYP3A4	Quinidine, astemizole, terfanadine, cyclosporine, sirolimus, tacrolimus, diergotamine, cisapride, ergotamine, pimozide, alfentanil, fentanyl thioridazine, diergotamine, dihydroergotamine, ergotamine
Moderate inhibitors of CYP3A4	Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, imatinib, Schisandra sphenanthera, tofisopam, verapamil
Moderate inducers of CYP3A4	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir
Medications which alter the pH of the GI tract[1]	Proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids.
Medications with established potential for QT prolongation or Torsades de pointes	Amiodarone, disopyramide, dofetilide, flecainide, ibutilide, procainamide, quinidine, sotalol, arsenic trioxide, vavdetanib, astemizole, terfenadine, azithromycin, clarithromycin, erythromycin, moxifloxacin, sparfloxacin, bepridil, chloroquine, halofantrine, chlorpromazine, haloperidol mesoridazine, pimozide, thioridazine, domperidone, droperidol, pentamidine, probucolm, citalopram, levomethadyl,

Substrates of BCRP to be administered with caution

Category	Drug Names
	methadone, cisapride
BCRP substrates	Rosuvatstatin, methotrexate, irinotecan, atorvastatin, simvastatin, topotecan, sulfasalazine

[1] BGJ398 should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.

Reference:
FDA Guidance for Industry, Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Accessed 10 November 2013 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf.
Indiana University School of Medicine's "Clinically Relevant" table (2009). http://medicine.iupui.edu/clinpharm/ddis/clinicalTable.aspx. Accessed 14 July 2011
University of Washington's Drug Interaction Database (2013) http://.druginteractioninfo.org
Drug-Drug Interactions (DDI) Database: Novartis Oncology Clinical Pharmacology Internal Memorandum, Final (v04), 12-Oct-2012

List of QT prolonging drugs

Prohibited medications causing QTc prolongation			
Antiarrhythmic:	**Anticancer:**	**Antibiotic:**	**Antianginal:**
amiodarone	arsenic trioxide	azithromycin	bepridil
disopyramide	vandetanib	clarithromycin*	**Antipsychotic:**
dofetilide	**Antihistamine:**	erythromycin*	chlorpromazine
flecainide	astemizole*	moxifloxacin	haloperidol*
ibutilide	terfenadine*	sparfloxacin	mesoridazine
procainamide	**Antimalarial:**	**Antinausea:**	pimozide
quinidine*	chloroquine	domperidone	thioridazine
sotalol	halofantrine	droperidol	**Opiate agonist**:
Antilipemic:	**Anti-infective:**	**GI stimulant:**	levomethadyl
probucol	pentamidine	cisapride*	methadone
Antidepressant:			
citalopram			

Please note: *CYP3A substrate
Source: Arizona Center for Education and Research on Therapeutics (CERT), Drugs that prolong the QT interval and/or induce Torsades de Pointes, http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm

Appendix F: List of prohibited medications with BGJ398

List of CYP3A inhibitors and inducers that are prohibited

Table 14-2 List of prohibited medication while on study

Category	Drug Names
Strong inducers of CYP3A4	Avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort
Strong Inhibitors of CYP3A4	Clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, voriconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, grapefruit juice, juice from Seville oranges
Medications which increase serum phosphorus and/or calcium	Calcium, phosphate, vitamin D, parathyroid hormone (PTH)

EIAEDs that are prohibited

Strong CYP3A inducers	Moderate CYP3A inducers
carbamazepine	felbamate
phenobarbital	topiramate (>200 mg/day)
phenytoin	oxcarbazepin
fosphenytoin	eslicarbazepin
primidone	rufinamide

Appendix G: Select High-Phosphorous Foods and Suggested Alternatives

High-Phosphorous Beverages: Beer, Ales, Dark Colas (Coca-Cola, Diet Coke, Pepsi, etc.), Chocolate drinks, Cocoa, Canned Iced Tea, Other drinks made with milk

Alternative Beverages: Ginger ale, Lemon-lime soda (Sprite, 7-Up); Nondairy creamer

High-Phosphorous Dairy Products: Cow's Milk, Cheese, Cottage cheese, Chocolate, Ice Cream, Pudding, Yogurt, Cream Soups

Alternatives to Dairy: Cream Cheese, Nondairy Creamer, Popsicles, Sherbet. Different brands of Rice, Almond, and Soy Milk have varying amounts of phosphorous, so individual nutrition labels should be compared.

High-Phosphorous Proteins: Carp, Crayfish, Fish roe, Liver and other organ meats, Oysters, Sardines

Alternative Proteins: Beef, Chicken, Pork

Other High-Phosphorous Foods: Bran cereals, whole grains, nuts, dried beans (black beans, chickpeas, lima beans, soybeans, lentils, split peas)

Alternatives: Cream of wheat, shredded wheat, rice or corn cereals; green beans, mixed vegetables

Adapted from National Kidney Foundation, http://www.kidney.org/atoz/content/phosphorus.cfm

Appendix H: Ophthalmology Forms

14-140 Screening Ophthalmology Examination

Subject Name: _____

MRN:_____

Ophthalmology Examination			
Date of Examination:	_ _/_ _ _/_ _ _ _ dd / mmm / yyyy		
Please evaluate for below:	**Yes**	**No**	**Comments**
Does the patient have a history of retinal degenerative disease?			
Does the patient have predisposing factors to CSR or RVO (i.e. uncontrolled glaucoma or ocular hypertension?)			
Does the patient have a history or current evidence of retinal vein occlusion (RVO)?			
Does the patient have a history or current evidence of Central Serous Retinopathy (CSR)?			
Does the patient have active corneal disorder?			
Does the patient have active keratopathy?			

Signature of Examiner: _____

Printed Name: _____ **Date:** _____

14-140 Ophthalmology Follow-up Exam

Name: _____

MRN: _____

Ophthalmology Examination						
Date of Examination:	_ _/_ _ _/_ _ _ _ dd / mmm / yyyy					
Please evaluate for below:	**Yes**	**No**	**CTCAE Grade**	**Related to study drug?**		**Comments:**
				YES	**NO**	
Does the patient have a history of retinal degenerative disease?						
Does the patient have predisposing factors to CSR or RVO (i.e. uncontrolled glaucoma or ocular hypertension?)						
Does the patient have a history or current evidence of retinal vein occlusion (RVO)?						
Does the patient have a history or current evidence of Central Serous Retinopathy (CSR)?						
Does the patient have active corneal disorder?						
Does the patient have active keratopathy?						

Signature of Examiner: _____

Printed Name: _____ **Date:** _____

Appendix I: Lab Manual

Memorial Sloan Kettering Cancer Center

Research Sample Processing Instructions and Participating Site Shipping Forms

MSK IRB 14-140: A Phase Ib/II Study of BGJ398 in Combination with Imatinib Mesylate in Patients with Untreated Advanced Gastrointestinal Stromal Tumor (GIST)

Phase Ib: Research Blood Collection

- Pharmacokinetic Samples for BGJ398
- Pharmacokinetic Samples for Imatinib

Research blood will be drawn on the Phase Ib portion at the time points noted in protocol Table 10.

Supplies for each sample collection and storage:

- (1) 8 mL K3-EDTA tubes – provided by site
- (2) 1.8 mL NUNC 2D coded tubes from Thermo – provided by the site
  Reference for tubes: 374502NOV (1D/2D coded tubes) or 374502 (480 tubes/10 bags). At timepoints* where blood is being collected for BGJ398 and imatinib testing (3) 1.8mL NUNC 2D coded tubes will be provided (* Schedule A: C1D2 0hr & C1D21 0hr; Schedule B: C1D2 0hr, C1D7 0hr,C1D21 0hr)

Phase I Collection Procedures and On-Site Storage for BGJ398 AND Imatinib PKs:

1. Use (1) 8mL K3-EDTA tube for collection at each timepoint.
2. All blood samples will be taken by either direct venipuncture or an indwelling catheter inserted in a forearm vein.
3. Immediately after blood draw, invert gently several times to ensure mixing of contents. Avoid prolonged blood sample content with the rubber stopper.
4. Place the tube upright in a test tube rack surrounded by ice or cryoblock until centrifugation.
5. Within 30 minutes, centrifuge the sample between 3-5^{o}C for 10 minutes at approximately 2000g.
6. Immediately after centrifugation, 2 aliquots of about 0.5 mL of the collected plasma should be transferred into labeled 1.8 mL NUNC 2D coded tubes from Thermo. At least 0.5 mL of plasma in the first tube and the remaining plasma into the remaining tubes.
7. Immediately freeze the tubes over dry ice (solid carbon dioxide) then keep frozen at ≤-15^{o}C.

Labeling and Shipping Instructions:

1. Label samples with MSKCC ID, date of collection, and study time point.
2. Participating sites will ship specimen to MSK. All shipments should be directed to the address listed on the tissue sample shipment form. Samples should be shipped frozen with dry ice by courier so that the package can be tracked appropriately (specifically, Federal Express or UPS).
3. Notify the Research and Laboratory Staff at MSKCC (listed on the requisition) when samples are shipped.
4. MSK will batch ship samples to the appropriate lab.

MSK Shipping procedures for BGJ398:

- Samples are to be batch shipped monthly to WuXi via World Courier.

MSK Shipping procedures for Imatinib:

- Samples are to be batch shipped monthlyto WuXi via World Courier.

Phase Ib PK Sample for BGJ398
Shipment Form (For Participating Sites)

1. Complete this requisition form and include one for each sample shipped.
2. Label all samples with MSKCC ID, date of collection, and study time point.
3. BGJ samples are to be shipped batched every month to:

BioAnalytic Services Department
WuXi Apptec Com.,Ltd. No.228,
FuTeZhong Road
WaiGaoQiao Free Trade Zone,
Shanghai, China, 200131

4. Notify the Research Staff at MSKCC samples are shipped by emailing the completed requisition form to: William Tap, MD (tapw@mskcc.org), Chloe Mcfadyen (mcfadyec@mskcc.org)), and MSK Multicenter Group Inbox (medmctcore@mskcc.org).

Please complete all fields below:

Participant Information (Schedule A)			
Institution:			
Participant Initials:			
MSKCC-Assigned Participant ID:			
Contents – Sample Information			
Date of Collection: (MM DD YYYY)	**Phase I Study Time Point:**	**Date of Collection:** (MM DD YYYY)	**Phase I Study Time Point:**
	☐ Cycle 1 Day 1 (Pre-dose)		☐ Cycle 1 Day 21 (Pre-dose)
	☐ Cycle 1 Day 1 (1 hour)		☐ Cycle 1 Day 21 (1 hour)
	☐ Cycle 1 Day 1 (2 hours)		☐ Cycle 1 Day 21 (2 hours)
	☐ Cycle 1 Day 1 (4 hours)		☐ Cycle 1 Day 21 (4 hours)
	☐ Cycle 1 Day 1 (6 hours)		☐ Cycle 1 Day 21 (6 hours)
	☐ Cycle 1 Day 1 (8 hours)		☐ Cycle 1 Day 21 (8 hours)
	☐ Cycle 1 Day 2 (24 hours)		

Shipment Information		Sender's Contact Information	
Shipping Date		**Name**	
Shipping Method		**Email**	
Tracking Number		**Telephone**	

For MSKCC Use ONLY: Date received at MSKCC: _ _ / _ _ / _ _ _ _ (MM DD YYYY)

Participant Information (Schedule B)			
Institution:			
Participant Initials:			
MSKCC-Assigned Participant ID:			
Contents – Sample Information			
Date of Collection: (MM DD YYYY)	**Phase I Study Time Point:**	**Date of Collection:** (MM DD YYYY)	**Phase I Study Time Point:**
	☐ Cycle 1 Day 1 (Pre-dose)		☐ Cycle 1 Day 7 (Pre-dose)
	☐ Cycle 1 Day 1 (1 hour)		☐ Cycle 1 Day 7 (1 hour)
	☐ Cycle 1 Day 1 (2 hours)		☐ Cycle 1 Day 7 (2 hours)
	☐ Cycle 1 Day 1 (4 hours)		☐ Cycle 1 Day 7 (4 hours)
	☐ Cycle 1 Day 1 (6 hours)		☐ Cycle 1 Day 7 (6 hours)
	☐ Cycle 1 Day 1 (8 hours)		☐ Cycle 1 Day 7 (8 hours)
	☐ Cycle 1 Day 2 (24 hours)		
			☐ Cycle 1 Day 15 (0 hours)
			☐ Cycle 1 Day 21 (0 hours)

Shipment Information		Sender's Contact Information	
Shipping Date		**Name**	
Shipping Method		**Email**	
Tracking Number		**Telephone**	

For MSKCC Use ONLY: Date received at MSKCC: _ _ / _ _ / _ _ _ _ (MM DD YYYY)

Phase Ib PK Sample for Imatinib

Shipment Form (For Participating Sites)

1. Complete this requisition form and include one for each sample shipped.
2. Label all samples with MSKCC ID, date of collection, and study time point.
3. Imatinib samples are to be shipped batched monthly to:

BioAnalytic Services Department
WuXi Apptec Com.,Ltd. No.228,
FuTeZhong Road
WaiGaoQiao Free Trade Zone,
Shanghai, China, 200131

4. Notify the Research Staff at MSKCC when samples are shipped by emailing the completed requisition form to: William Tap, MD (tapw@mskcc.org), () Chloe Mcfadyen (mcfadyec@mskcc.org), and MSK Multicenter Group Inbox (medmctcore@mskcc.org).

Please complete all fields below:

Participant Information (Schedule A)	
Institution:	
Participant Initials:	
MSKCC-Assigned Participant ID:	
Contents – Sample Information	
Date of Collection: (MM DD YYYY)	**Phase I Study Time Point:**
	☐ Cycle 1 Day 2 (24 hours post-first dose / Pre-dose on Day 2)
	☐ Cycle 1 Day 21 (Pre-dose)

Shipment Information		**Sender's Contact Information**	
Shipping Date		**Name**	
Shipping Method		**Email**	
Tracking Number		**Telephone**	

For MSKCC Use ONLY: Date received at MSKCC: _ _ / _ _ / _ _ _ _ (MM DD YYYY)

Participant Information (Schedule B)	
Institution:	
Participant Initials:	
MSKCC-Assigned Participant ID:	
Contents – Sample Information	
Date of Collection: (MM DD YYYY)	**Phase I Study Time Point:**
	☐ Cycle 1 Day 2 (24 hours post-first dose / Pre-dose on Day 2)
	☐ Cycle 1 Day 7 (Pre-dose)
	☐ Cycle 1 Day 21 (Pre-dose)

Shipment Information		Sender's Contact Information	
Shipping Date		**Name**	
Shipping Method		**Email**	
Tracking Number		**Telephone**	

For MSKCC Use ONLY: Date received at MSKCC: _ _ / _ _ / _ _ _ _ (MM DD YYYY)

Phase II: Research Blood Collection

Pharmacokinetic Samples for Imatinib and FGF Serum Levels

Supplies for each sample collection and storage:

- (2-4) 4-8 mL K3-EDTA tubes – provided by site
- (2) 1.8 mL NUNC 2D coded tubes from Thermo – provided by site
  Reference for tubes: 374502NOV (1D/2D coded tubes) or 374502 (480 tubes/10 bags)

Phase II Collection procedures for <u>Imatinib PKs and FGF Serum Research bloods</u>:

1. Use (4) 4-8mL K3-EDTA tubes for collection at timepoints: Week -2, C1D1, C1D15, C2D1. Use (2) 4-8mL K3-EDTA tubes at the time of progression.
2. All blood samples will be taken by either direct venipuncture or an indwelling catheter inserted in a forearm vein.
3. At specified timepoints, collect a 2mL blood sample in tubes with the specific coagulant K3-EDTA
4. Immediately after blood draw, invert gently several times to ensure mixing of contents. Avoid prolonged blood sample content with the rubber stopper.
5. Place the tube upright surrounded by ice or cryoblock until centrifugation.
6. Within 30 minutes, centrifuge the sample between 3-5^{o}C for 10 minutes at approximately 2000g.
7. Immediately after centrifugation, 2 aliquots of about 0.5 mL of the collected plasma should be transferred into labeled 1.8 mL NUNC 2D coded tubes from Thermo. At least 0.5 mL of plasma in the first tube and the remaining plasma into the second tube.
8. Immediately freeze the tubes over dry ice (solid carbon dioxide) then keep frozen at ≤-15^{o}C.

Labeling and Shipping Instructions:

1. Label samples with MSKCC ID, date of collection, and study time point.
2. Participating sites will ship specimen to MSK. All shipments should be directed to the address listed on the tissue sample shipment form. Samples should be shipped frozen with dry ice by courier so that the package can be tracked appropriately (specifically, Federal Express or UPS).
3. Notify the Research and Laboratory Staff at MSKCC (listed on the requisition) when samples are shipped.
4. MSK will batch ship samples to the appropriate lab.

MSK Shipping procedures for <u>Imatinib</u>:

- Samples are to be batch shipped monthly to WuXi via World Courier .

Phase II Research Bloods

Sample Shipment Form (For Participating Sites)

1. Complete this requisition form and include one for each sample shipped.
2. Label all samples with MSKCC ID, date of collection, and study time point.
3. All samples are to be shipped batched quarterly to:

Memorial Sloan Kettering Cancer Center
ATTN:Chloe Mcfadyen, 5th floor
160 East 53rd Street
New York, NY 10022

4. Notify the Research Staff at MSKCC when samples are shipped by emailing the completed requisition form to: William Tap, MD (tapw@mskcc.org), Chloe Mcfadyen (mcfadyec@mskcc.org), , and MSK Multicenter Group Inbox (medmctcore@mskcc.org).

Please complete all fields below:

Participant Information	
Institution:	
Participant Initials:	
MSKCC-Assigned Participant ID:	
Contents – Sample Information	
Date of Collection: (MM DD YYYY)	**Phase II Study Time Point:**
	☐ Week -2 (0 hour)
	☐ Cycle 1 Day 1 (0 hour)
	☐ Cycle 1 Day 15 (0 hour)
	☐ Cycle 2 Day 1 (0 hour)

Shipment Information		**Sender's Contact Information**	
Shipping Date		**Name**	
Shipping Method		**Email**	
Tracking Number		**Telephone**	

For MSKCC Use ONLY: Date received at MSKCC: _ _ / _ _ / _ _ _ _ (MM DD YYYY)

Phase II: Research Biopsies

Research blood will be drawn on the Phase II portion at the time points noted in protocol. See protocol section 10.2.2 and 10.2.4 for collection and preparation instructions. See 10.2.4 for Handling of Specimetn and 10.2.5 for Shipping of Specimens. Participating sites should complete the following requision and include with shipment. All shipments should be directed to the address listed on the tissue sample shipment form. Samples should be shipped by courier so that the package can be tracked appropriately (specifically, Federal Express or UPS). Notify the Research and Laboratory Staff at MSKCC (listed on the requisition) when samples are shipped.

Phase II Biopsy Collection (Flash Frozen Specimen)

Sample Shipment Form

1. Complete this requisition form and include with sample.
2. Label all samples with MSKCC ID and date of collection.
3. All samples are to be shipped batched approximately every 6 months to:

Attn: Ping Chi, MD, PhD - Sarcoma Biology Lab
Memorial Sloan Kettering Cancer Center
417 East 68th Street, Zuckerman Z527
New York, NY 10065
646-888-3349

4. Notify the Research Staff at MSKCC when samples are shipped by emailing the completed requisition form to: Ping Chi, MD, PhD (chip@mskcc.org), William Tap, MD (tapw@mskcc.org), Chloe Mcfadyen (mcfadyec@mskcc.org), and MSK Multicenter Group Inbox (medmctcore@mskcc.org).

Please complete all fields below:

Sample Information	
Institution:	
Participant Initials:	
MSKCC-Assigned Participant ID:	
Date of Collection:	
Study Time Point: **(check one)**	☐ Pretreatment ☐ Cycle 1 Day 8 ☐ Progression
Organ/Site of Collection:	
Histology Diagnosis:	
Biopsy Procedure & Amount of Tissue:	☐ Open Incisional Biopsy: _____ cm^3 ☐ Image-Guided Core Biopsy: # Cores: _____

Shipment Information		Sender's Contact Information	
Shipping Date		**Name**	
Shipping Method		**Email**	
Tracking Number		**Telephone**	

For MSKCC Use ONLY: Date received at MSKCC: _ _ / _ _ / _ _ _ _ (MM DD YYYY)

Phase II Biopsy Collection (Formalin-Fixed Specimen)

Sample Shipment Form

1. Complete this requisition form and include with sample.
2. Label all samples with MSKCC ID and date of collection.
3. All samples are to be shipped batched approximately every 6 months to:

Attn: Cristina Antonescu, MD Memorial
Sloan Kettering Cancer Center
Department of Pathology
1275 York Avenue, C-587
New York, NY 10065
212-639-5905

4. Notify the Research Staff at MSKCC when samples are shipped by emailing the completed requisition form to: Cristina Antonescu, MD (antonesc@mskcc.org), William Tap, MD (tapw@mskcc.org), Chloe Mcfadyen (mcfadyec@mskcc.org), and MSK Multicenter Group Inbox (medmctcore@mskcc.org).

Please complete all fields below:

Sample Information	
Institution:	
Participant Initials:	
MSKCC-Assigned Participant ID:	
Date of Collection:	
Study Time Point: **(check one)**	☐ Pretreatment ☐ Cycle 1 Day 8 ☐ Progression
Organ/Site of Collection:	
Histology Diagnosis:	
Biopsy Procedure & Amount of Tissue:	☐ Open Incisional Biopsy: _____ cm^3 ☐ Image-Guided Core Biopsy: # Cores: _____

Shipment Information		**Sender's Contact Information**	
Shipping Date		**Name**	
Shipping Method		**Email**	
Tracking Number		**Telephone**	

For MSKCC Use ONLY: Date received at MSKCC: _ _ / _ _ / _ _ _ _ (MM DD YYYY)