Pilot Study of BGJ398 in Non-Muscle-Invasive Urothelial Carcinoma of the Bladder

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is an open-label pilot study of the pan-fibroblast growth factor receptor (FGFR) kinase inhibitor BGJ398 in patients with recurrent high-risk non-muscle-invasive bladder cancer (NMIBC). Patients with previously demonstrated *FGFR3* mutant high-grade papillary tumors who have experienced disease relapse with clinical high-grade Ta disease after at least 1 induction course of intravesical bacillus Calmette-Guérin (BCG) therapy will be eligible. Potentially eligible patients will be identified in the Urology and Medical Oncology clinics. Cystoscopic evaluation by a study urologist will confirm eligibility. After providing informed consent, patients will undergo transurethral resection (TUR) of bladder tumor, at which time a small (≤1.0 cm) measurable marker lesion will be left in place. This lesion will be photographed and have its size and location documented.

After pathologic confirmation of TUR results, patients will then begin daily therapy with BGJ398 at 125 mg daily.

At the 7 week timepoint, a repeat cystoscopy will be performed and urine cytology will be collected. If there is residual tumor or new lesions, then patients will discontinue treatment with BGJ398 and undergo completion TUR. If there is no evidence of residual tumor (complete response, CR), patients with a maximal drug-related toxicity of ≤ Grade 2 (with the exceptions listed in Section 9.2.4) will be given the option to continue on BGJ398 and have interim follow-up evaluations at 5, 8, and 11 months or to discontinue treatment and have standard of care follow-up. Patients who decided to continue on BGJ398 and remain without evidence of disease recurrence at 11 months will stop treatment at that time. All patients who achieve a complete response and discontinue treatment will then be followed for recurrence or progression and vital status according to standard of care. Long-term follow-up will continue for up to two years after the last dose of BGJ398, after which patients will be removed from the study.

The planned accrual goal is 15 patients. Pre-treatment or archival tumor tissue will be tested using assays in CLIA-certified laboratories to verify *FGFR3* mutation status. Patients will be simultaneously consented to MSKCC protocol 12-245 (—Tumor Genomic Profiling in Patients Evaluated for Targeted Cancer Therapy‖) for this purpose. Pre- and post-treatment tumor tissue may also be sent for additional profiling studies to determine FGFR3 expression, gene fusions, and co-mutations. These results will be correlated with response to treatment with BGJ398.

Figure 1-1 Study Schema

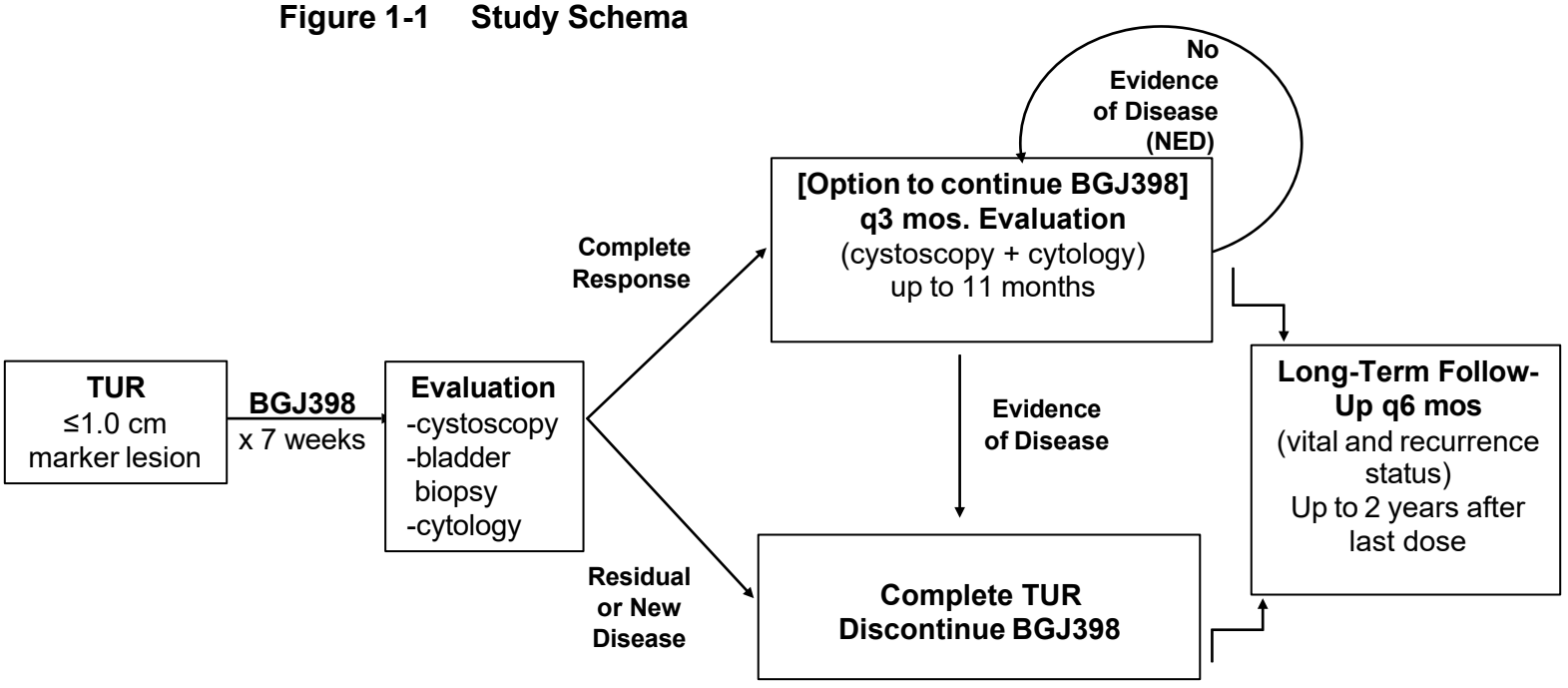

Table 1-2 Overview of Study

	Screening	TUR	**Cycles 1-2**		Follow-Up for Patients with CR (Cycles 3-11)[e]		Post-Treatment / Withdrawal	Long-Term Follow Up
Cycle (28 days)			**1**	**2**	**3-11**	**5, 8, 11**		**Every 6 months for up to 2 years after last dose**
Confirmation of *FGFR3* mutation status	**X**							
Cystoscopy	**X**			**X[c,d]**		**X[d]**	**X**	
Research bladder biopsy				**X[c,d]**				
Urine cytology	**X**			**X[c,d]**		**X[d]**	**X**	
BGJ398			**21 days with 7 days rest**		**Option to continue BGJ398[f]**			
Transurethral Resection (TUR)		**X[a,b]**					**X[b, d]**	
Vital and Recurrence Status								**X**

Cycle length: 28 days

[a]A small (≤1.0 cm) measurable marker lesion will be left in place.

[b]If pathology from TUR reveals ≥Stage T1 disease, patient will not initiate BGJ398 treatment and undergo completion TUR.

[c]These assessments occur during cycle 2 week 3. If residual tumor remains, or new lesions have developed at the Week 7 (cycle 2 week 3) cystoscopy assessment, the patient will discontinue treatment and completion TUR will be performed. If cytology is positive but there is no cystoscopic evidence of tumor, then patients will continue to hold BGJ398 and undergo evaluation in section 12.0. If there is no evidence of biopsy proven tumor, then patients may resume treatment on cycle 3 day 1 after recovery from the procedure.

[d]If there is evidence of disease recurrence or progression at any point, the patient will discontinue treatment and completion TUR will be performed. If patients complete the study without recurrence, post-treatment TUR is not required.

[e]All patients who achieve a complete response and discontinue treatment will be followed for recurrence or progression according to standard of care.

[f]Only patients whose maximal drug-related toxicity is ≤ Grade 2 (with the exceptions listed in Section 9.2.4) have the option to continue treatment with BGJ398.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary

- To determine the activity of BGJ398, as measured by complete response of a marker lesion at 7 weeks, in patients with activating *FGFR3* mutations or fusions with recurrent non-muscle-invasive bladder cancer (NMIBC) who have received at least one prior induction course of intravesical BCG therapy.

Secondary

- To evaluate the safety and toxicity of BGJ398 in patients with recurrent NMIBC who have received at least one prior induction course of intravesical BCG therapy.
- To determine the duration of response in patients with complete response to BGJ398.

Exploratory

- To determine the associations of BGJ398 response with intensity and localization of FGFR3 immunohistochemical staining.
- To determine the associations of BGJ398 response with non-*FGFR3* co-mutations.
- To correlate circulating tumor DNA and DNA collected from urine sampling with tumor-derived DNA for the detection and monitoring of NMIBC.
- To evaluate the pharmacokinetics of BGJ398 and its metabolites in blood, urine, and bladder tissue samples.

3.0 BACKGROUND AND RATIONALE

3.1 Non-Muscle-Invasive Bladder Cancer

3.1.1 Natural History of Bladder Cancer

More than 70,000 new cases of bladder cancer are diagnosed each year in the United States [1]. Seventy to 80% of bladder tumors are non-muscle-invasive tumors (stages Ta, Tis, T1), 25% are muscle-invasive (stages T2, T3, T4), and 5% are metastatic. Sixty to 70% of patients with non-muscle-invasive tumors will experience recurrence, while 20% to 30% will experience progression to more advanced stage or grade [2].

Non-muscle-invasive bladder cancer (NMIBC) includes stages Ta, T1, and Tis with frequencies of 60%, 30%, and 10%, respectively. NMIBC encompasses a spectrum of tumors with varying degrees of clinical behavior. For example, low-grade Ta lesions commonly recur but rarely progress to muscle-invasion. On the other hand, T1 tumors represent a heterogeneous group, some of which behave in an indolent fashion and typically respond to conservative therapy, while others behave more aggressively and progress to muscle-invasion and even metastatic disease. At present, we lack the ability to reliably predict the clinical behavior of recurrent NMIBC.

3.1.2 Recurrence and Progression in Non-Muscle-Invasive Bladder Cancer

The recurrence rate for patients with NMIBC after transurethral resection (TUR) ranges from 30% to 90%, depending on grade, stage, multifocality, size, presence of carcinoma in situ (CIS), and prior recurrence rate [3]. Each recurrence necessitates invasive treatment with cystoscopy and TUR or other ablative treatments.

Progression is defined as the development of muscle-invasion or metastasis and occurs in 20% to 30% of patients who present with NMIBC. However, we are unable to reliably predict which tumors will progress.

Risk factors for recurrence and progression of NMIBC include number of tumors, tumor size, prior recurrence rate, tumor grade, T stage, and presence of CIS [3].

The high recurrence rate and the unpredictability of the progression pattern of NMIBC have led to the use of adjuvant treatments (e.g., intravesical therapy with BCG or mitomycin C) as a supplement to TUR. Standard of care treatment for patients who experience recurrence or

progression despite intravesical treatments includes radical cystectomy, an extirpative proce dure to remove the entire bladder that is associated with significant morbidity and effects on quality of life.

3.1.3. Adjuvant Therapy for Non-Muscle-Inva sive Bladder Cancer

Multiple agents, including BCG, thiotepa, mitomycin C, and doxorubicin, have been used as intravesical agents for adjuvant therapy of NMIBC. The highest tumor-free success rates have been reported after intravesical BCG therapy.

However, BCG is associated with toxicity in the form of local complications, such as cystitis in 90% of patients, requiring interruption of treatment in 3.6%, hematuria in 9%, granulomatous prostatitis in 0.9%, epididymitis in 0.4%, ureteral obstruction in 0.3%, contracted bladder in 0.2%, and renal abscess in 0.1%. Of greater concern in BCG-treated complications are systemic complications. Fever up to 38.5°C is frequently observed, pneumonia and hepatitis have been reported in 0.9% of patients, and sepsis occurs in 0.4%.

Furthermore, patients with an initial incomplete response to BCG have a poor outcome. Thus, alternative therapies are needed for patients who fail BCG.

3.1.4. Risk Stratification of Non-Muscle-Inva sive Bladder Cancer

In order to stratify patients with NMIBC in terms of their risks of recurrence and progression, the European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Cancer Group (GUCG) developed a scoring system and risk tables [3]. The basis for these tables are individual patient data for 2,596 patients diagnosed with Ta and T1 bladder tumors who were randomized in seven EORTC-GUCG trials.

A scoring model for patients with NMIBC treated with BCG to predict the short- and long-term risks of recurrence and progression was published by the Club Urologico Espanol de Tratamiento Oncologico (CUETO) (Spanish Urologic Oncology Group) [4]. This model was based on individual patient data from 1,062 patients enrolled in four CUETO trials that compared different intravesical BCG treatments.

Based upon these data, the European Association of Urology (EAU) has recommended in their guidelines on non-muscle-invasive bladder cancer that patients be stratified into risk groups (low-risk, intermediate-risk, and high-risk) [5]. Low-risk tumors meet all of the following criteria: primary, solitary, Ta, LG/G1, <3 cm, no CIS. High-risk tumors meet any of the following criteria: T1, HG/G3, CIS, multiple and recurrent and large (>3 cm) Ta, G1, G2 tumors. Intermediate-risk tumors are all that do not fall into the low- or high-risk groups.

3.2 Introduction to Investigational Treatment

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).

3.2.1.1 Preclinical Studies

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 translocations [6]. In line with its cellular activity, BGJ398 shows anti-tumor activity in multiple models bearing FGFR genetic alterations [7, 8].

3.2.1.1.1 Animal drug metabolism and pharmacokinetics

In all species tested, BGJ398 exhibited a high plasma CL (clearance) and a large Vss (Volume of distribution at steady state). 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 IC50 value of 0.21μM. In addition, *in vitro* data indicate that BGJ398 is primarily a CYP3A4 substrate.

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 IC50 of 12μM. BGJ398 is also a time dependent inhibitor of CYP3A4 with a KI = 37.3 μM and Kinact = 0.0547 min -1. In addition, CQM157, a recently identified metabolite in circulating plasma from patients, is also shown to be an inhibitor of CYP2C8, CYP2C9, and CYP3A4 (IC50 less than 10 μM) and CYP2C19 (IC50 12 μM). CQM157 is also an inhibitor of transporters P-gp, BCRP, OATP1B1 and OATP1B3 (IC50 less than 5 μM).

3.2.1.1.2 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 considered to be at 10 mg/kg/day which resulted in premature death in one (1/30) animal. Doses of 20 mg/kg/day in rats did lead to vasculopathy associated with moribundity after 6 administrations.

In dogs, the highest non-severely toxic dose (HNSTD) was considered to be at 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.

3.2.1.2 Clinical Experience

3.2.1.2.1 Clinical safety

As of data cut-off date October 1, 2014, 120 patients have received at least one dose of BGJ398. Forty-three patients were enrolled to dose escalation cohorts and 77 patients to dose expansion arms. The 3 weeks on/1 week off schedule was implemented based on observations of the timing and duration of drug interruptions during Cycle 1 necessitated by episodes of hyperphosphatemia. The data indicated that the median time to drug interruption was 22 days and the median duration of the interruption was 7 days. At the time of data cutoff, 3 patients were still receiving study medication. Of the 117 patients who have discontinued from the study, 83 discontinued treatment due to progression of disease, 13 discontinued due to adverse events, 5 died while on study, 14 discontinued due to withdrawal of consent, 1 due to administrative problems, and 1 due to protocol deviation.

The treatment emergent adverse events as of the cutoff date of October 1, 2014, regardless of BGJ398 relationship, that occurred in 20% or more of patients are: increases in phosphorus levels (74%, which includes the preferred terms of hyperphosphatemia and blood phosphorus increased), constipation (40.8%), decreased appetite (40. 8%), diarrhea (36.7%), stomatitis (36.7%), nausea (32.5%), fatigue (31.7%), alopecia (25.8%), asthenia (20.0%), blood creatinine increased (20.0%) and dry mouth (20.0%). Forty-five percent of patients (54/120) experienced at least one grade 3 or 4 event regardless of the relationship to BGJ398. Grade 3 or 4 events that occurred in at least 5% of patients were ALT (6.7%), AST (5.0%), and lipase increase (5.0%). Overall, most adverse events reported have been mild to moderate in severity, reversible, and unrelated to BGJ398.

Four DLTs occurred in four patients enrolled in the dose escalation part of the study , which established 125mg QD as the MTD. The MTD as determined by DLT was based on the following events.

• One grade 3 event of AST/ALT elevation was reported in the 100mg cohort.

• One patient enrolled to the 125 mg cohort experienced hyperphosphatemia for greater than 14 days despite adequate therapy that resulted in study drug interruption.

• Two patients enrolled to the 150 mg cohort experienced DLTs. One patient experienced grade 1 corneal toxicity. The second patient experienced grade 3 AST/ALT elevations, which led to study treatment interruption and dose reduction.

Hyperphosphatemia has been seen in the majority of patients treated at doses of 100 mg qd and higher and is a pharmacodynamic (PD) marker of on-target FGFR pathway inhibition. Renal tubular phosphate secretion and reabsorption are controlled through the FGFR1 pathway. Inhibition of this pathway leads to inability to secrete phosphate and secondary elevations in FGF23. The hyperphosphatemia has been managed in the Phase 1 study by dietary phosphate restrictions, phosphate lowering therapy, and drug interruptions and dose reductions, which led to the introduction of the alternate 3 weeks on/1 week off drug schedule. Preliminary safety data with this schedule suggest improved tolerability and compliance with drug administration (e. g. fewer dose interruptions during cycle 1), though dose reductions in later cycles of therapy are not uncommon.

3.2.1.2.2 Preliminary efficacy of BGJ398

Among patients in the Phase 1 study, anti-tumor activity has been noted in several tumor types with FGFR genetic aberrations, including lung SCC, breast cancer, and squamous head and neck cancer with *FGFR1* amplifications, *FGFR3* mutated advanced invasive urothelial cell carcinoma, and cholangiocarcinoma with *FGFR2* gene fusion.

3.2.1.2.3 Clinical pharmacokinetics

The pharmacokinetics (PK) of BGJ398 and active metabolites have been evaluated following single and repeat daily doses in the ongoing phase 1 study (CBGJ398X2101).

At 5 and 10 mg/day, plasma concentrations were low and frequently below the lower limit of quantification. Plasma concentrations were consistently quantifiable starting at 20 mg/day.

Following a single dose, median T_{max} was approximately 2-3 hours. The mean AUC_{0-24} on Day 1 increased approximately 9 fold from 20 to 150 mg. A mean terminal elimination half-life on Day 1($T_{1/2}$) was 3-7 hr. Despite the relatively short half-life on Day 1, accumulation was observed with daily dosing at doses ≥ 60 mg, likely due to auto-inhibition of CYP3A4 mediated clearance pathways. Mean accumulation ratio (R_{acc}) ranged from 3 to 8 on Days 15 and 28. Since dose interruptions occurred frequently following continuous daily dosing of BGJ398, PK parameters on Day 28 should be viewed with caution. The inter-patient variability was high for BGJ398. When dosed at 125 mg with a schedule of 3 weeks on, 1 week off, the mean C_{max} and AUC_{0-24} were 230 ng/mL (n=12) and 3492.9 ng*hr/mL, (n= 10), respectively at day 15. The coefficient of variation for C_{max} and AUC_{0-24} ranged from approximately 50 – 75% and higher variability was observed while estimating secondary pharmacokinetic parameters like clearance and volume of distribution.

Concentration data from active metabolites BHS697 (desethyl metabolite) and BQR917 (N-oxide) was available across all cohorts. CQM157 (aniline metabolite) was analyzed in a few patients following Amendment 6 of the BGJ398X2101 clinical protocol. In most patients, BHS697 and BQR917 were measurable at levels of ~5-50%, and <15% of parent exposure, respectively. Mean exposures on Day 1 (n=8) for CQM157 relative to BGJ398 varied across patients (3% -300%). CQM157 (n=4) did not appear to accumulate on daily dosing, whereas accumulation was observed for BGJ398 and metabolites BHS697 and BQR917.

Please refer to Investigator's Brochure for more details.

3.3 Background and Rationale in Urothelial Carcinoma

3.3.1 BGJ398

BGJ398 is an orally bioavailable, selective, and ATP-competitive pan-fibroblast growth factor receptor (FGFR) kinase inhibitor belonging to the pyrimidinyl aryl urea chemical class. The FGFR family of receptor tyrosine kinases (RTKs) consists of four members (FGFR1, FGFR2, FGFR3, FGFR4) 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. Epidemiological and molecular studies of various cancer types have identified 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 also the growth of tumors in mouse and rat xenograft models association with aberrant expression and activation of FGFRs.

3.3.2 FGFR Pathway in Bladder Cancer

The FGFR3 pathway is activated by mutation (or gene fusion) in many urothelial carcinomas of the bladder, and is believed to be critical in the pathogenesis of the disease [9]. FGFR3 activation appears to be an early event, and non-muscle-invasive tumors are highly enriched for activating mutations. These *FGFR3* mutations occur in 50-70% of non-muscle-invasive bladder cancer

(NMIBC), and are more prevalent in tumors of low grade and low stage [10-14]. These tumors recur at the same frequency as *FGFR3* wild-type tumors, but have a lower rate of progression to muscle invasion, with one study demonstrating a 5 year progression free survival of 91% in *FGFR3* mutant patients compared to 74% in *FGFR3* wild-type patients [14]. The *FGFR3* mutation status in bladder tumor recurrences is often concordant with the primary tumor [15]. The high recurrence rate of NMIBC leads to significant morbidity and health care spending due to the need for frequent cystoscopic monitoring and operative intervention. Therefore, an effective oral agent to reduce the recurrence of NMIBC would be of high value.

Preclinical models indicate that FGFR3 is a relevant therapeutic target. Inhibition of FGFR3 activity by knock down of mutant *FGFR3* in urothelial cancer cell lines results in attenuation of cell growth and colony formation [16]. Cell line and xenograft studies have shown the anti-cancer effects of inhibition of mutant FGFR3.

Furthermore, *FGFR3* fusions with other genes have been recently reported in bladder cancer [17]. These gene fusions are predicted to be activating based on constitutive dimerization and sensitivity of cell lines containing these fusions to FGFR inhibitors [18].

In addition to mutation and gene fusion, FGFR3 overexpression by immunohistochemistry was observed in 42% of *FGFR3* wild-type tumors, equally across all grades and stages of localized bladder cancer [11]. FGFR3 inhibition in pre-clinical models of *FGFR3* wild-type bladder cancer cell lines lead to decreased proliferation and viability, suggesting dependence of the pathway in at least some contexts, regardless of mutation profile. In particular, cell lines with high levels of expression of FGFR3 were sensitive to FGFR3 inhibition [19, 20]. These findings provide the rationale to test FGFR3 targeted agents in wild-type patients as well. While some of these wild-type cell lines contained undetected FGFR3 fusion genes, others were not clearly shown to contain fusion proteins.

3.3.3 Recurrent Non-Muscle-Invasive Bladder Cancer

The high frequency of *FGFR3* mutation in NMIBC patients, high levels of expression in wild-type cell lines, and the preclinical activity of FGFR3 inhibition in *FGFR3* mutant cell lines and wild-type over-expressing cell lines suggest that targeting this pathway therapeutically will lead to clinical benefit in NMIBC. NMIBC tumors are less genomically unstable than invasive or metastatic tumors, and FGFR3 may represent the true driver pathway in this disease state. Based on the likelihood that mutation (and/or *FGFR3* fusion) predicts for oncogene addiction in NMIBC, we hypothesize that these benefits would be most likely to be observed in patients whose tumors harbor an *FGFR3* genomic alteration. However, patients with wild-type *FGFR3* tumors may also derive benefit based on the preclinical data cited above.

Patients with NMIBC have a high frequency of recurrence, and require frequent invasive tests (cystoscopy, transurethral resection) which lead to significant cost and morbidity. In addition, if patients fail intravesical therapy, radical cystectomy is the only curative option. Since this procedure is life-changing for patients, a therapy that has activity in recurrent disease and reduces the frequency of recurrence will be a useful tool in the therapeutic armamentarium.

3.4 Use of Marker Lesions in Phase II Studies of Non-Muscle-Invasive Bladder Cancer

The marker tumor concept was derived from phase II trials where patients with unresectable, often multifocal, tumors were treated by intravesical chemotherapy alone, intended as an ablative treatment on existing tumor(s). Intravesical drugs such as thiotepa, mitomycin C, and adriamycin were able to eradicate tumor(s). Instead of using multiple tumors of indeterminate number, size, grade, and stage, the concept of a single residual Ta, T1 bladder tumor was developed. After TUR of multiple papillary tumors, one single tumor is left untouched in the bladder. The marker lesion concept was first described in 1981 [21].

The use of a marker lesion within the bladder has precedent in multiple phase II studies of NMIBC [22-28]. The alternative approach – the evaluation of new agents in large adjuvant phase III trials without previously demonstrating anti-cancer activity in phase II studies does not seem justified. Studies showing the ablative activity of intravesical chemotherapy with drugs such as thiotepa, mitomycin, and doxorubicin have relied on the response of NMIBC tumors that remained in the bladder after incomplete endoscopic resection. These studies have demonstrated that short interval follow-up is safe, and that if the lesion persists, then the marker lesion can be resected at that time. Data from 6 previous phase II trials indicated that the risk of leaving an untreated muscle-invasive tumor or that a tumor might progress to muscle invasion during 10-12 weeks of phase II study was 0.8% [23].

The EORTC GU Group has performed 3 previous studies of marker tumors that provide data demonstrating the safety of this trial methodology [24, 25]. Furthermore, based on these data, the Fourth International Bladder Cancer Consensus Conference recommended that phase II tumor marker studies should be adopted as standard clinical trial practice for evaluating new agents in the future [29].

It has been proposed that the ideal cohort for marker tumor studies in NMIBC is the group of intermediate-risk patients [23]. Patients with low-risk NMIBC have a good prognosis that does not justify intensive therapy with intravesical chemotherapy or systemic agents. Patients with high-risk NMIBC, on the other hand, have a risk of progression that seems too high to expose them to a drug or regimen with unpredictable outcomes. Therefore, authors have proposed criteria for intermediate-risk patients to be included for marker lesion trials in NMIBC [23]. These criteria include: (1) primary or recurrent multiple Ta, T1 tumors, (2) the number of tumors should not exceed 7, (3) the marker tumor should be < 1 cm in diameter, (4) G3 tumors should be excluded, and (5) CIS should be excluded. Given that the grading system for bladder cancer has since been modified from a 3-tier grading system to a classification of urothelial carcinomas into low-grade and high-grade [30], we have included high-grade tumors in our study.

The results of two parallel phase II marker lesion trials instituted by the EORTC GU Group were published in a paper by Bono et al. [25]. These trials included patients with multiple primary or recurrent Ta-T1 bladder cancer. A well-defined tumor (marker lesion) was left in the bladder after TUR and patients received 8 weekly instillations of intravesical mitomycin C (EORTC study 30864) or epirubicin (EORTC study 30869). The authors reported on 96 evaluable patients treated with mitomycin C and 36 patients treated with epirubicin, with complete response rates of 50% and 56%, respectively.

Mack et al. utilized the marker tumor concept in their study of quarter-dose BCG in patients with intermediate-risk NMIBC [26]. Their cohort included patients with primary or recurrent multiple tumors of stages pTa/T1 and grades 1 to 2. Intravesical treatment was initiated 2 weeks after complete TUR of all visible tumors except 1 marker lesion no larger than 1 cm. Treatment was weekly administration of quarter-dose BCG for 6 consecutive weeks. Two weeks after completion of treatment (10 weeks after initial TUR), any residual tumor was completely resected. In cases of complete response of the marker lesion, deep biopsy of the tumor area was performed. Urine cytology was also performed. The study demonstrated a complete response in 27 of 44 patients (61%). There were no cases of disease progression to muscle-invasive disease.

Gontero et al. performed a phase II trial in which they assessed the tumor ablative efficacy of intravesical gemcitabine administered weekly for 6 weeks on a single marker tumor left in place after complete TUR of all other lesions [27]. Intravesical gemcitabine was started within 15 days of the TUR. Patients underwent TUR or biopsy at the site of the marker lesion 2 weeks after completion of treatment (10 weeks after baseline TUR). The study demonstrated a 56% complete response rate (22 of 39 subjects), with no instances of disease progression to muscle invasion or development of CIS.

These studies illustrate the feasibility and rationale for evaluating the efficacy of investigational agents in phase II marker lesion studies before expanding the evaluation to larger studies.

3.5 Rationale for this Study

Rationale for this study includes the following:

1) This proposed study targets patients with high-risk NMIBC (clinical stage Ta) who have failed or relapsed after intravesical BCG therapy. These patients have a significant risk of recurrence, approximately 61% at 1 year and 78% at 5 years .
2) Diagnosis and treatment of recurrent NMIBC requires frequent visits and invasive procedures (cystoscopy, TUR).
3) Mutation of *FGFR3* occurs in approximately 50-70% of NMIBC tumors, with highest frequency in low-grade non-invasive tumors and lower frequency in high-grade and invasive tumors. .

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is an open-label, pilot study of the FGFR inhibitor BGJ398 in patients with *FGFR3* mutant NMIBC which has recurred despite prior intravesical treatment with at least one induction course of BCG. The purpose of the study design is to evaluate the efficacy and safety of BGJ398 in patients with recurrent NMIBC using complete response rate of a marker lesion at 7 weeks as a primary endpoint.

The planned accrual goal is 15 *FGFR3* mutant patients. Pre-treatment or archival tumor tissue will be tested in CLIA-certified laboratories. In order to identify 15 eligible *FGFR3* mutant patients in our study cohort of patients with recurrent high-risk NMIBC after at least one induction course of intravesical BCG therapy, we estimate that approximately 75 patients will need to be screened for *FGFR3* mutation status.

4.1.1 Proposed Correlative Studies

Molecular profiling of pre-treatment tumor specimens will be performed using the MSK-IMPACT assay to examine alterations in cancer-related genes, particularly *FGFR3*. These results will be used in the evaluation of the primary endpoint of BGJ398 activity (as measured by complete response of the marker lesion at 7 weeks) in *FGFR3* mutant tumors. Additionally, the exploratory endpoint of determination of associations of BGJ398 response with non-*FGFR3* co-mutations will utilize the MSK-IMPACT results.

Immunohistochemical staining for FGFR3 expression will be performed in the MSKCC Department of Pathology. The stains will be evaluated by a pathologist specializing in GU malignancies. These results will be used in the evaluation of the exploratory objective of determining the associations of BGJ398 response with intensity and localization of FGFR3 immunohistochemical staining.

As an exploratory objective, blood and urine samples will be collected to evaluate circulating tumor DNA and urine DNA sampling for the detection and monitoring of NMIBC. We will compare mutations detected in circulating DNA and DNA isolated from urine to the ones detected in the tumor using Fisher‘s exact test. This will be analyzed in all patients.

The pharmacokinetics of BGJ398 in blood, urine, and bladder tissue will be evaluated as an exploratory objective. The measurement of BGJ398 in these specimens will be evaluated. The association of drug level and anti-tumor activity will be evaluated in an exploratory fashion.

4.2 Intervention

BGJ398 will be administered at a dose of 125 mg orally once daily on a three weeks on, one week off schedule. Intra-patient dose reduction may be required depending on the type and severity of

the individual toxicity encountered. Evaluation of tumor response with cystoscopy and cytology will occur during week 7 (C2 Week 3, up to and including D22). If patients demonstrate a complete response to therapy, they will have the option of continue BGJ398 for up to 11 months as long as they are tolerating therapy and remain free of disease recurrence or progression. All patients who achieve a complete response and discontinue treatment will then be followed for recurrence or progression according to standard of care.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Investigational Drug Description

BGJ398 is an orally bioavailable, selective, and ATP-competitive pan-fibroblast growth factor receptor (FGFR) kinase inhibitor

The drug product is a hard gelatin capsule for oral administration. The formulation has been optimized from a direct powder blend in a capsule (initial clinical service form) to a granule/powder blend in a capsule to achieve the desired process properties and capsule characteristics. The capsule fills are composed of the drug substance and commonly used excipients for solid oral dosage forms such as mannitol, lactose monohydrate, microcrystalline cellulose, polyvinylpolypyrrolidone, hypromellose, croscarmellose sodium (only in initial clinical service form), colloidal silicon dioxide, and magnesium stearate.

5.2 Drug Dispensing / Administration

Administration will be performed on an outpatient basis. BGJ398 will be dispensed as capsules at the beginning of each treatment cycle. In case of dose modification, patients may be asked to return all of their previously dispensed medication to the clinic and they may be dispensed new-strength capsules. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded.

BGJ398 will be provided by Novartis as 25 mg and 100 mg hard gelatin capsules for oral administration, packaged in bottles.

Medication labels will comply with US legal requirements and will be printed in English. Medication will be labeled for Clinical Trial use and will include storage conditions for the drug and the medication number.

Table 5-1 Packaging and Labeling

Study Drug	Packaging	Labeling
BGJ398	Hard gelatin capsules in bottles (25mg, 100mg)	Labeled as ‖BGJ398‖

5.3 Storage and Stability

BGJ398 hard gelatin capsules are packaged in white HDPE (high density polyethylene) bottles with aluminum induction seal and child-resistant screw cap closure. Based on current stability data, unopened bottles are to be stored between 2 and 8°C. Once opened, bottles are stored unrefrigerated but below 25°C to avoid potential problems related to condensation due to differences in temperature after having removed the aluminum seal. As further stability data becomes available, storage conditions may be adapted accordingly.

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.

Patients will be provided with adequate supply of BGJ398 for self-administration at home until their next scheduled study visit.

5.4 Source of Drug

Novartis, Inc. will supply BGJ398 free of charge.

5.5 Drug Accountability

All study drug supplies must be kept in a locked room with limited access. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinic, or allow supplies to be used other than directed by this protocol without prior authorization from Novartis , Inc.

The pharmacist will maintain a complete drug accountability record for each tablet strength with lot numbers of each drug received, including the number of bottles dispensed to each patient, the dates drug was dispensed, and the daily dose of BGJ398 the patient received. The prescribed dose should also be recorded in the patient‘s medical records.

At the conclusion of the study, and, as appropriate during the course of the study, all used and unused study drug, packaging, and drug labels will be destroyed as per prior agreement with Novartis. A copy of the completed drug accountability ledger will be returned to Novartis.

5.6 Drug Disposal and Destruction

The drug supply will be destroyed at a Novartis facility, or Novartis will provide guidelines for destruction, if investigational site is approved to destroy drug per prior agreement with Novartis.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Recurrent high-risk non-muscle-invasive bladder cancer after prior intravesical BCG therapy meeting all of the following criteria:
    - Histologically documented diagnosis of urothelial carcinoma confirmed by the Department of Pathology at MSKCC.
    - Documentation of activating *FGFR3* mutation or gene fusion on an assay performed in a CLIA-certified laboratory.
    - History of high-grade non-muscle-invasive bladder cancer (NMIBC).
    - Clinical evidence of high-grade, stage pTa NMIBC.
    - Prior intravesical therapy with at least one induction course of BCG.
    - Multiple papillary lesions with at least one amenable to marker tumor study (≤1 cm, non-invasive; or could be partially resected to leave a non-invasive lesion ≤1 cm) OR solitary papillary lesion amenable to marker tumor study (≤1 cm, non-invasive).
- Patient must be willing to consent to MSKCC protocol 12-245 (—Tumor Genomic Profiling in Patients Evaluated for Targeted Cancer Therapy‖)
- Age 18 years or older.
- Patient must be willing and able to comply with scheduled visits, treatment plan, and laboratory tests.
- Patient must be able to swallow and retain oral medication.
- Karnofsky performance status of ≥80.
- Recovery from adverse events of previous systemic anti-cancer therapies to baseline or grade 1, except for:

- Alopecia
- Stable neuropathy of ≤ grade 2 due to prior cancer therapy

- Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must agree to use highly effective methods of contraception during dosing and for 3 months following the discontinuation of study treatment.
  Highly effective contraception methods include:
  - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
  - Male sterilization (at least 6 months prior to screening). For female subjects the vasectomized male partner should be the sole partner.
  - Combination of any two of the following (a+b, a+c, or b+c):
    a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%); for example, hormone vaginal ring or transdermal hormone contraception.
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/ vault caps) with spermicidal foam/ gel/film/cream/ vaginal suppository.

  Oral contraceptives (OC), injected or implanted hormonal methods are not allowed as the sole method of contraception because BGJ398 has not been characterized with respect to the potential to interfere with PK and/or the effectiveness of OCs.
- If a woman is of non-childbearing potential, she must either:
  - Be post-menopausal as defined by 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), OR
  - Have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, the reproductive status of the woman must be confirmed by follow-up hormone level assessment.
- Sexually active males must use a condom during intercourse while taking drug and for three months after the last dose of the study drug. They should not father a child during this period. Men who have undergone vasectomy are also required to use a condom during interco urse to prevent delivery of the drug via seminal fluid.

6.2 Subject Exclusion Criteria

Patients eligible for this study must not meet **any** of the following criteria:

- Clinical suspicion of active CIS.
- Evidence of >1 area of CIS not associated with papillary tumor at this time.
- Evidence of >7 tumors present in the bladder.
- History or evidence of advanced urothelial carcinoma, including enlarged lymph nodes and/or distant metastases.
- Evidence of upper tract urothelial carcinoma.
- History of another primary malignancy within the last 3 years except:
  - Adequately treated in situ carcinoma of the cervix
  - Non-melanoma carcinoma of the skin
  - Any other curatively treated malignancy that has not been treated in the prior 3 months and is not expected to require treatment for recurrence during the course of the study.

- Patients who received prior treatment with a selective FGFR inhibitor.
- Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BGJ398 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
- History and/or current evidence of tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium, and lung with the exception of calcified lymph nodes and asymptomatic vascular calcification.
- Current evidence of endocrine alterations of calcium/phosphate homeostasis, e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis, etc.
- Use of medications that increase serum levels of phosphorus and/or calcium (e.g., calcium, phosphate, vitamin D, parathyroid hormone; see Section 9.3.2).
- Current evidence of corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, corneal abrasion, inflammation/ulceration, and/or keratoconjunctivitis, confirmed by ophthalmologic examination
- Treatment with any of the following anti-cancer therapies prior to the first dose of BGJ398 within the stated timeframes:
    - Cyclical chemotherapy (intravenous) within a period of time that is shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C).
    - Biological therapy (e.g., antibodies – including bevacizumab) within a period of time that is ≤ 5 half-lives or ≤ 4 weeks, whichever is shorter, prior to starting study drug.
    - Continuous or intermittent small molecule therapeutics within a period of time that is ≤ 5 half-lives or ≤ 4 weeks (whichever is shorter) prior to starting study drug.
    - Any other investigational agents within a period of time that is ≤ 5 half-lives or less than the cycle length used for that treatment or ≤ 4 weeks (whichever is shortest) prior to starting study drug.
    - Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug.
- Patients who are currently receiving treatment with agents that are known strong inducers or inhibitors of CYP3A4 (see Section 9.3.2. and Appendix B).
- Consumption of grapefruit, grapefruit juice, grapefruit hybrids, pomelos, pomegranates, star fruits, Seville oranges or related products within 7 days prior to first dose
- Use of herbal preparations/medications (including, but not limited to: St. John‘s wort, Kava, ephedra (ma huang), gingko bilboa, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng; see Section 9.3.2) within 7 days prior to first dose.
- Use of medications that are known to prolong the QT interval and/or are associated with a risk of Torsades de Pointes 7 days prior to first dose (see Appendix B).
- Use of amiodarone within 90 days prior to first dose.
- Current use of therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulants. Heparin and/or low molecular weight heparins are allowed.
- Insufficient bone marrow function as evidenced by:
    - ANC <1,000/mm^3 [1.0 x 10^9/L]
    - Platelets < 75,000/mm^3 [75 x 10^9/L]
    - Hemoglobin < 10.0 g/dL
- Insufficient hepatic and renal function as evidenced by:
    - Total bilirubin > 1.5x ULN
    - AST/SGOT and ALT/SGPT > 2x ULN
    - Serum creatinine > 1.5x ULN
    - Calculated (using the CKD-EPI equation) or measured creatinine clearance < 75% LLN
- Calcium-phosphate homeostasis as evidenced by:
    - Inorganic Phosphorus outside of normal limits
    - Total serum calcium (can be corrected) outside of normal limits
- Clinically significant cardiac disease including any of the following:
    - Congestive heart failure requiring treatment (NYHA grade ≥ 2)
    - LVEF < 50 as determined by MUGA scan or ECHO

- Uncontrolled hypertension (refer to WHO-ISH guidelines [31])
- History or presence of clinically significant ventricular arrhythmias, atrial fibrillation, resting bradycardia, or conduction abnormality
- Unstable angina pectoris or acute myocardial infarction ≤ 3 months prior to starting study drug
- QTcF > 480 msec (males and females)
- History of congenital long QT syndrome

- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the end of gestation, confirmed by a positive hCG laboratory test.
- Known positive serology for HIV, active Hepatitis B, and/or active Hepatitis C infection.

7.0 RECRUITMENT PLAN

Patients found to have recurrent non-muscle invasive bladder cancer will be approached . Patients will be recruited from the outpatient clinics of the Urology Service and the Medical Oncology Service at MSKCC. Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, and/or the research team. The patient's medical records will be screened for suitability. The potential for enrolling in the research study will be discussed with the patient. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. The patient's conversations with the investigator/research staff and portions of the patient's MSKCC medical records will be used to confirm that the patient is eligible for study participation.

8.0 PRETREATMENT EVALUATION

The following will be completed within 30 days prior to enrollment to determine eligibility (unless otherwise indicated):

- **Vital signs**

Vital sign assessment consists of height, pulse, blood pressure, respiration rate, temperature, and weight.

- **Physical examination**

Physical examination will be performed which must comprise a total body examination

- **Karnofsky performance status**

Performance status (Appendix A) will be assessed at screening and per the visit schedule (Table 10-1).

- **Pregnancy test**

A serum pregnancy test (β-HCG) is required for all women of child-bearing potential (WOCBP) at screening, within 14 days of enrollment. Note: See Section 6.1 for definitions and additional information. Additional pregnancy tests should be performed as clinically indicated.

- **Serum Chemistry**

Serum Chemistry includes the following parameters:

  - Comprehensive metabolic panel with conjugated bilirubin (urea or blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, glucose, bicarbonate, albumin, total protein, total bilirubin (direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT))
  - Phosphorus
  - Ionized calcium
  - Amylase, lipase

- **Hematology**

Hematology includes the following parameters: complete blood count (CBC) consisting of red blood cell (RBCs), a total white blood cell count (WBC) with differential (total neutrophil count including bands, lymphocyte, monocyte, eosinophil, and basophil counts); hemoglobin (Hgb); and platelet count.

- **Urinalysis**

Urinalysis includes macroscopic (protein, glucose, ketones, blood, and specific gravity). A microscopic (WBC/hpf, RBC/hpf, and any additional findings) exam need only be performed if the urinalysis result is abnormal.

- **Ophthalmologic Evaluation**

At screening, an ophthalmologic examination including slit lamp examination of the anterior eye segment, intraocular pressure (IOP), and fundoscopy will be performed. Additional examination methods such as specular microscopy to enable a direct magnified view of the corneal epithelium, corneal pachymetry, and dilated fundoscopy should be performed as clinically indicated.

- **ECG**

A standard 12 lead ECG is to be performed and significant findings must be recorded.

- **ECHO/MUGA**

An echocardiogram or MUGA will be performed.

- **Chest X-ray**

A chest x-ray will be performed. A CT chest may be performed instead if clinically relevant.

- **Radiologic Assessment**

A CT urogram or MR urogram will be performed at screening to assess for evidence of advanced disease or upper tract urothelial carcinoma.

9.0 TREATMENT/INTERVENTION PLAN

9.1 Transurethral Resection with Marker Lesion

Transurethral resection (TUR) will be performed by an Investigator according to standard practice, with the exception that a suitable marker lesion (papillary, ≤1.0 cm, non-invasive appearance) will be left unresected. This lesion will be photographed and its size (e.g., estimated in relation to the 0.8 cm resectoscope loop) and location will be documented. Post-TUR management will be conducted according to the standard of care.

Within 7 days of a finalized pathology report confirming non-invasive disease from the study TUR, the patient will start treatment with BGJ398. If invasive disease is discovered, the patient will be taken off protocol and will undergo standard-of-care re-resection which would be performed for an invasive bladder cancer.

If the patient has a solitary papillary lesion amenable to a marker tumor study (papillary, ≤1.0 cm, appears non-invasive) and has archival pathologic material available for profiling with MSK-IMPACT and immunohistochemistry, the TUR may be omitted [15]. The lesion will be photographed and its size (e.g., estimated in relation to a 0.2 cm Bugbee electrode) and location will be documented.

Pre-treatment tumor tissue (either from study TUR or archival material) will be collected for profiling with MSK-IMPACT, immunohistochemistry, and other possible profiling.

9.2 Treatment with BGJ398

The investigational drug will be BGJ398 as an oral formulation. The investigator will instruct the patient to take the study drug as per protocol. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded appropriately.

9.2.1 Administration

BGJ398 will be taken once daily on a three weeks on, one week off schedule. BGJ398 will be dosed orally on a flat dosing scale of mg/day, irrespective of size and weight.

Table 9-1 Treatment and Treatment Schedule

Study treatment	Pharmaceutical form and route of administration	Dose	Frequency and/or regimen
BGJ398	Capsule for oral use	125 mg (administered as one 100 mg capsule and one 25 mg capsule)	Daily (3 weeks on, 1 week off schedule in 28-day cycles)

9.2.2 Instructions for Administration of BGJ398

The following general guidelines should be followed for BGJ398 administration:

- Patients should be instructed to take the daily dose of BGJ398 in the morning, at approximately the same time each day.
- Phosphate binding therapy such as sevelamer hydrochloride should be taken as indicated in Section 9.3.1.1.
- Patients should consume a light breakfast each day (e.g., non-grapefruit-based juice, toast and jam), including days which involve pharmacokinetic blood sampling. 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.
- Patients will be provided with a pill diary to record their dosing. Patients will be instructed (during both protocol teaching and via a printed instruction on the diary) to notify their study doctor if they skip or delay a dose.
- On the days of PK sampling, the patients should take their doses at the investigative site where the administration of BGJ398 will be supervised and administration time recorded.
- BGJ398 should be taken at least 1 hour before or 2 hours after a meal.
- If vomiting occurs following the dosing of study drug, re-dosing is not permitted that same day. Dosing should resume the next day. If the vomiting occurs on full PK sampling days within the first 4 hours post-dosing, this event needs to be noted appropriately.
- 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), H_2-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 grapefruits, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or juice within 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.
- If a patient is required to be NPO for a procedure, the patient will hold BGJ398.
- For cycle 2 week 3 cystoscopic biopsy, patients will take BGJ398 that morning, and the time of drug administration will be noted.

9.2.3 Dose Modification and Dose Delay

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. The following guidelines need to be applied:

- These changes must be recorded appropriately.

- All dose modifications should be based on the worst preceding toxicity.
- Following resolution of toxicity to baseline or ≤ grade 1, treatment is resumed at either the same or lower dose of study drug as per the criteria in Table 9-3. If treatment is resumed at the same dose of study drug, and the same toxicity recurs with the same or worse severity regardless of duration, the dose must be reduced to the next lower dose level. If treatment is resumed at the lower dose of study drug and the same toxicity recurs with the same or worse severity, the patient must discontinue study treatment.
- 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.
- Patients who discontinue the study for a study-related adverse event or an abnormal laboratory value must be followed as described in Table 9-3.

Table 9-2 Dose Reduction Table

Dose Reduction			
	Starting dose level 0	**Dose level -1**	**Dose level -2**
BGJ398	125 mg	100 mg	75 mg

A third or subsequent reduction (to 50 mg) in dose may be allowed if the patient is clearly benefiting from study treatment (i.e., partial response or complete response) but is experiencing adverse events that prevent continued treatment at the already reduced dose.

Table 9-3 Recommended Dose Modifications for BGJ398 Treatment

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**Recommended Dose Modifications any time during a cycle of therapy**
Cardiac Disorders	
Cardiac - Prolonged QTcF interval	
Grade 1: QTcF ≥ 450 msec and ≤ 480 msec (asymptomatic)	Maintain dose level of BGJ398 ECG (Electrocardiogram) 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 ≥ 450 msec and ≤480 msec), then ECG monitoring must continue at the same frequency as in cycle 1 for all subsequent cycles.
Grade 2 and 3: QTcF ≥ 481 msec 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.

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
	Once the QTcF prolongation has resolved and if the QTcF prolongation was confirmed by Cardiology at MSKCC, patients may be re-treated at one lower dose level at the investigator's discretion • ECG assessments should be performed for 2 additional cycles at the same frequency as in cycle 1 or as clinically indicated 1. If ECG assessments show no QTcF ≥ 450 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule. 2. If ECG assessments are still abnormal (QTcF ≥ 450 msec and ≤480 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 ≥ 481 msec 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 > 500msec is observed, a plasma sample for determination of BGJ398 concentration should be obtained with the time of sample collection noted.
Cardiac Disorders – Others	
Clinically significant and symptomatic Grade ≥ 2, not present at baseline	Discontinue patient from study treatment.
Investigations – Hematology	
ANC decreased (Neutropenia)	
Grade 2 (ANC < 1.5 – 1.0 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.
Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	Hold dose of BGJ398 until resolved to CTCAE ≤ Grade 1, ↓ 1 dose level of BGJ398.
Grade 4 (ANC < 0.5 x 10^9/L)	Discontinue patient from study treatment.
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)	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.
Grade 4	Discontinue patient from study treatment.
Hemoglobin	
Grade 2 (< 10.0 – 8.0 g/dL)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline, then maintain dose level.

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Grade 3 (< 8.0 g/dL – 6.5 g/dL)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level.
Grade 4 (< 6.5 g/dL)	Discontinue patient from study treatment.
Platelet Count Decreased (Thrombocytopenia)	
Grade 2 (PLT < 75 – 50 x 10^9/L) without bleeding	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 2 (PLT < 75 – 50 x 10^9/L) with bleeding, or Grade 3 (PLT < 50 – 25 x 10^9/L without bleeding)	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level.
Grade 3 (PLT < 50 - 25 x 10^9/L) with bleeding, or Grade 4 (PLT < 25 x 10^9/L)	Discontinue patient from study treatment.
Investigations – Renal	
Serum Creatinine	• If serum creatinine CTCAE Grade ≥ 2 has been demonstrated in conjunction with hyperphosphatemia, serum creatinine levels must be repeated at least weekly until resolution. 24-hour urine collection should be obtained as clinically indicated for total phosphate, calcium, protein, and creatinine clearance. Ultrasound examination of the kidneys should be performed as indicated to evaluate *de-novo* calcifications until resolution or stabilization of creatinine.
Grade 2 (> 1.5 - 3.0 x ULN)	Hold dose of BGJ398 until resolved to Grade ≤1 or baseline: • If resolved within ≤ 7 days, maintain dose level of BGJ398. • If resolved within > 7 days, ↓ 1 dose level of BGJ398.
Grade ≥ 3 (> 3.0 x ULN)	Discontinue patient from study treatment.
Investigations – Hepatic	
Blood Bilirubin (in patients with Gilbert Syndrome, these dose modifications apply to changes in direct bilirubin only)	
Grade 1 (> ULN – 1.5 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.
Grade ≥ 2 (>1.5 – 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 2 (> 3.0 – 5.0 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 ≥ 3 (> 5.0 - 20.0 x ULN) without bilirubin elevation > 2.0 x ULN	Discontinue patient from study treatment.

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
AST or ALT and Bilirubin	
AST or ALT > 1.5 – 3.0 x ULN and total bilirubin > 2.0 x ULN	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 > 3.0 – 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	
Grade 2 (> 1.5 – 2.0 x ULN)	• Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1 • ↓ 1 dose level of BGJ398.
Grade 3 (> 2.0 - 5.0 x ULN)	For any grade 3 asymptomatic lipase or amylase elevation, drug should be held and continuation of therapy should be discussed with the Principal Investigator following resolution to ≤ grade 1. Note*:* A CT scan or other imaging study to assess the pancreas, liver, and gallbladder should be performed as clinically indicated within 1 week of the first occurrence of any CTCAE ≥ Grade 3 amylase and/or lipase.
Hyperphosphatemia	
Serum phosphorus > 5.5 – 7.0 mg/dL	Maintain dose level of BGJ398 and optimize phosphate lowering therapy as clinically indicated.
Serum phosphorus > 7.0 mg/dL for more than 7 days despite maximal phosphate lowering therapy (Sevelamer), **Or**, Single serum phosphorus > 9.0 mg/dL regardless of duration or dose of phosphate lowering therapy (Sevelamer). (Optimize/maximize dose and schedule of phosphate lowering therapy in accordance with package insert, country or institutional guidelines.)	Hold BGJ398 dose until resolved to serum phosphorus ≤ 5.5 mg/dL: Restart BGJ398 at the same dose level with maximal phosphate binder dosing if the patient did not receive maximal phosphate binder dosing for serum phosphorus > 7.0 mg/dL for > 7 days. Reduce one dose level of BGJ398 if the patient had received maximal phosphate lowering therapy for serum phosphorus > 7.0 mg/dL for > 7 days **or** if patient had a one-time serum phosphorus of > 9.0 mg/dL. Restart BGJ398 with maximal phosphate binder dosing. It is recommended that phosphate binder dosing continues during BGJ398 dose interruptions for hyperphosphatemia and that serum phosphorus values be monitored frequently, e.g. every 2-3 days. Phosphate binder dosing should be held during the week off BGJ398 therapy each cycle (Days 22-28) and during BGJ398 dose interruptions for non-hyperphosphatemia adverse events.
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.

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
	• If resolved > 7 days after suspending BGJ398, ↓ 1 dose level.
Serum calcium ≥ Grade 3	Discontinue patient from the study treatment.
Nervous System Disorders	
Neurotoxicity	
Grade 2	Hold 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	Discontinue patient from study drug treatment.
Diarrhea	
Grade 1	Maintain dose level of BGJ398, but initiate anti-diarrheal treatment. Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools, or overt diarrhea
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.
Vomiting	
Grade 2	Hold BGJ398 dose until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398.
≥ Grade 3	Discontinue patient from study treatment.
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 other eye disorders	Discontinue patient from study treatment.
Other Ocular/Visual Toxicity	
≥ Grade 2	Hold BGJ398 until resolution to ≤ grade 1 • If resolution in ≤14 days, ↓ 1 dose level, otherwise discontinue BGJ398.
General Disorders	
Fatigue	

Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Grade 2	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 Possibly, Probably, or Definitely Related to BGJ398 Therapy	
Grade 2	Hold dose of BGJ398 until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398.
≥ Grade 3	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 unless they meet the criteria specified in Section 9.2.3. 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 discontinued.	

9.2.4 Maximal Drug-Related Toxicity Allowable For Continuation of BGJ398 Through Cycles 3-11

Patients who experience a complete response at week 7 will be given the option to continue treatment with BGJ398 for Cycles 3-11 if their maximal drug-related toxicity is ≤ Grade 2. Patients who experienced Grade 3 neutropenia, Grade 3 febrile neutropenia, Grade 3 anemia, Grade 3 thrombocytopenia without bleeding, Grade 3 diarrhea, Grade 3 retinal disorders, Grade 3 eye disorders, and Grade 3 fatigue may also be given the option to continue treatment with BGJ398 for Cycles 3-11, at the Investigator's discretion.

9.3 Concomitant Therapy

The patient must notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including herbal/natural medications and blood transfusions) administered during the study must be documented.

9.3.1 Ancillary Treatments

9.3.1.1 Phosphate-Lowering Therapy

Phosphate-lowering treatment, including low phosphate diet and phosphate binding therapy, such as sevelamer hydrochloride, should be implemented prophylactically at study drug initiation and modified as clinically indicated throughout BGJ398 administration. Recommendations for treatment are provided in Table 9-3, but should be modified as per country or institutional practice.

9.3.1.2 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 Torsades de Pointes, and therefore need to be used with caution. Aprepitant is both a sensitive

substrate and a moderate CYP 3A4 inhibitor and can be used with caution if an alternative is not available.

9.3.1.3 Hematopoietic Growth Factors

Prophylactic use of recombinant hematopoietic growth factors (e.g., G-CSF and related analogues, erythropoietin alfa and related analogues) should not be used during Cycle 1. However, they are allowed during future cycles for prophylaxis of neutropenia and treatment of anemia if deemed medically appropriate or if, in the opinion of the investigator, failure to do so could compromise the patient's ability to remain in the study. Patients receiving erythropoietin alfa or related analogues at time of enrollment may continue therapy with initiation of Cycle 1 of treatment.

9.3.2 Permitted Concomitant Therapy Requiring Caution and/or Action

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 (molecular transport protein).

Corticosteroids

Chronic dosing of systemic 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 CYP 3A4 and has the potential to increase the systemic exposure of corticosteroids that are metabolized by CYP3A4.

Systemic corticosteroid treatment can be used with caution.

CYP Substrate s and Inhibitors

BGJ398 was shown to inhibit the cytochrome p450 isoenzyme CYP 3A4 in *in-vitro* assays, thus, suggesting an increased risk of drug interactions with concomitant medications that are metabolized by CYP3A 4. However, such interactions have not been confirmed in patients. Therefore, investigators may administer medications that are known to be metabolized by CYP3A4 (see Appendix B). Patients must be monitored for potentiation of toxicity and may require dose titration or reduction of the CYP 3A4 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 with caution. Please refer to the following website http://medicine.iupui.edu/clinpharm/DDIs/main-table/ for a more complete list of the substrates of CYP 3A4.

Caution is advis ed when BGJ398 is co-administered with opioid analgesics. Inhibition of opioid metabolism by CYP 3A4 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 CYP 3A4 substrate with narrow therapeutic window, should be full avoided whenever possible. The use of methadone and levomethadyl is prohibited. Please note that the list might not be comprehensive.

Hormonal contraceptives may be affected by cytochrome P450 interactions and are therefore not considered effective for this study. Highly effective contraception should be maintained throughout the study.

BGJ398 is a substrate of CYP 3A4. Therefore moderate inhibitors and inducers should be used with caution if no other alternative is available.

Transporter Substrate s

In vitro data show that BGJ398 is an inhibitor of BCRP. In the absence of data confirming whether such interactions occurs in patients receiving such medications must be monitored for potential toxicity and may require dose titration or reduction of the medication.

QT/QTc Interval Prolongation or Torsades de Pointe s Medications

Medications that have the potential to prolong the QT/QTc interval or induce torsade de pointes are allowed with caution (see Appendix B). Investigators at their discretion may co-administer such medications, as listed below, but patients should be carefully monitored.

a. Class IA antiarrhythmics (e.g., quinidine, procainamide, disopyramide)
b. Class III antiarrhythmics (e.g., amiodarone, sotalol, ibutilide)
c. Class 1C antiarrhythmics (e.g., flecainide, propafenone)
d. Antipsychotics (e.g., chlorpromazine, pimozide, haloperidol, droperidol)
e. Antidepressants (e.g., fluoxetine, venlafaxine, tricyclic/tetracyclic antidepressants e.g. amitriptyline, imipramine, maprotiline)
f. Opioids (e.g., methadone)
g. Macrolide antibiotics & analogues
h. Quinolone antibiotics (e.g., moxifloxacin, gatifloxacin)
i. Pentamidine
j. Antimalarials (e.g., quinine)
k. Azole antifungals (e.g., voriconazole)
l. Domperidone
m. 5-HT3 antagonists (e.g., dolasetron)
n. Beta-2 adrenoceptor agonists (e.g., salmeterol, formoterol)

9.3.3 Prohibited Concomitant Therapy

Other Investigational and Antineoplastic Therapies

Other investigational therapies must not be used while the patient is on the study. Anticancer therapy (chemotherapy, biologic therapy, radiation therapy, and surgery) other than the study treatments must not be given to patients while the patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from study treatment.

CYP Inhibitors

Strong inhibitors of CYP3A4, as listed below, are prohibited because BGJ398 is a likely substrate of this isoenzyme (see Appendix B). Caution should be used during administration of moderate inhibitors. Please note that this list may not be comprehensive. In addition, the following food products are prohibited: Seville oranges or juice, grapefruit, grapefruit juice, grapefruit hybrids, and pomelos.

a. Anti-fungal agents: Ketoconazole, itraconazole, fluconazole
b. Anti-retroviral agents: Ritonavir, nelfinavir, indinavir, saquinavir, amprenavir, atazanavir, fosamprenavir
c. Anti-biotic agents: Clarithromycin, telithromycin, erythromycin
d. Others: Aprepitant, diltiazem, verapamil, nefazodone, grapefruit juice

Patients on strong or moderate CYP 3A4 inducers or inhibitors or medications that rely on CYP 3A4 for metabolism should switch whenever possible to a product with less interaction with/reliance on the pathway or patients should be on a stable dose of the medication prior to enrollment.

CYP Inducers

Strong inducers of CYP3A4 (see Appendix B) are prohibited because their usage would likely decrease the exposure of BGJ398. **Phosphorus and Calcium**

Medications that increase the serum levels of phosphorus and/or calcium are prohibited. Medications 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 enrollment.

Medications with a known Risk of QT/QTc interval prolongation or torsade de pointes

Preliminary data have shown that BGJ398 has no effect on cardiac conduction or ECG intervals (See current version of the BGJ398 Investigator Brochure). However, medications that are known to prolong the QT/QTc interval or induce Torsade de Pointes (Risk of TdP/QT prolongation) are prohibited. List of these medications is given in Appendix B. Please note that the list might not be comprehensive.

9.4 Study Drug Discontinuation

Patients who discontinue study treatment should be scheduled for an End of Study Visit within 14 - 28 days after discontinuing study treatment, at which time all of the ass essments listed for the End of Study Visit will be performed.

The study team must attempt to contact all patients (or a knowledgeable informant) who discontinue study treatment and refuse to return for the End of Study Visit within 28 days following the last dose of study treatment. If contact is made, safety evaluations, anti-neoplastic therapies received after discontinuation of study drug, and survival information should be assessed.

Patients whose treatment is interrupted or permanently discontinued due to a study-related adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks and subsequently at 4-week intervals until resolution or stabilization of the event or until patient starts receiving a new anti-cancer therapy, whichever comes first.

Patients whose treatment is interrupted or permanently discontinued due to any dose-limiting ocular/visual toxicity will have appropriate follow-up ophthalmologic examinations weekly until the toxicity has resolved or until the toxicity is considered to have stabilized after at least 6 months of follow-up.

If a patient requires a delay of ≥ 14 days since the last dose, the patient must be discontinued from study treatment. However, the patient will continue to be followed for toxicity as previously described.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Table 10-1 Evaluation and Visit Schedule

	Screening	Pre-Treatment Evaluations	TUR	Cycle 1[1]					Cycle 2[1]				Cycles 3-11[1]			End of Treatment Visit	Long-Term Follow Up[25]
Day of Cycle		≤30 days prior to enrollment		1[2]	8[3]	15[3]	21[3]	22	1[3]	8[3]	15[3]	W3[4]	1[3]	15[3]	W4[4]	within 14-28 days of last treatment	Every 6 months after last dose, for up 2 years
Procedure Informed Consent	X																
Vital Signs, Physical Examination		X		X	X	X	X		X	X	X		X	X		X	
Karnofsky Performance Status		X		X					X				X			X	
Serum Pregnancy Test (WOCBP)[5]		X	**As clinically indicated**														
Concomitant Medications		X		X					X				X			X	
Patient Pill Diary[6]				X					X				X				
Adverse Events[7]				X					X				X			X	
Serum Chemistry[8]		X		X	X	X	X		X	X	X		X	X		X	
Hematology[9]		X		X	X	X	X		X	X	X		X	X		X	
Ophthalmology Evaluation[10]		X				X			X				X			X	
12-lead ECG[11]		X		X	X	X			X	X	X		X	X		X	
ECHO or MUGA[12]		X							X				X				
Chest X-ray or CT Chest[13]		X															
CT or MR Urogram[14]		X															
Cystoscopic Assessment[15]	X											X			X	X	
Bladder biopsy[15]												X					
Urine cytology[15]		X										X			X	X	
Urinalysis		X															
Transurethral Resection[16, 17]			X[16]													X[17]	
BGJ398[18]				**Continuous (21 days with 7 days of rest)**									**Pt option to continue BGJ398[24]**				
Prophylactic Phosphate-lowering Therapy				**Continuous (21 days with 7 days of rest)**													
Confirmation of *FGFR3* mutation status[19]	X																
Collection of Tissue Specimen[20]			X													(X)	
MSK-IMPACT Blood Sample[21]	X																
Pharmacokinetic Blood Samples[22]							X	X				X					
Pharmacokinetic 24 Hour Urine Collection							X										
Pharmacokinetic Tissue Sample[23]												X					
Research Blood Sample		X		X					X				X			X	
Research Urine Sample		X		X					X				X			X	

	Screening	Pre-Treatment Evaluations	TUR	Cycle 1[1]					Cycle 2[1]				Cycles 3-11[1]			End of Treatment Visit	Long-Term Follow Up[25]
Day of Cycle		≤30 days prior to enrollment		1[2]	8[3]	15[3]	21[3]	22	1[3]	8[3]	15[3]	W3[4]	1[3]	15[3]	W4[4]	within 14-28 days of last treatment	Every 6 months after last dose, for up 2 years
Vital and Recurrence Status																	**X**

1 **Cycle = 28 days, Day 29 = Day 1 of next cycle.**
2 **Treatment with BGJ398 (C1D1) will begin within 7 days of finalized pathology report from TUR confirming non-invasive bladder cancer.**
3 **Evaluations on C1D8, C1D15, C1D22, C2D1, C2D8, C2D15, and D1/D15 of subsequent cycles will occur within a ± 2 day time window.**
4 **Evaluations with cystoscopy and cytology will occur any time during the third week (up to and including D22) of cycle C2 and the fourth week of cycles C5, C8, and C11.**
5 **Serum pregnancy test will be performed for all women of childbearing potential within 14 days of enrollment. Additional testing will be performed as clinically indicated.**
6 **At the start of each cycle, patients will be given a Pill Diary and asked to record the time and date of each dose of BGJ398 taken. Patient diaries are collected at the end of each cycle.**
7 **Adverse Events: Patients must be followed for adverse events from the first day of study treatment until at least 28 days after the last on-study treatment administration, or until all serious or study drug-related toxicities have resolved or are determined to be "chronic" or "stable," whichever is later. Serious adverse events should be monitored and reported as described in the protocol.**
8 **Serum Chemistry: These tests should be performed on D1, D8, D15, and D21 of cycle 1, D1 and D15 of cycle 2, and D1 of all subsequent cycles. These may be performed up to 48 hours prior to the scheduled visit.**
Serum Chemistry includes:
- **Comp with conjugated bilirubin (urea or blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, glucose, albumin, total protein, total bilirubin (direct and indirect), alkaline phosphatase, AST (SGOT), ALT (SGPT)**
- **Ionized calcium, phosphorus, amylase, lipase**

9 **Hematology includes the following parameters: complete blood count (CBC) consisting of red blood cell (RBC), a total white blood cell count (WBC) with differential (total neutrophil count including bands, lymphocyte, monocyte, eosinophil, and basophil counts), hemoglobin (Hgb), and platelet count. This should be performed on D1 and D15 of cycle 1 and cycle 2 and D1 of all subsequent cycles. These may be performed up to 48 hours prior to the scheduled visit.**
10 **Ophthalmologic evaluations include: visual acuity testing, slit lamp examination of the anterior eye segment, intraocular pressure measurement, and fundoscopy. Additional examination methods such as specular microscopy (that enables a direct, magnified view of the corneal epithelium), corneal pachymetry, and dilated fundoscopy as clinically indicated. Exams may be performed up to 48 hours prior to scheduled visit.**
11 **A standard 12 lead ECG will be performed at screening and significant findings will be recorded. Repeat ECGs will be performed at the beginning of each cycle.**
12 **An echocardiogram (ECHO) or multigated acquisition scan (MUGA) will be performed at screening and repeated as clinically indicated.**
13 **A Chest X-Ray will be performed for all patients at screening. Chest CT is an acceptable alternative.**
14 **A CT Urogram will be performed for all patients at screening. MR Urogram is an acceptable alternative.**
15 **Flexible cystoscopy (with collection of urine cytology) will be performed at screening to determine eligibility.**
Flexible cystoscopy will be performed in the third week of cycle 2 (up to and including D22) to determine marker lesion response. A cystoscopic cold cup biopsy of the bladder wall will be obtained for pharmacokinetic evaluation.
If C2W3 cystoscopy reveals an incomplete response of marker lesion or new tumors, the patient will discontinue treatment and will undergo completion TUR.
Flexible cystoscopy will be performed in the fourth week of cycles 5, 8, and 11 to evaluate evidence of disease.
If cystoscopy at the end of cycles 5, 8, or 11 reveals recurrent or progressive disease, the patient will discontinue treatment and will undergo completion TUR.
At completion of the study, or if the patient withdraws from the study, cystoscopy and cytology will be performed according to standard of care.
16 **Study TUR of all visible lesions except appropriate marker tumor (≤1.0 cm).**
If patient has a solitary recurrent papillary tumor that meets requirements of a marker tumor and prior pathologic material for tumor profiling is available, can forgo TUR.
If pathology from study TUR reveals ≥stage T1 disease or multifocal CIS, the patient will not initiate treatment with BGJ398 and undergo completion TUR.
17 **If pathology from study TUR reveals ≥stage T1 disease or multifocal CIS, the patient will not initiate treatment with BGJ398 and undergo completion TUR.**
If cystoscopy at the end of cycle 2 reveals an incomplete response of marker lesion or new tumors, the patient will discontinue treatment and will undergo completion TUR.
If cystoscopy at the end of cycles 5, 8, or 11 reveals recurrent or progressive disease, the patient will discontinue treatment and will undergo completion TUR.
If patient continues to have no evidence of disease at end of study evaluation, the patient will be followed according to standard of care.

18 BGJ398: BGJ398 will be orally self-administered, once daily in the morning, at a dose of 125 mg, on a 3 week on, 1 week off schedule. Patients will receive drug at the beginning of each cycle. The BGJ398 drug bottles (including any unused capsules) will be returned to the clinic for drug accountability at the end of each cycle. Patients who have a complete response at 7 weeks will be given the option to continue BGJ398 with q3 month evaluations for up to 11 months.

19 *FGFR3* mutation status will be tested using an assay in a CLIA-certified laboratory.

20 Pre-treatment tumor tissue specimens for all patients will be analyzed using MSK-IMPACT for *FGFR3* mutation (and potential fusion) status and immunohistochemistry for FGFR3 expression levels. All immunohistochemistry and mutation studies will be performed at MSKCC. 21 Blood for MSKCC protocol 12-245 will be collected at the time of another blood draw. This may be omitted if MSK-IMPACT testing was previously performed.

22 Blood for pharmacokinetics measurements will be collected on C1D21 (0 hr, 2 hr, 4 hr, 8 hr) and C1D22 (0 hr) and during week 3 immediately prior to the cystoscopic evaluation.

23 A small biopsy of bladder mucosa will be obtained for pharmacokinetic studies. Tissue samples will be collected in Hanks solution, weighed (if possible), and snap frozen in liquid nitrogen.

24 Only patients with a maximal drug-related toxicity of ≤ Grade 2 (with the exceptions listed in Section 9.2.4) will be given the option to continue BGJ398 for Cycles 3-11.

25 Patients will undergo long-term follow-up for up to two years after their last dose of BGJ398. Vital status and recurrence/progression status will be assessed by phone call or clinic visit every six months (+/- 1 month).

10.2 Tumor Profiling

Pre-treatment tumor specimens will be analyzed as described below. Archival specimens from initial diagnosis and post-treatment (resistant) samples may also be collected and analyzed if available.

10.2.1 Molecular Profiling of Tumors

FGFR3 mutation/fusion status will be tested usings assays in a CLIA -certified laboratory. *FGFR3* mutations and fusions will be reviewed by at least one member of a virtual molecular tumor board to determine that they represent putative activating alterations.

Molecular profiling of tumors may be performed using the MSK-IMPACT assay via MSKCC protocol 12-245, which provides full exon coverage of 410 cancer-related genes [32, 33]. This assay can be used to detect base substitutions, small indels, copy number alterations, and select gene rearrangements. Analysis of pre-treatment specimens and tissue collected from progression/recurrence resections will be performed using either clinical MSK-IMPACT via MSKCC protocol 12-245 or research MSK-IMPACT.

If patients have not previously participated in MSKCC protocol 12-245 (—Tumor Genomic Profiling in Patients Evaluated for Targeted Cancer Therapyll), they will be consented for the purpose of this study. Newly consented patients will provide a single tube of whole blood for the purposes of obtaining normal germline DNA. This sample will be collected at the time of another planned blood draw.

10.2.2 Immunohistochemical Evaluation of Tumors

FGFR3 immunohistochemistry will be performed on pre- and post-treatment (resistant) tumors. Stain in the tumor cells will be designated as nuclear, cytoplasmic, and/or membranous. Intensity of the stain will be scored as absent (negative), weak, weak-moderate, moderate, or strong based on previously reported scoring systems [11, 19, 20].

10.3 Evaluation of Circulating Tumor DNA and DNA Isolated from Urine

Blood and urine will be collected as outlined in Table 10-1. Blood specimens will be processed for isolation of cell-free DNA (cfDNA). A next-generation sequencing assay will be developed and utilized to define the proportion of NMIBC patients who have detectable cfDNA in pre-treatment specimens. Furthermore, the sensitivity of cfDNA in low-grade NMIBC can be compared to high-grade NMIBC.

All patients will have additional longitudinal specimens (during treatment, during surveillance in patients with a complete response, and at the time of treatment failure in incomplete responders or complete responders who subsequently develop recurrence), so we will assess if detectability of cfDNA is associated with tumor volume and response to treatment.

Next-generation sequencing of pre-treatment urine cytology specimens from these patients will be performed in parallel. The sensitivities of the cfDNA assay and the urine-based assay on pre-treatment specimens (i.e., in patients with active NMIBC) can thus be compared.

10.4 Pharmacokinetics Measurements

Samples for pharmacokinetics (PK) evaluation (blood, urine, and tissue) will be collected from all enrolled patients participating in the study. Note that additional PK samples may be drawn at the discretion of the investigator as unscheduled samples. Time points of blood and tissue sample collection for PK are outlined in Tables 10-2 and 10-3, respectively. On the day of tissue sample collection, a blood sample will be drawn to measure drug concentrations of BGJ398 and its active metabolites after the morning dose of BGJ398.

10.4.1 Pharmacokinetic Blood and Tissue Sample Collection

Blood (3 mL of blood per sample) and a tissue sample (weight to be recorded if possible) will be collected for the measurement of the concentrations of BGJ398 (see Tables 10-2 and 10-3). Pharmacokinetic blood samples will be drawn as indicated in Table 10-2. At the week 7 (C2W3) cystoscopic assessment, blood will be drawn and normal bladder tissue will be sampled as indicated in Table 10-3. The tissue sample will be collected in Hanks solution, weighed (if possible) and snap frozen in liquid nitrogen.

Table 10-2 Pharmacokinetic blood collection for BGJ398

Sample number	Cycle	Day	Scheduled time points for PK only (hours)	Blood volume (mL)	Description
501	1	21	0 hr [a] (within 30 minutes prior to dose)	3	Pre-dose
502	1	21	2 hr (+/- 10 minutes)	3	Post-dose
503	1	21	4 hr (+/- 10 minutes)	3	Post-dose
504	1	21	8 hr (+/- 30 minutes)	3	Post-dose
505	1	22	0 hr [b] (+/- 60 minutes)	3	Post-dose

[a] PK samples should be taken immediately prior to the next administration of BGJ398.
[b] BGJ398 dosed on a 3 week on/1 week of schedule. No dose administration on Day 22.

Table 10-3 Blood and tissue collection for BGJ398 PK assessment

Sample number	Cycle	Week	Scheduled time points (hours)	Blood volume (mL)	Description
1	2	3	Before cystoscopy[a] (within 30 minutes before cystoscopy)	3	Plasma sample to be collected within approximately 30 minutes of tissue sample
101	2	3	During cystoscopy [b]	NA	Tissue sample

[a, b:] Study drug administration, dosing time and collection time should be accurately recorded. Weight of tumor sample should be recorded if possible.

10.4.2 Pharmacokinetic Urine Collection

A 24-hour urine collection will be obtained, after the dose on Cycle 1 Day 21. Each patient should void their bladder before drug administration and at the end of the urine collection interval. During the 24 hour collection interval, the urine portions will be pooled in a polypropylene container stored at 2 -8 °C in a refrigerator. Total urine volume will be recorded.

Table 10-4 Urine collection

Dose reference ID	Sample #	Cycle	Day	Scheduled Time Point (h)[a]	
				Start	End
12	301	1	21	0	24

[a]Scheduled time points are relative to BGJ398 ingestion

10.4.3 Pharmacokinetics Analytical Methods

Plasma concentrations of BGJ398 and its active metabolites will be measured using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay with a lower limit of quantification (LLOQ) of approximately 1.0 ng/mL. Urine and tissue concentration of BGJ398 and its metabolites will be measured by a non-validated method with a LLOQ of approximately 1 ng/mL for urine and 10 ng/g for tissue samples. Concentrations below the LLOQ will be reported as 0 ng/mL and missing samples will be labeled accordingly. Study samples may be reanalyzed at other Novartis approved facilities for the determination of long term stability or cross-check between Novartis approved laboratories. These additional investigations are not considered part of this study and, as such, the results of any such analysis will not necessarily be included in the final report.

11.0 TOXICITIES/SIDE EFFECTS

As of data cut-off date October 1, 2014, 120 patients have received at least one dose of BGJ398. Forty-three patients were enrolled to dose escalation cohorts and 77 patients to dose expansion arms. The 3 weeks on/1 week off schedule was implemented based on observations of the timing and duration of drug interruptions during Cycle 1 necessitated by episodes of hyperphosphatemia. The data indicated that the median time to drug interruption was 22 days and the median duration of the interruption was 7 days. At the time of data cutoff, 3 patients were still receiving study medication. Of the 117 patients who have discontinued from the study, 83 discontinued treatment due to progression of disease, 13 discontinued due to adverse events, 5 died while on study, 14 discontinued due to withdrawal of consent, 1 due to administrative problems, and 1 due to protocol deviation.

The treatment emergent adverse events as of the cutoff date of October 1, 2014, regardless of BGJ398 relationship, that occurred in 20% or more of patients are: increases in phosphorus levels (74%, which includes the preferred terms of hyperphosphatemia and blood phosphorus increased), constipation (40.8%), decreased appetite (40.8%), diarrhea (36.7%), stomatitis (36.7%), nausea (32.5%), fatigue (31.7%), alopecia (25.8%), asthenia (20.0%), blood creatinine increased (20.0%) and dry mouth (20.0%). Forty-five percent of patients (54/120) experienced at least one grade 3 or 4 event regardless of the relationship to BGJ398. Grade 3 or 4 events that occurred in at least 5% of patients were ALT (6.7%), AST (5.0%), and lipase increase (5.0%). Overall, most adverse events reported have been mild to moderate in severity, reversible, and unrelated to BGJ398.

Four DLTs occurred in four patients enrolled in the dose escalation part of the study. The MTD as determined by DLT was based on the following events.

• One grade 3 event of AST/ALT elevation was reported in the 100mg cohort.

• One patient enrolled to the 125 mg cohort experienced hyperphosphatemia for greater than 14 days despite adequate therapy that resulted in study drug interruption.

• Two patients enrolled to the 150 mg cohort experienced DLTs. One patient experienced grade 1 corneal toxicity. The second patient experienced grade 3 AST/ALT elevations, which led to study treatment interruption and dose reduction.

As of the sponsor‘s cutoff date of October 1, 2014, SAEs have been reported among a total of 41 patients. Ten events were reported as suspected, unexpected, serious adverse reactions (SUSARs) and resulted in the distribution of Investigator Notifications.

The events of cardiac dysfunction with left ventricular ejection fraction (LVEF) decrease occurred in two different male patients with advanced squamous NSCLC. The first patient, who received 100 mg qd of BGJ398, experienced a > 20% decrease in LVEF (66% to 42%) after receiving and responding to 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 in association with dehydration and electrolyte disturbances related to acetazolamide treatment for hyperphosphatemia. 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 months later due to progressive disease. The events of acute renal injury (grade 1 elevation of creatinine) and hypercalcemia, and secondary hypophosphatemia and hypocalcemia were associated with initial occurrences of hyperphosphatemia, which is known to be an on-target effect of BGJ398 due to the inhibition of FGF23/FGFR in the renal tubule. The latter patient received therapy for hypercalcemia which resulted in secondary hypocalcemia. The progressive hepatic failure was associated with end-stage metastatic breast cancer to liver occurring over 6 months after the last dose of study drug, though felt to be drug related due to calcification of liver metastases.

Five patients died while on study drug, and seven patients died within 28 days of their last dose of BGJ398. Eight deaths were due to progressive disease. One death was assessed by the investigator as related to study drug, as detailed below. One patient, a 74-year-old male with advanced NSCLC, died due to a suspected cardiac arrest while on study, one day after the last dose of study medication. The patient had no clinical symptoms for myocardial infarction. The investigator suspected clinical progression, but reported that in the absence of a follow up CT, the possibility of a cardiac arrest or lung embolism could not be excluded. Suspected progression of NSCLC was reported as another possible contributory factor for the event cardiac arrest. The investigator r eported that the event was suspected to be related to treatment with study medication BGJ398; the rationale for causality assessment was that the reason for the death remained unclear and therefore study drug could not be ruled out.

11.1 Toxicity Monitoring

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, regular monitoring of hematology and blood chemistry, regular measurement of vital signs, and the performance of physical examinations.

Safety and tolerability will be assessed according to the NIH/NCI CTCAE v4.0, http://ctep.cancer.gov/ protocolDevelopment/ electronic_applications/docs/ctcaev4.pdf.

Information about all adverse events, whether volunteered by the subject, discovered by invest igator questioning, or detected through physical examination, laboratory tests, or other means will be collected, recorded, and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting study drug (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Advers e events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (mild, moderate, severe or grade 1-4)
2. Its relationship to the study drug (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken; study drug dosage adjusted/tem porarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it constitutes a serious adverse event (SAE)

To ensure patient safety each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence (see Section 17.2. 1). A serious adverse event is an undesirable sign, symptom, or medical condition which:

1. Is fatal or life-threatening
2. Required or prolonged hospitalization
3. Results in persistent or significant disability/incapacity
4. Constitutes a congenital anomaly or a birth defect
5. Is medically significant, may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed above.

E vents not considered to be serious adverse advents are hospitalizations for the:

1. Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
2. Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen.
3. Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse events, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

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

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigators‘ Brochure. This information should be included in the patient informed consent and should be discussed with the patient during the study as needed.

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed as outlined in Section 9. All patients must be followed for adverse events and serious adverse events for 28 days following the last dose of BGJ938.

11.2 Calcium-Phosphate Homeostasis and Ectopic Mineralization

In preclinical studies of BGJ398 in rats and dogs, increased levels of serum phosphorus and slightly elevated serum calcium associated with ectopic mineralization of various tissues (kidney – as most sensitive organ, lung, vascular and digestive systems) were observed, also correlating with increased levels of FGF23. It is hypothesized that this toxicity may be mechanistic and specifically related to inhibition of the FGF23/FGFR/Klotho pathway. Changes in renal function parameters, including increased serum creatinine and bone remodeling, were found in rats and dogs.

Since the administration of BGJ398 at therapeutic doses is associated with hyperphosphatemia, patients with significant pre-existing ectopic calcifications (except calcified lymph nodes) and/or endocrine alteration of calcium-phosphate homeostasis, e.g. tumoral calcinosis, are currently excluded from protocol enrollment and should not be treated with BGJ398. This includes patients with significant pre-existing cardio- and cerebrovascular disease who have evidence of vascular calcifications. Medications known to increase serum phosphate and calcium levels are prohibited while taking BGJ398.

11.2.1 Management of Alterations of Calcium-Phosphate Homeostasis

At screening, patients with a history and/or current evidence of tissue calcification (with the exception of calcified lymph nodes and asymptomatic vascularvascular calcification), patients with a history and/or current evidence of endocrine alterations of calcium/phosphate homeostasis (e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis, etc .), and patients who use medications that increase serum levels of phosphorus and/or calcium will be excluded from

participation. Furthermore, patients are required to have baseline levels of inorganic phosphorus, total calcium, and ionized serum calcium within normal limits.

Serum phosphorus and calcium levels will be closely monitored while on BGJ398 treatment. Hyperphosphatemia will be carefully managed with a low phosphate diet and phosphate lowering therapy, as described in Section 9.3.1.1. These measures will be instituted prophylactically on the first day of BGJ398 treatment and the dose of phosphate binders will be titrated as clinically indicated. If necessary, BGJ398 dosing will be interrupted to allow for normalization of serum levels of phosphorus and calcium and then resumed at a lower dose. In the event of acute, severe hyperphosphatemia and clinical evidence of emerging calciphylaxis, additional phosphate lowering strategies, including hemodialysis, will be considered.

11.3 Ocular / Corneal Toxicity

Preclinical studies in rats treated with BGJ398 for four weeks revealed corneal changes, which included dose-dependent incidence of irreversible, slight corneal opacity and reversible, diffuse epithelial keratopathy at the highest dose of 10 mg/kg.

In clinical studies, at the time of the data cut off (24Sep2013) in CBGJ398X2101, three suspected ophthalmologic adverse events have been reported. In the 100mg cohort, one patient experienced visual changes during Cycle 2, discontinued drug for an unrelated reason, and was then diagnosed with bilateral serous retinal detachments which subsequently resolved. In the 150mg cohort, one patient experienced grade 1 corneal toxicity which was considered to be a DLT. An adverse event of corneal abrasion was reported during cycle 2 for a second patient enrolled to this cohort. On the same day, the patient discontinued treatment due to progressive disease.

11.3.1 Management of Ocular / Corneal Toxicity

At screening, an ophthalmologic examination including slit lamp examination of the anterior eye segment, intraocular pressure (IOP), and fundoscopy will be performed. Additional examination methods such as specular microscopy to enable a direct magnified view of the corneal endothelium, corneal pachymetry and dilated fundoscopy should be performed as clinically indicated. Patients with evidence of corneal disorder/ keratopathy, e.g., bullous/ band keratopathy, corneal abrasion, inflammation/ulceration will be excluded as described in Section 6.2.

Patients will be closely monitored for early signs of corneal changes at baseline and periodic intervals (C1D15, day 1 of every cycle thereafter, end of treatment). In patients who develop symptoms and/or complaints while on study, ophthalmologic examinations will be performed as soon as possible and repeated as clinically indicated during follow-up.

11.4 Cardiac / Arrhythmia

In preclinical studies, BGJ398 inhibited the hERG channel *in vitro* with an IC_{50} of 2.0 µM, although no effects were seen on ECG including QT/QTc interval, heart rate and arterial blood pressure in a GLP dog telemetry study following single oral gavage at BGJ398 doses of 2, 20 and 200mg/kg. Despite the absence of ECG changes in dogs, a potential for QT prolongation in humans cannot be excluded as the peak plasma concentration (C_{max}) at the highest tolerated dose in dogs which did not lead to any changes in cardiovascular parameters was one magnitude below the hERG IC_{50} of BGJ398 and its metabolite BHS697. Predicted C_{max} at pharmacologically active doses in humans approach/exceed C_{max} in dog.

Until mature clinical information becomes available, patients with pre-existing cardiac arrhythmias, conduction abnormalities, or a history of congenital long QT- syndrome and/or severe hypokalemia which cannot be corrected should not be exposed to BGJ398. Additionally, medication associated with QT/QTc interval prolongation and/or Torsades de Pointes (TdP) tachycardia should be administered with caution to patients while on treatment with BGJ398. For the reasons above, close ECG monitoring, including at predicted T_{max} time points, is required in order to assess early signs of potential delayed ventricular repolarization.

Since hypokalemia, hypomagnesaemia and hypocalcemia are known to increase the risk of dysfunction of ion channels in the myocardial cell membrane and therefore TdP tachycardia, attention

to these serum electrolytes should be applied and low serum levels normalized by oral and/or intravenous replacement therapy, accordingly.

At the time of the data cut off (24Sep13) in CBGJ398X2101, no occurrences of QTcF or QTcB >500msec have been observed and no clinically significant QTc prolongation has been reported in any patient at any dose level. There have been no reports of ventricular arrhythmias.

Two patients with lung SCC with confirmed partial responses were noted to have decreases in LVEF. In the 100mg cohort, one patient with lung SCC had an SAE/SUSAR of left ventricular dysfunction which occurred after approximately 10 months on therapy and was associated with a >20% decrease in left ventricular ejection fraction and ventricular thrombus. These events were noted at the same time as progression of the underlying lung cancer. The second patient, enrolled to the 125 mg qd dose escalation cohort, experienced a grade 3 decrease in LVEF after approximately 3.5 months. After a 14 day drug interruption, dosing resumed at 100 mg qd due to improvement in LVEF. The patient discontinued from the study approximately 2 months later due to progressive disease. Evaluation of results of echocardiograms performed in patients enrolled on CBGJ398X2101 did not reveal dose-related changes in LVEF. Patients will continue to be monitored for changes in cardiac function through monthly echocardiograms while on BGJ398 studies.

11.4.1 Management of Cardiac Events

At screening, a 12-lead electrocardiogram (ECG) and an ECHO/MUGA will be performed at the Screening Visit to assess eligibility (Section 10.0). Repeat ECGs will be performed at the beginning of every cycle and echocardiograms will be performed as clinically indicated. Please refer to Table 9-3 for the management of specific cardiac toxicities and drug dose adjustments.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

A complete response will be defined as complete disappearance of the marker lesion at the week 7 evaluation, as determined by a negative cystoscopy and cytology.

The suggested evaluation for patients with a negative cystoscopy but a positive cytology includes selective ureteral washing for cytology and transurethral resection of the prostatic urethra in addition to consideration of upper tract imaging. Patients with an isolated positive cytology but negative cystoscopy will be described as having a partial response. If the suggested evaluation demonstrates no cystoscopic or biopsy proven evidence of recurrent tumor, these patients may resume study treatment following recovery from the procedure (cycle 3 day 1).

The size of marker lesions that have not resolved by the week 7 cystoscopic evaluation will be estimated at time of completion TUR. Any persistent lesion identified at the marker lesion site during cystoscopy at 7 weeks is still considered a treatment failure regardless of its size. The size of the marker lesion will be noted for descriptive purposes. Muscosal irregularities without clinical evidence of tumor will be monitored, and biopsy of any suspicious areas may be considered.

13.0 CRITERIA FOR REMOVAL FROM STUDY

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

- Persistence of marker lesion or development of new tumors at 7 weeks or subsequent time points
- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse events
- Dose delay of > 14 days from the intended day of the next scheduled dose
- Patient decides to withdraw from the study

- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Inability of subject to comply with study requirements
- Completion of 11 months of study treatment

Patients who come off treatment for either progression or patient/investigator decision will not be removed from the study and will enter long-term follow up. Long-term follow up will include vital status and disease progression and/or recurrence status and may be assessed either by phone, record review, or during a clinic visit. Once two years of follow-up after discontinuation of treatment are complete, patients will be discontinued from the study.

14.0 BIOSTATISTICS

This is a pilot study testing the efficacy of BGJ398 as treatment for NMIBC. Fifteen *FGFR3* mutant patients will be accrued. With this sample size, we can estimate the rate of complete response within +/- 26%; this pilot study would provide preliminary evidence of activity to justify further development.

An accrual rate of 1 patient per month is anticipated with an expected accrual time of approximately 10-20 months for this study. Duration of response in patients with complete response to BGJ398 will be summarized using descriptive statistics.

To establish the safety and toxicity of BGJ398, the frequency of toxicity will be tabulated in all patients according to the NCI Common Toxicity Criteria, version 4.0.

A hypothesis-generating exploratory endpoint involves correlating outcome with intensity and localization of FGFR3 immunohistochemical staining. Patients will be categorized on the basis of FGFR3 expression levels as outlined in Section 10.2.2 and the associations of FGFR3 expression in all patients with complete response rates will be explored.

An exploratory endpoint in this trial involves the description of the co-mutation pattern in patients with recurrent NMIBC and its association with response. These results will be evaluated in all patients and presented in a purely descriptive manner.

Another additional exploratory endpoint involves the evaluation of circulating tumor DNA and urine DNA sampling for the detection and monitoring of NMIBC. We will compare mutations detected in circulating DNA and DNA isolated from urine to the ones detected in the tumor using Fisher's exact test. This will be analyzed in all patients.

The evaluation of the pharmacokinetics of BGJ398 in blood, urine, and bladder tissue samples will be performed as described in Section 10.4. Pharmacokinetic parameters for plasma will include C_{max} (maximum observed concentration after drug administration), T_{max} (time to reach C_{max}), C_{min} (trough plasma concentration), and AUC (area under the concentration-time curve from time zero to the last measureable concentration). Urine concentrations, amount in urine (based upon urine volume collected), and bladder tissue concentrations of BGJ398 and its metabolites will be measured. The ratio of bladder tissue to plasma concentrations of BGJ398 will be calculated. Exploratory comparisons will be made to historical pharmacokinetic data. Additional exploratory analyses will be conducted to identify possible relationships of pharmacokinetic parameters with response rates. These will be analyzed in all patients.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. 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. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

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 coordination of the activities of the protocol study team. The data collected for this study will be entered into the Clinical Research Database. Source documentation will be available to support the computerized patient record.

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.

16.2 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://mskweb2.mskcc.org /irb/index.htm*

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.

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: Patients will be enrolled without regard to gender or minority status.

Exclusion of Lactating or Pregnant Women: Lactating or pregnant women will be excluded from this study for safety reasons.

Inclusion of Children in Research: This protocol does not include children younger than the age of 18.

Benefits

Potential benefits of the study include reduction of the risks of recurrence and/or progression of NMIBC, potential avoidance of additional intravesical therapy, and potential avoidance of radical cystectomy. It is possible that the tumor genotyping performed in this study will provide information to the patient and/or Investigator that may be used to help inform future treatment decisions.

Risks

Potential risks to human subjects include drug-related toxicity, pain and discomfort associated with BGJ398 side effects, phlebotomy, and possible psychological discomfort from the stresses associated with participation in a clinical trial. The side effects and potential toxicities of BGJ398 are listed in Section 11. All efforts will be made to avoid any adverse events by completely reviewing patients' symptoms, providing appropriate management, and monitoring blood and other diagnostic tests. If an adverse medical event occurs, the patient will first contact the primary oncologist or the principal investigator. At nights and weekends, there is an oncology physician on call at all times. Patients may either call or come directly to the urgent care center at Memorial Hospital (or to their local emergency room) to be seen. Patients suffering serious adverse reactions must be carefully followed and all follow-up information recorded.

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations. These assessments should be performed within ±2 days of the scheduled day of assessment except for adverse events, which will be evaluated continuously through the study.

Alternatives/Options for Treatment

Patients can elect to refuse participation in this voluntary clinical study . They can elect to undergo standard-of-care management of their recurrent NMIBC, which may include additional intravesical therapy or radical cystectomy. Patients can also elect to participate in another clinical trial.

Financial Costs

Since tumor genetic testing is not considered standard of care for urothelial carcinoma, subjects will not be billed for tumor testing performed in this protocol. Participants will bear no costs directly related to the research assays.

Confidentiality

Every effort will be made to maintain patient confidentiality. Research and hospital records are confidential. Patients name or any other personally identifying information will not be used in reports or publications resulting from this study.

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 Serious Adverse Event (SAE) Reporting to Novartis

17.2.1.1 Reporting responsibility

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

17.2.1.2 Reporting procedures

The investigator must report all serious adverse events by fax 1.888.299.4565 within 24 hours to the local Novartis Clinical Safety & Epidemiology (CS&E) Department. The investigator must ensure that the report is accurate and fully completed with follow-up information and fax those to Novartis CS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. The original and the duplicate copies of the SAE form and fax confirmation sheet must be retained at the study site.

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The SAE form and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

17.2.1.3 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

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

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 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

18.1.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
3. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
4. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

18.1.2 Institutional Review Board / Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to Novartis. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

18.1.3 Discontinuation of the Study

Novartis reserves the right to discontinue support for any study under the conditions specified in the clinical trial agreement.

18.1.4 Amendments to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB. A copy of the written approval of the IRB/IEC/REB, must be sent to Novartis.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes.

18.1.5 Publication of Results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least twenty-one working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis‘ responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

18.1.6 Disclosure and Confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/ IEC/ REB. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

18.1.7 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www. wma.net/e/policy/ 17-c_e.html.

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20.0 APPENDICES

Appendix A Karnofsky Performance Status

Condition	Performance Status %	Comments
A. Able to carry on normal activity and to work. No special care is needed.	100	Normal. No complaints. No evidence of disease.
	90	Able to carry on normal activity. Minor signs or symptoms of disease.
	80	Normal activity with effort. Some signs or symptoms of disease.
B. Unable to work. Able to live at home, care for most personal needs. A varying degree of assistance is needed.	70	Care of self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs.
	50	Requires considerable assistance and frequent medical care.
C. Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled. Requires special care and assistance.
	30	Severely disabled. Hospitalization is indicated although death not imminent.
	20	Hospitalization necessary, very sick active supportive treatment necessary.
	10	Moribund. Fatal processes progressing rapidly.
	0	Dead.

Adapted from Karnofsky DA, Burchenal JH: The clinical evaluation of chemotherapeutic agents in cancer [34].

Appendix B

Table B-1 List of prohibited CYP3A inhibitors and CYP3A inducers

Strong CYP3A inhibitors	Moderate CYP3A inhibitors	Strong CYP3A inducers	Moderate CYP3A inducers
clarithromycin	amprenavir	avasimibe	bosentan
conivaptan	aprepitant	phenobarbital (barbiturates)	efavirenz
grapefruit juice	atazanavir	carbamazepine	etravirine
indinavir	cimetidine	phenobarbital	modafinil
itraconazole	ciprofloxacin	phenytoin	nafcillin
ketoconazole	darunavir	rifabutin	ritonavir
lopinavir	diltiazem	rifampin	talviraline
mibefradil	elvitegravir	St. John‘s Wort	tipranavir
nefazodone	erythromycin		
nelfinavir	fluconazole		
posaconazole	fosamprenavir		
ritonavir	suboxone		
saquinavir	tipranavir		
telithromycin	tofisopam		
voriconazole	verapamil		
Juice from Seville oranges			

This database of CYP inhibitors was compiled from the Indiana University School of Medicine‘s —Clinically Relevantǁ Table and from the University of Washington‘s Drug Interaction Database based on *in vitro* studies. Strong inhibitors are predicted to increase BGJ398 AUC > 5-fold, and moderate inhibitors are predicted to increase BGJ398 AUC ≥ 2-fold but < 5-fold.

This database of CYP inducers was compiled from the FDA’s “Guidance for Industry, Drug Interaction Studies,” the Indiana University School of Medicine’s “Clinically Relevant” Table, and from [35].

Table B-2 List of CYP450 substrates to be used with caution

CYP3A**	
alpha-dihydroergocryptine	fosamprenavir
amprenavir	genistein
aplaviroc	imatinib
aprepitant	indinavir
aprepitant	levomethadyl
atazanavir	lopinavir
atorvastatin	lovastatin
Bosentan	lumefantrine
brecanavir	lurasidone
brotizolam	maraviroc
budesonide	midazolam
buspirone	modafinil
capravirine	nafcillin
casopitant	neratinib
casopitant	nisoldipine
cimetidine	perospirone
ciprofloxacin	quetiapine
conivaptan	ridaforolimus
cyclosporine	ritonavir
darifenacin	saquinavir
darunavir	schisandra
darunavir	sildenafil
dasatinib	simvastatin
diltiazem	sphenanthera
dronedarone	talviraline
dronedarone	thioridazine
ebastine	ticagrelor
efavirenz	tipranavir
eletriptan	tipranavir
eplerenone	tofisopam
erythromycin	tolvaptan
etravirine	triazolam
everolimus	vardenafil
felodipine	verapamil
fluconazole	vicriviroc
fluticasone	

* This database of CYP substrates was compiled from the Indiana University School of Medicine‘s —Clinically Relevant‖ Table, and from [36].

** CYP3A substrates were compiled from the Indiana University School of Medicine‘s —Clinically Relevant‖ Table and supplemented by the FDA‘s —Guidance for Industry, Drug Interaction Studies‖ and the University of Washington‘s Drug Interaction Database.

References:

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/ucm2923

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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

Table B-3 List of QT prolonging drugs to be used with caution

Drug	QT risk (*)	Comment
alfuzosin	possible risk for TdP	
amantadine	possible risk for TdP	
amiptriptyline	conditional risk for TdP	
amisulpride	conditional risk for TdP	
atazanavir	possible risk for TdP	
chloral	possible risk for TdP	
ciprofloxacin	conditional risk for TdP	
clomipramine	conditional risk for TdP	
clozapine	possible risk for TdP	
desipramine	conditional risk for TdP	
diphenhydramine	conditional risk for TdP	
dolasetron	possible risk for TdP	
doxepin	conditional risk for TdP	
dronedarone	possible risk for TdP	
eribulin	possible risk for TdP	
escitalopram	possible risk for TdP	
famotidine	possible risk for TdP	
felbamate	possible risk for TdP	
fingolimod	possible risk for TdP	
fluconazole	conditional risk for TdP	
fluoxetine	conditional risk for TdP	
foscarnet	possible risk for TdP	
fosphenytoin	possible risk for TdP	
galantamine	conditional risk for TdP	
gatifloxacin	possible risk for TdP	
gemifloxacin	possible risk for TdP	
granisertron	possible risk for TdP	
hydrate	possible risk for TdP	
iloperidone	possible risk for TdP	
imipramine	conditional risk for TdP	
indapamide	possible risk for TdP	
isradipine	possible risk for TdP	
itrazonazole	conditional risk for TdP	
ketoconazole	conditional risk for TdP	
lapatinib	possible risk for TdP	
levofloxacin	possible risk for TdP	
lithium	possible risk for TdP	
moexipril	possible risk for TdP	
nicardipine	possible risk for TdP	
nilotinib	possible risk for TdP	
nortriptyline	conditional risk for TdP	
octreotide	possible risk for TdP	
ofloxacin	possible risk for TdP	Not available in the US
ondansetron	possible risk for TdP	

oxytocin	possible risk for TdP	
paliperidone	possible risk for TdP	
paroxetine	conditional risk for TdP	
pasireotide	possible risk for TdP	
protriptyline	conditional risk for TdP	
quetiapine	possible risk for TdP	
ranolazine	possible risk for TdP	
ranolazine	possible risk for TdP	
risperidone	possible risk for TdP	
ritonavir	conditional risk for TdP	
roxithromycin	possible risk for TdP	
sertindole	possible risk for TdP	
sertraline	conditional risk for TdP	
solifenacin	conditional risk for TdP	
sunitinib	possible risk for TdP	
tacrolimus	possible risk for TdP	
tamoxifen	possible risk for TdP	
telithromycin	possible risk for TdP	
tizanidine	possible risk for TdP	
trazodone	conditional risk for TdP	
trimethoprim-sulfa	conditional risk for TdP	
trimipramine	conditional risk for TdP	
vardenafil	possible risk for TdP	
venlafaxine	possible risk for TdP	
voriconazole	possible risk for TdP	
ziprasidone	possible risk for TdP	
(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT		

Table B-4 Prohibited QT prolonging drugs with risk of Torsades de Pointes

Drug	QT risk (*)	Comment
Amiodarone	known risk for TdP	Females>Males, TdP risk regarded as low
Anagrelide	known risk for TdP	
Arsenic trioxide	known risk for TdP	
Astemizole	known risk for TdP	No longer available in the U.S. CYP3A4 substrate with narrow therapeutic index.
Azithromycin	known risk for TdP	
Bepridil	known risk for TdP	No longer available in the U.S. Females>Males
Chloroquine	known risk for TdP	
Chlorpromazine	known risk for TdP	
Cisapride	known risk for TdP	No longer available in the U.S. Females>Males.
Citalopram	known risk for TdP	
Clarithromycin	known risk for TdP	
Cocaine	known risk for TdP	
Disopyramide	known risk for TdP	Females>Males
Dofetilide	known risk for TdP	
Domperidone	known risk for TdP	Not available in the US.
Dronedarone	known risk for TdP	
Droperidol	known risk for TdP	
Erythromycin	known risk for TdP	
Escitalopram	known risk for TdP	
Flecainide	known risk for TdP	
Grepafloxacin	known risk for TdP	Not available worldwide.
Halofantrine	known risk for TdP	Females>Males
Haloperidol	known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	known risk for TdP	Females>Males
Levofloxacin	known risk for TdP	
Levomethadyl	known risk for TdP	No longer available in the U.S. Sensitive CYP 3A substrate.
Mesoridazine	known risk for TdP	No longer available in the U.S.
Methadone	known risk for TdP	Females>Males
Moxifloxacin	known risk for TdP	
Ondansetron	known risk for TdP	
Pentamidine	known risk for TdP	Females>Males
Pimozide	known risk for TdP	Females>Males. Sensitive CYP 3A substrate with narrow therapeutic index
Probucol	known risk for TdP	No longer available in the U.S.
Procainamide	known risk for TdP	Oral drug no longer available in the U.S.
Quinidine	known risk for TdP	Females>Males. Sensitive CYP 3A substrate .
Sevoflurane	known risk for TdP	
Sotalol	known risk for TdP	Females>Males
Sparfloxacin	known risk for TdP	No longer available in the U.S.
Sulpiride	known risk for TdP	Not available in the U.S.
Terfenadine	known risk for TdP	No longer available in the U.S.
Thioridazine	known risk for TdP	
Vandetanib	known risk for TdP	

(*) Classification according to the Qtdrugs.org Advisory Board of the Arizona CERT
Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

Table B-5 List of BCRP substrates to be used with caution

BCRP Substrates	
rosuvastatin	simvastatin
methotrexate	topotecan
irinotecan	sulfasalazine
atorvastatin	

Table B-6 Drugs that alter the pH of the GI tract and to be used with caution

Medications which alter the pH of the GI tract[1]	
Proton-pump inhibitors (e.g. omeprazole)	Antacids
H2-antagonists (e.g., ranitidine)	

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

Appendix C Phosphorus Content of Protein-Containing Foods

Food	Common Measure	Phosphorus (mg)
Beans, Legumes, Tofu		
Beans, Kidney	1 cup	251
Beans, Lima	1 cup	209
Beans, Navy	1 cup	286
Beans, Black	1 cup	241
Beans, Refried	1 cup	217
Soybeans, Boiled	1 cup	421
Soybeans, Roasted	1 cup	624
Sunflower Seeds	1 oz	322
Tofu, Firm	100 g	76
Tofu, Soft	100 g	52
Tofu, Lite	100 g	68
Cheese/Cheese Products		
Cheese, Cheddar	1 oz	145
Cheese, Swiss	1 oz	171
Cottage Cheese, Regular	1 cup	297
Cottage Cheese, 1%	1 cup	151
Cottage Cheese, 2%	1 cup	340
Cottage Cheese, Nonfat	1 cup	151
Cheese, Cream	2 tbsp	30
Combination Foods		
Bean/Cheese Burrito, FF	2 small	180
Breakfast Biscuit, FF	1 egg/cheese/bacon	459
Cheeseburger, FF	Single w/ condiments	310
Chicken Sandwich, FF	1 sandwich	405
Fried Shrimp, FF	6 to 8 small	344
Hot Fudge Sundae	1 small	227
Morningstar Breakfast Patty	1 patty	106
Pepperoni Pizza	1 slice	222
Roast Beef Sandwich	1 sandwich	239
Sub Sandwich, FF	1 cold cuts	287
Taco, FF	Large	313
Dairy and Milk		
Buttermilk	1 cup	219
Cream Light	1 cup	192
Cream Sour	1 tbsp	32
Cream, Half and Half	1 cup	230
Cream, Heavy	1 cup	149
Milk, 2%	1 cup	232
Milk, 1%	1 cup	235
Milk, Low-Sodium	1 cup	209
Milk, Nonfat	1 cup	247
Milk, Whole	1 cup	227
Yogurt, Lowfat	4 oz	162
Yogurt, Nonfat	4 oz	177

Yogurt, Regular	4 oz	107
Fish and Seafood		
Crab, Blue	3 oz	175
Crab, Dungeness	3 oz	149
Halibut	3 oz	214
Oysters, Fried	3 oz	196
Salmon	3 oz	282
Shrimp	3 oz	116
Meats/Poultry/Egg		
Beef Liver	3 oz	392
Beef, Top Sirloin	3 oz	203
Chicken, breast	3 oz	196
Chicken, thigh	3 oz	148
Egg, Large	1 large	86
Ham	3 oz	239
Lamb Sirloin Chop	3 oz	190
Pork Loin	3 oz	146
Turkey	3 oz	210
Veal Loin	3 oz	189
Nuts/Nut Butter		
Almonds	1 oz	139
Macadamia	1 oz	56
Peanut Butter, Chunky	2 tbsp	101
Peanut Butter, Smooth	2 tbsp	118
Peanuts, Roasted	1 oz	147
Walnuts	1 oz	98
Other Sources of Phosphorus		
Beer	12 oz	43
Chocolate, Milk	1 miniature	95
Chocolate, Semi-Sweet	1 oz	37
Coffee, Brewed	1 cup	2.3
Coffee, Instant	1 tsp	4.5
Cola	12 oz	44
Soda, Lemon Lime	12 oz	0
Lemonade	1 cup	5
Root Beer	12 oz	0
Tea, Brewed	1 cup	2.4

Abbreviations: *FF*, fast food; *g*, grams; *oz*, ounce; *tbsp*, tablespoon; *tsp*, teaspoon
Adapted from: http://www.kidney.org/professionals/kdoqi/guidelines_bone/guide4.htm
Note: Considering all common sources of protein, the average phosphorus content per gram of protein is 17.8. If all dairy products, nuts, beans, and seeds are eliminated, but meats and tofu are considered, the average phosphorus content per gram of protein is 10.3.

Appendix D Clinical Laboratory Parameters Collection Plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Red blood cell count, Platelets, White blood cells, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils)
Biochemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Calcium (can be corrected), Chloride, Creatinine, Blood Urea Nitrogen (BUN), Potassium, Sodium, Magnesium, Phosphate. Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Lipid profile (Total Cholesterol, Triglycerides), Total Protein, Urea, Uric Acid, Amylase, Lipase
Urinalysis	Macroscopic Panel (Dipstick) (Blood, Glucose, Ketones, pH, Protein, Specific Gravity). Microscopic Panel (Red Blood Cells, WBC)
Coagulation	Prothrombin time (PT) or International normalized ratio [INR]), Partial thromboplastin time (PTT)
Pregnancy Test	Serum hCG at screening; EOT and other times points serum hCG or urine