Study Title:	**Phase IIa study of the efficacy of BGJ398 (infigratinib) in FGFR1-3 translocated, mutated, or amplified squamous cell carcinoma of the head and neck**
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This study is being conducted by institutional members of the Personalized Cancer Care Consortium (PCCC), as well as additional sites.

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List of abbreviations

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
BCRP	Breast cancer resistance protein
BID	bis in diem/twice a day
CK	Creatine Phosphokinase
Cmax	Maximum (peak) concentration of drug
Cmin	Minimum (peak) concentration of drug
CapSeq	University of Chicago's DNA and RNA based genetic profiling assay
CCTO	University of Chicago Comprehensive Cancer Center Clinical Trials Office
CHGC	University of Chicago HNC Genomics Cohort
CR	Complete Response
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria Adverse Events
DLT	Dose Limiting Toxicity
DoR	Duration of tumor Response
DMC	Data Monitoring Committee
DS&E	Drug Safety and Epidemiology
EC	Ethics committee
ECG	Electrocardiogram
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FFPE	Formalin-Fixed Paraffin-Embedded
FGFR	Fibroblast Growth Factor Receptor
GCP	Good Clinical Practice
Hgb	Hemoglobin
HNC	Head and Neck Cancer
HNSCC	Head and Neck Squamous Cell Carcinoma
HPV	Human Papilloma Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LLOQ	Lower limit of quantification
MTD	Maximum Tolerated Dose
ORR	Objective Response Rate
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics

PFS	Progression Free Survival
PK	Pharmacokinetics
QD	Quaque die/ once a day
REB	Research Ethics Board
RECIST	Response Criteria in Solid Tumors
SAE	Serious Adverse Event
SCC	Squamous Cell Carcinoma
SD	Stable Disease
SGOT	Serum glutamic oxaloacetic transaminase; aspartate aminotransferase; AST
SGPT	Serum glutamic pyruvic transaminase; alanine aminotransferase; ALT
SUSAR	Serious and Unexpected Suspected Adverse Reaction
TCGA	The Cancer Genome Atlas
UCCCC	University of Chicago Comprehensive Cancer Center
WBC	White Blood cells
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being testing in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study.
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/healthy volunteer who enrolls in the study
Phase	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples, it is important to judge investigational treatment component relationship relative to a study treatment combination; study treatment in this case refers to the investigational and non-investigational treatments in combination.
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

1 Background

1.1 Overview of Disease to be studied

Head and Neck squamous cell carcinoma (HNSCC) is the 6th most common cause of cancer death worldwide with more than 600,000 annual cases. In the United States alone, there are over 40,000 new HNSCC cases and 11,000 deaths per year. HNSCC results in significant morbidity because major vital functions such as nutrition, respiration and communication are impaired.

Approximately two thirds of patients with HNSCC will present with locoregional disease and despite aggressive local therapy, close to than half will succumb to recurrent and/or metastatic disease. If untreated, the median survival of patients with metastatic disease is dismal and on the order of 4 months (Bentzen 2005; Ang, Berkey et al. 2002).

In patients with recurrent or metastatic HNSCC, therapeutic options are usually palliative consisting of systemic chemotherapy and the EGFR inhibitor cetuximab in the first-line treatment setting (Vermorken et al. 2007; Vermorken et al. 2008). Median survival is estimated at 10.1 months using a combination of cisplatin/5-FU/cetuximab. Cytotoxic chemotherapy can have significant toxicities, consisting of bone marrow suppression, nausea/vomiting, rash, hand-foot syndrome, and many others. Better therapeutic options are necessary. Second line treatment options include methotrexate, taxanes, or clinical trials. Targeted therapies after the failure of cetuximab are generally considered inactive, e.g. use of sorafenib in a clinical trial resulted in a response rate of ≤5% (Williamson et al. 2010, de Souza et al 2012), and generally a drug with ≤5% response rate is not considered active/worthy of further study.

1.2 Introduction to investigational treatment

1.2.1 Overview of BGJ398 (infigratinib)

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

BGJ398 (infigratinib) 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).

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

1.2.1.1 Non-clinical experience

At the cellular level, BGJ398 (infigratinib) selectively inhibits the kinase activity of FGFR1 FGFR2, FGFR3, and FGFR 4 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 (infigratinib) inhibits FGFR downstream signaling and proliferation of human cancer cell lines harboring genetic alterations of the FGFRs. These include, among others, lung and breast cancer cell lines with FGFR1 gene amplification, gastric cancer with FGFR2 gene amplification, endometrial cancer with FGFR2 mutations and bladder cancer with FGFR3 mutations or FGFR3 translocations (Wesche, 2011). In line with its cellular activity, BGJ398 (infigratinib) shows anti-tumor activity in multiple models bearing FGFR genetic alterations (Guagnano, 2012; Konecny, 2013).

In vivo, BGJ398 significantly inhibits growth of tumors in a dose-dependent manner in various mouse and rat xenograft subcutaneous or orthotopic models. These include models of bladder cancer (RT112, MGHU3), multiple myeloma (KMS11), endometrial cancer (AN3CA), and gastric cancer (SNU16). The dose ranges needed to induce tumor growth inhibition; stasis and regression are well tolerated based on body weight monitoring. In vivo pharmacokinetic/pharmacodynamic (PK/PD) analyses of tumor tissues and blood biomarkers show a good correlation between the given dose, AUC in plasma and tumor tissues, the effects. on the FGFR pathway as measured by the phosphorylation status of FRS2 and MAPK activation and the antitumor activity.

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

1.2.1.1.1 Animal drug metabolism and pharmacokinetics

In all species tested, BGJ398 (infigratinib) 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 (infigratinib) is widely distributed to tissues in the rat and has a high affinity to melanin containing tissues. *In vitro* hepatic systems metabolize BGJ398 (infigratinib) predominantly to 2 pharmacologically active metabolites: BHS697 and BQR917. Biotransformation of BGJ398 (infigratinib) 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 (infigratinib) is primarily a CYP3A4 substrate.

BGJ398 (infigratinib) 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 (infigratinib) 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).

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

1.2.1.1.2 Preclinical Safety

BGJ398 showed no evidence of genotoxicity (in vitro and in vivo) and no evidence of phototoxicity in a 3T3 photo-cytotoxicity test. In vitro safety pharmacology assessment of BGJ398 revealed a potential for QTc prolongation.

In repeated dose (oral gavage; up to 13 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 and dogs. These effects were deemed to be on-target effects mediated by pharmacological inhibition of FGFR.

In rat toxicity studies, ophthalmoscopic examination revealed increased severity of mainly bilateral corneal opacity during the treatment period. This finding showed a trend towards reversibility. The ophthalmoscopic finding of cornea opacity correlated histopathologically with cornea thinning/keratopathy, mineralization and meibomian gland atrophy which likewise showed a trend towards reversibility.

In the 13-week rat toxicity study, besides the cornea thinning, additional effects on the epithelium (thinning or degeneration) were reported mainly for the tongue, nasal cavity and incisors (non-growing teeth such as the molar teeth were not affected). In the 13-week dog toxicity study only, atrophy of the meibomian and sebaceous gland was reported. In rat and dog 13-week toxicity study, a change in the coat appearance (denoted by relatively longer hair/fur) was noted. This finding did not show any microscopic correlate.

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

1.2.1.1.3 Pharmacology and toxicology

BGJ398 (infigratinib) 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 (infigratinib) 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 (infigratinib) 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 (infigratinib) 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 morbidity after 6 administrations. In dogs, the highest non-severely toxic dose 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 were observed

1.2.1.2 Clinical experience

BGJ398 is being evaluated in the following studies:

- Two phase I studies (BGJ398X1101 and BGJ398X2101)
- Three phase II studies (CBGJ398X2201, CBGJ398X2204, and CBGJ398XUS04)
- One phase Ib study that is evaluating BGJ398 in combination with the PI3K alpha specific inhibitor BYL719 (BGJ398X2102). (Not referenced here → See investigator brochure)
- Four healthy volunteer studies, CBGJ398X2103, CBGJ398X2105 CBGJ398A2104 and CBGJ398X2106 have been conducted. (Not referenced here → See investigator brochure)

1.2.1.2.1 Clinical safety

CBGJ398X1101

The purpose of this first in human study is to evaluate safety and to determine the MTD of BGJ398 in the Japanese population. As of the September 4, 2015 cutoff date for this clinical database, nine patients were enrolled to two dose escalation cohorts, 50 mg BGJ398 (N=4) and 100 mg BGJ398 (N=2) and one safety run-in cohort in the Chinese population 100 BGJ398 (N=3). No dose limiting toxicities (DLTs) have been reported.

CBGJ398X2101

As of data cut-off date January 30, 2017, 208 patients have received at least one dose of BGJ398. Forty-three patients were enrolled to dose escalation cohorts and 165 patients to dose expansion arms.

Enrollment to the dose escalation cohorts was as follows: 5mg [N=3], 10mg [N=3], 20mg [N=4], 40mg [N=6], 60mg [N=3], 100mg [N=6], 50 mg bid [N=4], 125mg [N=8], and 150mg [N=6]. MTD was identified to be 125 mg qd on a continuous dosing schedule.

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Dose expansion consists of 4 arms enrolling different patient populations on two different dosing schedules at 125 mg (daily or 3 weeks on/1 week off in 28-day cycles). Arm 1 [N=28] enrolled FGFR1-amplified advanced or metastatic squamous NSCLC with FGFR1 amplification on the continuous dosing schedule. Arm 2 [N=21] enrolled advanced solid malignancies with any FGFR mutation or amplification dosed continuously. Arm 3 [N=49] enrolled advanced solid malignancies with any FGFR genetic alteration, mutation, or amplification on the 3 weeks on/1 week off dosing schedule. Arm 4 [N=67] enrolled advanced or metastatic urothelial cell carcinoma (UCC) with FGFR3 mutation or gene fusion on the 3 weeks on/1 week off dosing schedule.

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 for continuous dosing before the alternative regimen was introduced 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, 11 patients were still receiving study medication. Of the 197 patients who have discontinued from the study, 145 discontinued treatment due to progression of disease, 30 discontinued due to adverse events, 6 died while on study, 14 discontinued due to withdrawal of consent, 1 due to administrative problems, and 1 due to lost to follow-up.

Adverse events

The treatment emergent adverse events as of the cutoff date of January 30, 2017, regardless of BGJ398 relationship, that occurred in 20% or more of patients are: hyperphosphatemia, 65.4%, constipation (39.9%), decreased appetite (37.5%), fatigue (36.1%), stomatitis (34.1%), nausea (32.2%), blood creatinine increased/hypercreatininaemia (29.8%), diarrhea (28.4%), alopecia (26.4%), dry mouth (24.5%), vomiting (21.6%), and anemia, 20.7%, (Table 5-14). Approximately 59percent of patients (122/208) experienced at least one grade 3 or 4 event regardless of the relationship to BGJ398, (Table 5-15). Grade 3 or 4 events that occurred in at least 5% of patients were lipase increased (6.7%) and alanine aminotransferase increased (5.3%). 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.

CBGJ398X2204

This study is designed to evaluate the efficacy of BGJ398 when administered as a single agent to patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions/translocations or other FGFR genetic alterations. The treatment dose of BGJ398 is 125 mg q.d. for the first 3 weeks (21days) of a 28-day cycle, followed by a 7 day break. The dosing regimen for BGJ398 was chosen based on data obtained from the CBGJ398X2101study.

As of June 01, 2017, 63 patients have been treated which included fifty patients with FGFR2 fusions and thirteen patients with other FGFR alterations.

Adverse Events

Table 5-20 lists the treatment emergent adverse events that have been reported for the CBGJ398X2204 study. The most commonly reported treatment emergent adverse event of any grade was hyperphosphatemia, reported in 82.5% of patients. Other frequently reported adverse event include fatigue (49.2%), constipation (41.3%), stomatitis (38.1%), alopecia (38.1%), dysgeusia (31.7%), blood creatinine increased (27.0%), hypophosphatemia (27.0%), nausea (27.0%), diarrhea (25.4%), dry eye (25.4%), arthralgia (23.8%), dry mouth (23.8%), dry skin (23.8%), palmar plantar erythrodysesthesia syndrome (23.8%), aspartate aminotransferase increased (22.0%), decreased appetite (20.6%), hypercalcemia (20.6%), alanine aminotransferase increased (19.0%), vision blurred (19.0%), anemia (17.5%), dyspepsia (17.5%), vomiting (17.5%), weight decreased (17.5%), epistaxis (17.5%), onychomadesis (17.5%), myalgia (17.5%), pain in extremity (16.1%) and cough (16.1%).

Forty one of 63 patients (65.1%) experienced at least one grade 3 or 4 event regardless of the relationship to BGJ398, Table 5-20. Grade 3 or 4 events that occurred in at least 5% of patients were hyperphosphatemia (15.9%), hypophosphatemia (6.3%), hyponatremia (12.7%), lipase increased (7.9%), and stomatitis (7.9%).

Twenty nine of 63 patients (46.0%) experienced at least one grade 3 or 4 suspected to be related to BGJ398, Table 5-21. Grade 3 or 4 events that occurred in at least 5% of patients were hyperphosphatemia (15.9%) and stomatitis (7.9%).

Overall, most adverse events reported have been mild to moderate in severity, reversible, and unrelated to BGJ398.

CBGJ398XUS04

This is a phase II, open label study to determine the efficacy and safety of single agent BGJ398 in patients with a diagnosis of solid tumors or hematological malignancies that have been pre-identified (prior to study consent) to have FGFR genetic alterations and whose disease has progressed on or after standard treatment. The treatment dose of BGJ398 is 125 mg q.d. on a 3 week on (21 day) /1 week off (7 day) schedule. This dose level and regimen was selected based on experiences from the CBGJ398X2101 trial.

As of October 5, 2017, 85 patients have been treated on this study. The study is closed to enrollment.

Adverse events

The most commonly reported treatment emergent adverse event of any grade regardless of BGJ398 relationship was hyperphosphatemia, occurring in 48% of patients. Other frequently reported treatment emergent adverse events include fatigue (45%), nausea (29%), constipation (28%), diarrhoea (23%), dry mouth (22%), stomatitis (22%), blood creatinine increased (21%), decreased appetite (21%), dysgeusia (20%), blood phosphorus increased (19%), vomiting (17%), abdominal pain (15%), alopecia (15%), dehydration (15%), dry eye (15%), urinary tract infection (15%), weight decreased (15%), mucosal inflammation (14%), dyspnoea (13%), hypomagnesaemia (13%), aspartate aminotransferase increased (12%), anaemia 10)%), blood alkaline phosphatase increased (10%), hyponatraemia (10%), pain in extremity (10%) and pyrexia (10%).

Grade 3 or 4 events that occurred in at least 5% of patients were hyperphosphatemia (8%) fatigue (8%) and nausea (5%). Overall, most adverse events reported have been mild to moderate in severity, reversible, and unrelated to BGJ398.

Please refer to the Investigator Brochure for additional information on BGJ398 (infigratinib).

1.2.1.2.2 Preliminary efficacy of BGJ398 (infigratinib)

CBGJ398X2101

Preliminary antitumor efficacy has been shown in patients treated at ≥ 100 mg in squamous NSCLC and urothelial carcinoma with FGFR genetic alterations. As of 15 May 2015, 4/36 patients with NSCLC and 3/8 patients with urothelial carcinoma achieved PR (Nogova L et al JCO 2017). In addition, as of 1 Mar 2016, of 37 evaluable patients in a dedicated arm for urothelial carcinoma, 12 achieved PR, and 1 achieved CR (Pal et al ASCO 2016).

CBGJ398X2102

Preliminary anti-tumor activity has been detected in patients treated at doses of ≥100 mg of BGJ398 in combination with 300 mg BYL719. This activity has been detected in patients with the following tumor types; bladder, breast, ovarian, and head and neck.

CBGJ398X2204

Preliminary antitumor activity has been observed in cholangiocarcinoma patients harboring FGFR2 fusion or other FGFR genetic alteration treated with 125mg BGJ398 on 3 weeks on, 1 week off schedule. Of the 63 patients enrolled to the BGJ398X2204 study, there were 59 patients evaluable for efficacy (with valid baseline and at least one valid post-baseline assessment). Out of these 59 patients, 15 (23.8%) patients had BOR of confirmed partial response and 33 (52.4%) experienced BOR of stable disease. Therefore, the primary endpoint of investigator-assessed ORR (confirmed responses only) is 23.8%. Disease control rate is 76.2% (48 patients). Additionally, out of the 33 patients who achieved stable disease, 4 patients achieved PR in one scan (did not have subsequent scan confirming the PR). The median PFS is estimated at 6.7 months (95% CI: 4.8-7.6 months). Of the 63 patients,49 (77.8%) had a PFS event (4 deaths and 45 patients progressed as per RECIST). (Javle M et al JCO 2018)

1.2.1.2.3 Conclusion of safety and efficacy in humans

Preliminary data obtained from the CBGJ398X2101 first in human trial indicate that the main safety findings in patients treated with BGJ398 (infigratinib) were as expected based on the preclinical studies: The on-target effects on calcium-phosphate homeostasis result in the observed increases in calcium, phosphorus, and creatinine, and not associated with clinical symptoms. In general, the increases have been mild to moderate in severity and manageable and reversible upon interruption or discontinuation of BGJ398 administration.

Ocular adverse events are frequent, but generally mild to moderate in severity and reversible. Corneal or retinal adverse events are recognized on ophthalmologic evaluations.

No effect of BGJ398 (infigratinib) on ECG intervals, including QTc has been noted. Reversible and largely asymptomatic decreases in LVEF have been noted in patients enrolled on study as measured by serial TTE or MUGA scans.

The preliminary efficacy signals were observed in multiple patients including patients with squamous cell histology.

1.2.1.2.4 Clinical pharmacokinetics

The pharmacokinetics (PK) of BGJ398 (infigratinib) and active metabolites have been evaluated following single and repeat daily doses in the ongoing phase 1 study (CBGJ398 (infigratinib)X2101).

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 Tmax was approximately 2-3 hours. The mean AUC0-24 on Day 1 increased approximately 9 fold from 20 to 150 mg. A mean terminal elimination half-life on Day 1(T1/2) 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 (Racc) ranged from 3 to 8 on Days 15 and 28. Since dose interruptions occurred frequently following continuous daily dosing of BGJ398 (infigratinib), PK parameters on Day 28 should be viewed with caution. The inter-patient variability was high for BGJ398 (infigratinib). When dosed at 125 mg with a schedule of 3 weeks on, 1 week off, the mean Cmax and AUC0-24 were 230 ng/mL (n=12) and 3492.9 ng*hr/mL, (n=10), respectively at day 15. The coefficient of variation for Cmax and AUC0-24 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 BGJ398 (infigratinib)X2101 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 (infigratinib) varied across patients (3% -300%). CQM157 (N=4) did not appear to accumulate on daily dosing, whereas accumulation was observed for BGJ398 (infigratinib) and metabolites BHS697 and BQR917.

Please refer to Investigator’s Brochure for more details.

2 Study purpose/rationale

Head and neck cancer (HNC) is the 6th most common cancer worldwide (~50,000 cases/year in the US; 60,000 cases/year in Europe). Once recurrent or metastatic, head and neck cancer carries a poor prognosis with a median survival of only 6-10 months (Vermorken et al. 2008; Seiwert et al. 2008). Cetuximab is the only approved targeted therapy for this disease and the response rate is 13% (Vermorken et al. 2007; Seiwert et al. 2012). Better treatments are needed.

Over the past decade, it has become clear that HPV-related (HPV (+)) head and neck cancer represents a distinct epidemiologic, molecular, pathologic, and clinical entity. In recent years, HNSCC, in particular, oropharyngeal cancer, has shown a sharp increase in incidence related to oncogenic HPV16 infections (Marur et al. 2010). These cancers arise almost exclusively in the oropharynx (base of tongue and tonsil) for reasons that have not yet been identified, and tend to affect younger patients, appear to metastasize early to regional lymph nodes, and carry better prognosis than "classic" smoking and alcohol related, HPV (-) HNSCC (Marur et al. 2010). Interestingly, up to 70% of oropharyngeal cancers in several developed countries, including the US, is felt to be HPV-related (Chaturvedi et al. 2011). HPV has also been detected in smaller subsets of laryngeal and oral cavity cancers, though these estimates are closer to 10% (Halec et al. 2013). HPV origin of HNSCC in individual patients can be established by direct assessment of HPV based on detection of HPV DNA or RNA (i.e. in situ hybridization or PCR). However, more frequently, p16 immunohistochemistry can serve as a surrogate marker for oropharyngeal cancers, albeit concerns about accuracy have been voiced (Vokes et al. 2013).

Along with the classification of HNC into HPV (+) and HPV (-) diseases, the head and neck cancer (HNC) genome has been defined in several cohorts. The Cancer Genome Atlas (TCGA) sequenced tumor samples from 279 patients with HNC containing primarily HPV (-) tumors (87%) while the University of Chicago HNC Genomics cohort (CHGC) analyzed tumor samples from 134 patients with a large HPV (+) cohort (41%). While HPV (+) and HPV (-) HNSCC are genetically distinct tumors, with HPV negative HNSCC paralleling the genomic landscape of lung squamous cell carcinoma and HPV (+) HNSCC resembling cervical carcinoma (Hayes et al 2013), both large cohorts confirm fibroblast growth factor receptor (FGFR) as an emerging target for HNC.

With the changing epidemiology of head and neck cancers and the rise of HPV-related (HPV (+)) HNSCC largely in developed countries, it is becoming increasingly important to recognize HPV (+) and HPV (-) HNSCC as two distinct tumor types, which may have differential response to targeted therapeutics. Interestingly, one of the most common potentially targetable aberration in both HPV (-) and HPV (+) SCCHN are alterations in the fibroblast growth factor receptor family, with the spectrum of alterations being distinct in both subtypes of HNSCC.

Fibroblast growth factor receptor plays an important role in cancer and is an emerging treatment target for lung, bladder, and other cancer types. Data from the University of Chicago HNC Genomics cohort show FGFR2-3 mutations in HPV (+) head and neck cancer at rates of 15% in our cohort – and 8% in the TCGA cohort. Most of these mutations are canonical/predicted driver mutations (six S249C FGFR3 mutations (validated by Sanger sequencing in the CHGC cohort), as well as two N569K/D FGFR2 mutations also in our cohort). Pre-clinically, the multikinase inhibitor ponatinib, which does inhibit FGFR1-4 has demonstrated in vitro and in vivo single agent clinical activity against such driver mutations (Wu et al. 2013).

While the prevalence of FGFR2-3 mutations in HPV (-) HNSCC is lower (4% in HNC TCGA), FGFR1 amplification has been demonstrated in 10% of HPV (-) head and neck cancer in the TCGA cohort, interestingly primarily in laryngeal cancers (Vermorken et al. 2008). FGFR1 amplifications have also been reported in oral carcinoma (Freier et al. 2007). More recently, autocrine signaling loops involving FGFR2 and FGFR1 have been reported in HNC cell lines (Marshall et al. 2011). As investigators have used varying definitions of gene amplification, we prefer to adopt copy number ≥ 6 as a standard definition of high level amplification, which seems to be most predictive of response to therapy, with copy number assessed through next generation sequencing.

Furthermore, the HNC-TCGA data has reported three TACC3-FGFR3 translocations, two in HPV (+) (incidence of ~5% in HPV (+)) tumors), with a slightly different breakpoint from bladder/lung SCC, as well as a functionally unclear FGFR1 translocation (Hayes et al. 2013). Cell lines harboring FGFR3 fusion proteins have exhibited exquisite susceptibility to pharmacologic inhibition in vitro and in vivo (Wu et al. 2013). As the FGFR3 breakpoint can occur with different partner proteins, we utilize RNA based detection to avoid interrogation of large intronic areas. At the University of Chicago we have established a next generation sequencing based genetic profiling assay (comparable to Foundation One assay) that includes detection of TACC3-FGFR3 translocations. In summary:

FGFR1: FGFR1 amplification has been demonstrated in 10% of HPV (-) head and neck cancer in the TCGA cohort primarily in laryngeal cancers. FGFR1 amplifications have also been reported in oral carcinoma. More recently, autocrine signaling loops involving FGFR2 and FGFR1 have been reported in HNC cell lines.

FGFR2-3: Data from the University of Chicago HNC Genomics cohort show FGFR2-3 mutations in HPV (+) head and neck cancer at rates of 15% in our cohort – and 8% in the TCGA cohort. Most of these mutations are canonical/predicted driver mutations (six S249C FGFR3 mutations (validated by Sanger sequencing), N569K/D FGFR2 mutations in our cohort). Pre-clinically, the multikinase inhibitor ponatinib has demonstrated in vitro and in vivo single agent clinical activity against such driver mutations.

FGFR3: The HNC-TCGA data has reported three TACC3-FGFR3 mutations, with a slightly different breakpoint from bladder/lung SCC, as well as a functionally unclear FGFR1 translocation. Cell lines harboring FGFR3 fusion proteins have exhibited exquisite susceptibility to pharmacologic inhibition in vitro and in vivo.

Oncogenic translocations involving FGFR3, and recurrent FGFR3 and FGFR2 mutations have been reported in >10% of HPV (+) tumors, while HPV (-) tumors have a ~10% rate of FGFR1 amplification and ~5% rate of FGFR2/3 mutations. In brief, while the spectrum of alterations seems to be distinct in both subtypes of HNSCC, fibroblast growth factor receptor (FGFR) emerges as a targetable pathway in both HPV (+) and HPV (-) HNSCC.

Unlike cancers in which genetic aberrations correlate with activity of certain targeted agents, there are currently no such therapies approved for squamous cell carcinomas including HNSCC. While cetuximab is approved both upfront in combination with radiation or in the recurrent/metastatic disease setting, there are no biomarkers to predict response to therapy (Vermorken et al. 2008). Based on the literature from the Cancer Genome Atlas as well as our Chicago HNC Genome cohort, we propose to assess the oral specific and potent pan-FGFR inhibitor BGJ398 (infigratinib) in patients with head and neck cancer with a focus on FGFR relevant biomarkers that hold potential to identify patients who will benefit from therapy with BGJ398 (infigratinib).

This study analyses a novel pathway and attempts to establish **fibroblast growth factor receptor (FGFR)** as a targetable pathway in HPV (+) and HPV (-) **FGFR1-3 translocated, mutated, or amplified squamous cell carcinoma of the head and neck.**

3 Objectives and endpoints

3.1 Primary Objectives

	Objective	Endpoint/Analysis
Primary	Assess efficacy of BGJ398 (infigratinib) in FGFR altered HNSCC	**Objective Response Rate (RECIST 1.1) (complete or partial response)**

3.2 Secondary Objectives

	Objective	Endpoint/Analysis
Secondary	Assess safety and tolerability of BGJ398 (infigratinib) in patients with Head and Neck Cancer	**AE / SAE**
Secondary	Assess duration of response, progression free and overall survival	**DOR / PFS* / OS****

*Progression-free survival [days] = date of progression (or of death if no earlier progression) – date of randomization +1

*Progression-free survival (censored) [days] = date of last adequate assessment per RECIST 1.1 with negative imaging before patient withdrawal of consent or start of new therapy – date of randomization +1

**Overall survival [days] = date of death – date of randomization +1

Trial termination is synonymous with off study / end of treatment.

3.3 Exploratory Objectives

	Objective	Endpoint/Analysis
Exploratory	Determine mechanisms of resistance to FGFR inhibition at disease progression	**Genomic profiling of pre-response tumor tissue and comparison with acquired resistance tumor specimen**
Exploratory	Assess efficacy of BGJ398 (infigratinib) in relation to specific genetic aberrations in FGFR altered HNSCC (i.e. FGFR3-TACC3 translocation, FGFR1 high copy number/amplification, FGFR2 mutation, FGFR3 mutation)	**Response Rate in subgroups of patients (as defined by certain genetic changes in FGFR1-3)**
Exploratory	Efficacy by HPV status	**Descriptive response rate in both HPV(+) and HPV(-) patients.**

Overall, we hypothesize that:

1) ***BGJ398 (infigratinib) will have clinical activity in FGFR altered HNSCC***
2) ***BGJ398 (infigratinib) will demonstrate clinical activity in FGFR altered HNSCC***
3) ***BGJ398 (infigratinib) will demonstrate clinical activity in all FGFR subgroups (i.e. FGFR1 high copy number/amplification, FGFR2 mutation, FGFR3 mutation, FGFR3 translocation)***
4) ***Re-biopsy of patients who demonstrate initial response, followed by subsequent disease progression, will elucidate mechanisms of resistance to FGFR inhibition***

4 Investigational plan

Definitions

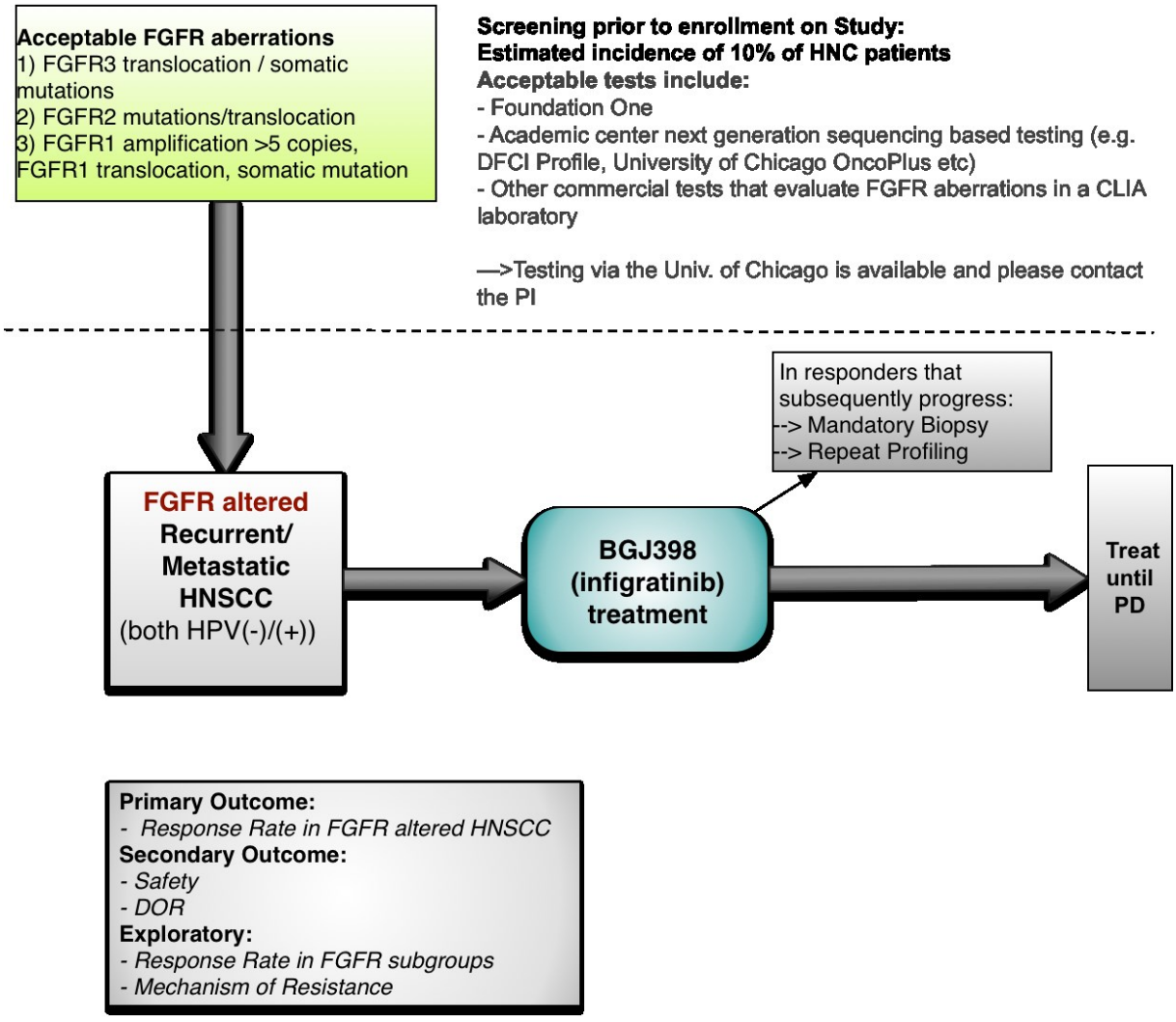
Cycle	A 4-week period of treatment with study medication BGJ398 (infigratinib)
End of treatment (EOT) visit	Clinic visit/assessment within 14 days of permanent termination of trial drug intake
End of post treatment follow-up	Clinic visit/assessment at Day 28 ± 8 days after the EOT visit

4.1 Overview of Study Design and Schema

Open label single arm study in FGFR altered HNSCC. There is no dose escalation; we will employ the established phase II dose.

Intervention Status: Interventional

Study Phase: Phase IIa



NB: In order to allow a representative sampling of genetic aberrations each type of genetic aberration should be represented and enrollment for other genetic aberrations can be limited (see inclusion criteria). Such adjustments can be made by the Lead Investigator via a memo.

This phase IIa proof-of-concept trial will be an open-label single arm study in multiple centers through the University of Chicago personliazed cancer care Consortium (PCCC), in which all eligible patients with histologically-confirmed recurrent/metastatic HNSCC and FGFR alteration will receive BGJ398 (infigratinib) at 125 mg PO daily. Patients with FGFR1-3 high level amplification, mutation, or translocation will be included.

4.1.1 FGFR aberration (pre-screening)

In order for patient to be eligible one of the following genetic aberrations need to be present in the tumor:

- FGFR1 amplification, FGFR1 somatic mutations, FGFR1 translocations.
- FGFR2 somatic mutations, FGFR2 translocations, FGFR2 amplification.
- FGFR3 somatic mutations, FGFR3 translocations, FGFR3 amplification.

NB: In order to allow a representative sampling of genetic aberrations each type of genetic aberration should be represented and enrollment for other genetic aberrations can be limited (see inclusion criteria). Such adjustments can be made by the Lead Investigator via a memo.

A number of next generation sequencing based tests are acceptable including Foundation One based testing, academic center CLIA laboratory based testing (e.g. DFCI Profile, University of Chicago large and small mutation and/or translocation panels, others). Additional commercial tests, and tests using other methodologies in a CLIA laboratory are potentially acceptable, but should be confirmed by the Lead Investigator prior to use (Dr. Seiwert, tseiwert@medicine.bsd.uchicago.edu, 773-702-2452)

Testing is not part of this study, but the University of Chicago does offer limited testing for outside centers and centralized genomic profiling/prescreening can be offered through the U Chicago molecular pathologic laboratory. Please contact Dr. Tanguy Seiwert if requesting Univ. of Chicago molecular analysis/testing.

Each cycle is 4 weeks. CT scans will be obtained every 2 cycles. This study will enroll 15 HPV (+) and 15 HPV (-) patients with HNSCC and FGFR alterations.

Primary objective will be objective response rate (ORR; complete or partial response) of BGJ398 (infigratinib) in FGFR altered HPV (-) and HPV (+) SCCHN (Simon Two Stage Design). As genomic profiling will be used as a prescreening tool to identify FGFR altered tumors, an exploratory objective will be to assess efficacy of BGJ398 (infigratinib) in relation to specific genetic aberrations in HPV (+) and HPV (-) FGFR altered HNSCC (i.e. FGFR3-TACC3 translocation, FGFR1 high copy number/amplification, FGFR2 mutation, FGFR3 mutation). Please refer to statistical considerations, methods, and data analysis in Section 11.

In responders who subsequently demonstrate disease progression (acquired resistance), mandatory tissue biopsy will be performed and genomic profiling of pre-treatment tissue will be compared to genomic profiling of acquired resistance tumor to explore mechanisms of acquired resistance to FGFR inhibition. Primary (and secondary/exploratory) endpoints will be assessed through RECIST 1.1 defined response rate.

4.2 4.1.2 Methods of FGFR screening

This trial requires screening for FGFR aberration prior to patient trial enrollment.
Both DNA and RNA based assay that detect FGFR1-3 mutation, amplification, and translocations are acceptable.

FGFR1-3 aberrations can be determined by any next generation sequencing based assay prior to enrolling a patient on study. Alternative assays may be acceptable (e.g. FISH, Sanger Sequencing, qPCR) after discussion with the Lead Investigator (Dr. Seiwert). Commercial assays as well as academic assays will be acceptable if done in a CLIA laboratory.

In case a patient tumor is not already characterized, characterization is available via the University of Chicago. A separate (non-study related) consent form is provided to perform FGFR testing. This pre-screening is NOT considered enrollment on the actual trial.

The following genetic aberrations will be screened for:

- **FGFR1 amplification, FGFR1 somatic mutations, FGFR1 translocations.**
- **FGFR2 somatic mutations, FGFR2 translocations, FGFR2 amplification**
- **FGFR3 somatic mutations, FGFR3 translocations, FGFR3 amplification**

Other genetic FGF/FGFR pathway aberrations may be acceptable should such genetic changes be observed to emerge and require approval per the Lead Investigator for enrollment (e.g. FGF amplification).

Should one genetic aberration be overrepresented in one or both of the arms, the Lead Investigator (Dr. Seiwert) may decide to restrict enrollment of such patients. A notification/memo will be sent out to all participating investigators should such a restriction on enrollment be implemented (see inclusion criteria).

4.1.3 Investigational treatment, other study treatment, study treatment, supportive treatment

The investigational study drug used in this trial is BGJ398 (infigratinib), which is supplied as capsules.

4.3 Treatment

Treatment Arm/Cohort	# of Pts Planned	Type of Study Drug	Compound *(specify brand or generic)*	Min Dose and unit	Max Dose and unit	Frequency	Admin Route
FGFR altered HNSCC	20	Investigational	BGJ398 (infigratinib)	125mg	n/a	Daily, 21 days on, 7 days off (28-day cycle)	PO

4.4 Definition of a treatment cycle

A complete treatment cycle is defined as 21 days of uninterrupted continuous treatment with the study drug BGJ398 (infigratinib) followed by a 7 day break. The first dose of BGJ398 (infigratinib) defines Cycle 1 Day 1. All treatment cycles have a duration of 28 days. There will be no delays between cycles, i.e. study day 29 represents Cycle 2 Day 1.

4.5 Treatment duration

CT scan assessment of response / tumor measurements (RECIST) will be every 2 cycles (= 8 weeks) for all patients. Patients will continue on therapy until disease progression, death, intercurrent illness that prevents further administration of treatment, unacceptable adverse events, patient elects to withdraw from study, or conditions which render the patient unacceptable for further treatment in the judgment of the investigator. Patients will be followed ≤ every 1-3 months for survival until 5 years post treatment or until death, whichever occurs first. Patients removed from this study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

4.6 Treatment assignment/randomization

Patients in will receive study medication BGJ398 (infigratinib) 125 mg PO daily for 21 days, followed by a 7 day break.

An exception may be made per approval by the Lead Investigator and Novartis to switch to continual dosing 28-days, potentially at a reduced dose should evidence emerge that tumor progression occurs during the one-week off.

4.7 Rationale for the study design

Based on the TCGA and our University of Chicago HNC cohort:
- FGFR2-3 mutations are estimated to occur in 5-8% of HPV (-) HNC and 10-15% of HPV (+) HNC.
- FGFR1 amplification is estimated to occur in 7-10% of HPV (-) HNC.
- FGFR3-TACC3 translocation is estimated to occur in 3-5% of either HPV (+) or HPV (-) head and neck cancers (in TCGA two TACC3-FGFR3 translocations occurred in HPV (+) HNC).
- Other translocations of FGFR genes as well as amplification of FGFR2/3 have been described to be oncogenic in other cancer types but based on absence in the TCGA HNC and Chicago HNC genomics cohort (CHGC) datasets to be rare in HNC.

The primary endpoint will be: **objective response rate** (ORR; complete or partial response).

With a **Simon Two Stage Design**, a preset **alpha level of 0.1** and **power of 80%**, we determined the minimum sample size required to detect the hypothesized response rate of 21% for BGJ398 (infigratinib): A sample of 20 FGFR altered patients will be large enough to detect a response rate of ≥21% for BGJ398 (infigratinib) compared to a null response rate of 5% (Williamson et al. 2010) with 80% power and one-sided type I error rate of 0.10.

An interim analysis for futility will be conducted after 11 evaluable patients have been enrolled without interruption of enrollment. If 0/11 responses are seen, the study will be stopped prematurely for futility.

If at least one response is seen, an additional 9 patients will be enrolled. The results will be deemed negative (i.e., the 21% alternative will be rejected) if ≤2 responses are seen in 20 patients.

5 Population

Study population must meet both criteria below.

A. Patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) not amenable to curative intent therapy (palliative treatment intent).

B. Must harbor an FGFR genetic alterations (FGFR1-3 translocated, mutated, or amplified squamous cell carcinoma of the head and neck).

Enrollment target: N=20 patients. We estimate to have at least 3-5 patients with repeat tumor biopsies (mandatory for responders who subsequently demonstrate disease progression). All patients must have tumor material available for biomarker evaluation or confirmed FGFR1-3 translocated, mutated, or amplified squamous cell carcinoma of the head and neck.

5.1 Inclusion criteria

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

1. Histologically documented diagnosis of squamous cell carcinoma of the head/neck including nasopharyngeal carcinomas (lymphephithelioma histology is ok if criteria 2 is met).

   → Patients must have progressed on prior platinum based therapy (or have become intolerant) prior to enrollment on this study.

   → Prior anti-PD-1 or other immunotherapy is acceptable

2. FGFR genetic alterations (specifically FGFR1-3 mutation, amplification, or translocation) via DNA or RNA based assay. Prescreening has to be completed prior to enrollment on this study. Commercial or local testing is typically expected, but samples can also be sent to the Univ. of Chicago for testing (see 4.1.1).

   The following genetic aberrations will be screened for (please also see 4.1.1):
   - **FGFR1 amplification, FGFR1 somatic mutations, FGFR1 translocations.**
   - **FGFR2 somatic mutations, FGFR2 translocations, FGFR2 amplification.**
   - **FGFR3 somatic mutations, FGFR3 translocations, FGFR3 amplificiation.**

   Other genetic FGF/FGFR pathway aberrations may be acceptable should such genetic changes be observed to emerge and require approval per the Lead Investigator for enrollment (e.g. FGF amplification).

   Should one genetic aberration be overrepresented in one or both of the arms the Lead Investigator (Dr. Seiwert) may decide to restrict enrollment of such patients. A notification/memo will be sent out to all investigators should such a restriction on enrollment be implemented (see inclusion criteria). For example, if more than 5 pts with FGFR1 amplification are enrolled further enrollment of FGFR1 amplified patients will be put on hold, or if FGFR translocations are under-represented enrollment may be focused on this aberration.

3. Consent to undergo a fresh biopsy in case of benefit from therapy and subsequent progression (see 7.2.5)
4. ECOG performance status ≤1
5. Patients must provide written informed consent prior to any screening procedures.
6. Age 18 years or older.
7. Willing and able to comply with scheduled visits, treatment plan and laboratory tests
8. Patient is able to swallow and retain oral medication, unless approval per the manufacturer of other administration routes/methods is provided.
9. 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

10. HPV status in Oropharyngeal Carcinomas. While HPV status (e.g. via p16) does not have to be known prior to consenting, the HPV status (e.g. using p16 IHC) needs to be established prior to start of therapy.
11. Presence of measurable disease by RECIST 1.1
12. Availability of tumor tissue (e.g. FFPE) for genomic profile (typically 12 unstained FFPE 5-10 micron slides, minimum of 10).

5.2 Exclusion criteria

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

1. History of another primary malignancy except adequately treated in situ carcinoma of the cervix or non-melanoma carcinoma of the skin or any other curatively treated malignancy that has not been treated in the prior 3 months or expected to require treatment for recurrence during the course of the study.
2. Patients with metastatic CNS tumors are allowed provided that they are clinically stable for a period of 30 days prior to study entry and there is not a requirement for steroid (other than close to physiologic doses) or anti-convulsant therapy. Patients with leptomeningeal involvement are excluded.
3. Patients who received a prior selective FGFR inhibitor in the recurrent/metastatic disease setting. Prior use of a multikinase inhibitor that includes anti-FGFR activity is acceptable after review by the Lead Investigator (Dr. Seiwert).
4. 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 coronary calcification
5. Current evidence of corneal or retinal disorder/keratopathy including, but not limited to , bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjuctivitis, confirmed by ophthalmologic examination
6. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral BGJ398 (infigratinib) (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection)
7. History and/or current evidence of endocrine alterations of calcium/phosphate homeostasis, e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis, etc unless the lead investigator obtains approval from Novartis.
8. Treatment with any of the following anti-cancer therapies prior to the first dose of BGJ398 (infigratinib) within the stated timeframes
    - Cyclical chemotherapy (intravenous) within a period of 2 weeks unless there are ongoing side effects > Grade 2.
    - Biological therapy (including small molecules, and/or) within a period of time that is ≤2 weeks prior to starting study drug unless there are ongoing side effects > Grade 2.
    - Any other investigational agents within a period ≤ 2 weeks prior to starting study drug unless there are ongoing side effects > Grade 2.
    - Wide field radiotherapy (including radioisotopes) ≤ 2 weeks prior to starting study drug unless there are ongoing side effects > Grade 2.

9. Patients who are currently receiving treatment with agents that are known strong inducers or inhibitors of CYP3A4 are prohibited.
10. Enzyme inducing anti-epileptic drugs.
11. Consumption of grapefruit, grapefruit juice, pomegranates, star fruits, Seville oranges or products within 7 days prior to first dose.
12. 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.
13. Use of amiodarone within 90 days prior to first dose.
14. Use of medications that increase serum levels of phosphorus and/or calcium.
15. Current use of therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulants. Heparin and/or low molecular weight heparins or other anticoagulants are allowed.
16. Insufficient bone marrow function
    - 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
17. Insufficient hepatic and renal function
    - Total bilirubin > 1.5x ULN (unless evidence of Gilbert's disease)
    - AST/SGOT and ALT/SGPT > 2.5x ULN
    - Serum creatinine ≥ ULN and/or calculated or measured creatinine clearance < 75% LLN
18. Calcium-phosphate homeostasis
    - Inorganic phosphorus outside of normal limits
    - Total and ionized serum calcium outside of normal limits
19. 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, or uncontrolled hypertension (refer to WHO-ISH guidelines)
    - 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 > 450 msec (both genders)
    - History of congenital long QT syndrome
20. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
21. Known positive serology for HIV, active Hepatitis B, and/or active Hepatitis C infection.
22. Study medication cannot be administered through G-tube, unless additional information from the manufacturer becomes available in the future.

23. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 3 months following the discontinuation of study treatment must be used by both sexes (=female patients and their male partners). 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 taking 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 on the study the vasectomized male partner should be the sole partner for that subject.
    - Combination of the following (a+b or 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

    Note: Oral contraceptives (OC), injected or implanted hormonal methods are not allowed as the sole method of contraception because BGJ398 (infigratinib) has not been characterized with respect to the potential to interfere with PK and/or the effectiveness of OCs.

    Post-menopausal women are allowed to participate in this study. Women are considered post-menopausal and not of child bearing potential if they have had 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, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

24. Sexually active males unless they use a condom during intercourse while taking drug and for 3 months after the last dose of the study drug and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

6 Treatment

The investigational drug will be BGJ398 (infigratinib) as an oral formulation.

6.1 Treating the patient

The treating investigator needs to 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.

6.1.1 Administration

BGJ398 (infigratinib) will be taken once daily on a three weeks on, one week off schedule. BGJ398 (infigratinib) will be dosed orally on a flat dosing scale of 125 mg/day, irrespective of size and weight.

Table 6-1 Treatment and treatment schedule

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

6.1.2 Instructions for Administration of BGJ398 (infigratinib)

The following general guidelines should be followed for BGJ398 (infigratinib) administration:

- Patients should be instructed to take the daily dose of BGJ398 (infigratinib) in the morning, at approximately the same time each day (24 ± 2 hr interval).

- BGJ398 (infigratinib) should be administered in the fasted state, at least 1 hour before or 2 hours after a meal.
- Phosphate binders should be given with meal (low phosphate diet), every day on days BGJ398 (infigratinib) is given. No treatment with phosphate binders is needed during the BGJ398 (infigratinib) off week in a cycle, unless the lab results indicate higher serum phosphorus levels that require continuous treatment with phosphate binders.
- BGJ398 (infigratinib) 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 the patient forgets to take the scheduled dose in the morning, he/she should not take the dose more than 2 hours after the usual time and should continue treatment the next day. Any doses that are missed should be skipped altogether and should not be replaced or made up at the next scheduled dosing.
- If vomiting occurs following the dosing of study drug, re-dosing is not permitted that same day. Dosing should resume the next day.

- BGJ398 (infigratinib) is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper gastro-intestinal tract may alter the solubility of both compounds, and limit bioavailability. These agents include, but are not limited to, proton-pump inhibitors (e.g., omeprazole), H2-antagonists (e.g., ranitidine) and antacids. Therefore, BGJ398 (infigratinib) should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.
- Patients must avoid consumption of grapefruit, pomelos, pomegranates, star fruits, Seville oranges or products containing the juice of each during the entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.
- Patients on strong or moderate CYP3A4 inducers or inhibitors or medications that rely on CYP3A4 for metabolism, should switch whenever possible to a product with less interaction with/reliance on the pathway or patient should be on a stable dose of the medication prior to enrollment

6.1.3 Ancillary treatments with anti-emetics, phosphate lowering agents, anti-diarrheals, and growth factors

Anti-emetics

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

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 (infigratinib) administration

Anti-diarrheals

No prophylactic anti-diarrhea therapy is recommended. However, patients should have loperamide tablets at home in case BGJ398 (infigratinib) induced diarrhea occurs and should call the study doctor or study staff at the first onset of loose stools. Patients should also be instructed to record the number of stools and report severe symptoms (e.g., fever or dizziness on standing). Initial management of mild to moderate diarrhea should include dietary modifications (e.g., eliminating all lactose-containing products and high-osmolar dietary supplements), extra fluids to prevent dehydration and loperamide at an initial dose of 4mg followed by 2 mg every 4 hours or after every unformed stool but not to exceed 16 mg/day.

In case of persistent, (i.e. >48 hrs on loperamide), or aggravated diarrhea, the patient should be seen at the investigational site or in the physician's office/outpatient center for further evaluation, including complete stool and blood work-up and intensified anti-diarrhea treatment per institutional guidelines.

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 treating 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.

6.1.4 Dosing and treatment schedule

BGJ398 (infigratinib) will be dosed at 125 mg PO daily with three weeks on therapy, and one week off therapy. Dosing information will be captured per cycle given the mandated off week. There is no dose escalation. Dose is the established phase II dose.

6.1.5 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 doses of study drugs as per the criteria in Table 6-3. If treatment is resumed at the same doses of study drugs, and the same toxicity recurs with the same or worse severity regardless of duration, doses must be reduced to the next lower dose level. If treatment is resumed at the lower doses of study drugs, and the same toxicity recurs with the same or worse severity, the patient must discontinue study treatment.

If a patient requires a dose delay of > 14 consecutive days of BGJ398 (infigratinib) from the intended day of the next scheduled dose, then the patient should be discontinued from the study treatment, unless extenuating circumstance occur and approval from Novartis is obtained.

Patients who discontinue the study for a study related adverse event or an abnormal laboratory value must be followed as described in Section 6.1.5.

Table 6-2 Dose reduction table

Dose reduction			
	Starting dose level 0	Dose level - 1	Dose level - 2
BJG398	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., stable disease, partial response, or complete response) but is experiencing adverse events that prevent continued treatment at the already reduced dose.

Table 6-3 Recommended dose modifications for BGJ398 (infigratinib) treatment

6.2 Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	**6.3 Recommended Dose Modifications any time during a cycle of therapy**
Cardiac disorders	
Cardiac - Prolonged QTcF interval	
Grade 1 and 2 : QTcF ≥ 481msec and ≤ 500 msec (asymptomatic)	Maintain dose level of BGJ398 (infigratinib) ECG assessments should be performed for 2 additional cycles at the same frequency as in cycle 1, or as clinically indicated • If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule. • If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in cycle 1 for all subsequent cycles.
Grade 3 : QTcF > 500msec as identified on the ECG by the investigator	• Hold BGJ398 (infigratinib). • 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 (infigratinib) until electrolytes are documented to be within normal limits. Once the QTcF prolongation has resolved and if the QTcF prolongation was confirmed by the central reader, 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

6.2 Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	6.3 Recommended Dose Modifications any time during a cycle of therapy
	○ If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule. ○ If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in cycle 1 or as clinically indicated, for all subsequent cycles • Patients who experience recurrent QTcF ≥ 500msec after one dose reduction will be discontinued from study. NB: If ventricular arrhythmia or Torsades de Pointes is observed in a patient, he/she will be discontinued from the study.
Cardiac disorders - others Grade ≥ 3, or congestive heart failure ≥ 2	Discontinue patient from study treatment.
Investigations-Hematology	
ANC decreased (Neutropenia) Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1or baseline, then • If resolved in ≤ 7 days, maintain dose level of BGJ398 (infigratinib) • If resolved in > 7 days, ↓ 1 dose level of BGJ398 (infigratinib). Hold dose of BGJ398 (infigratinib) until resolved to CTCAE ≤ Grade 1, ↓ 1 dose level of BGJ398 (infigratinib).
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) Grade 4	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1, then • If resolved by ≤ 7 days, ↓ 1 dose level of BGJ398 (infigratinib). • If not resolved within 7 days discontinue patient from study drug treatment. Discontinue patient from study treatment.
Hemoglobin Grade 3 (<8.0 mg/dL – 6.5 mg/dL) Grade 4 (< 6.5 mg/dL)	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 or baseline, then maintain dose level Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level

6.2 Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	6.3 Recommended Dose Modifications any time during a cycle of therapy
Platelet count decreased (Thrombocytopenia)	
Grade 3 (PLT < 50 - 25 x 10^9/L) without bleeding	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of BGJ398 (infigratinib). • If resolved in > 7 days, ↓ 1 dose level of BGJ398 (infigratinib)
Grade 3 (PLT < 50 - 25 x 10^9/L) with bleeding or Grade 4 (PLT < 25 x 10^9/L)	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level
Investigations – Renal	
Serum creatinine	
Grade 1 and Pi >5.5 mg/dL and/or tCa x Pi >55 mg^2/dl^2 and despite phosphorus lowering therapy for at least 14 days	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of BGJ398 (infigratinib). • If resolved in > 7 days, ↓ 1 dose level of BGJ398 (infigratinib).
Grade 2 (> 1.5 - 3.0 x ULN)	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of BGJ398 (infigratinib). • If resolved in > 7 days, ↓ 1 dose level of BGJ398 (infigratinib).
Grade 2 and Pi >5.5 mg/dL and/or tCa x Pi >55 mg^2/dl^2 and despite phosphorus lowering therapy for at least 14 days	Discontinue patient from study treatment
Grade ≥ 3 (> 3.0 x ULN)	Discontinue patient from study treatment.
Investigations – Hepatic	
Blood bilirubin (patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)	
Grade 2 (>1.5 – 3.0 x ULN)	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 • If resolved in ≤ 7 days, maintain dose level of BGJ398 (infigratinib). • If resolved in > 7 days, ↓ 1 dose level of BGJ398 (infigratinib).
Grade ≥ 3 (> 3.0 x ULN)	Discontinue patient from study treatment.

6.2 Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	6.3 Recommended Dose Modifications any time during a cycle of therapy
	Note: If CTCAE Grade 3 or 4 hyperbilirubinemia is due to hemolysis, then ↓ 1 dose level of BGJ398 (infigratinib) and continue treatment at the discretion of the Investigator.
AST or ALT Grade 3 (> 5.0 - 20.0 x ULN) without bilirubin elevation > 2.0 x ULN	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 or baseline • If resolved in ≤ 7 days, maintain dose level of BGJ398 (infigratinib). • If resolved in > 7 days, ↓ 1 dose level of BGJ398 (infigratinib).
Grade 4 (> 20.0 x ULN) without bilirubin elevation >2.0 x ULN	Discontinue patient from study treatment.
AST or ALT and Bilirubin AST or ALT > 3.0 – 5.0 x ULN and total bilirubin > 2.0 x ULN without liver metastasis or evidence of disease progression in the liver	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 • If resolved in ≤ 7 days, ↓ 1 dose level of BGJ398 (infigratinib). • If resolved in > 7 days, discontinue patient from study treatment.
AST or ALT > 5.0 x ULN and total bilirubin > 2.0 x ULN	Discontinue patient from study treatment.
Laboratory / Metabolic disorders	
Asymptomatic amylase and/or lipase elevation Grade 3 (> 2.0 - 5.0 x ULN)	• Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 2. • ↓ 1 dose level of BGJ398 (infigratinib) Note*:* A CT scan or other imaging study to assess the pancreas, liver, and gallbladder must be performed within 1 week of the first occurrence of any CTCAE ≥ Grade 3 amylase and/or lipase. If asymptomatic CTCAE Grade 2 elevations of lipase and/or amylase occur again at the reduced dose, patients will be discontinued permanently from study treatment.
Grade 4 (> 5.0 x ULN)	Discontinue patient from study treatment
Hyperphosphatemia Serum phosphorus > 5.5 – 7.0 mg/dL	Maintain dose level of BGJ398 (infigratinib), but modify phosphate lowering therapy Hold BGJ398 (infigratinib) dose until resolved to serum phosphorus ≤ 5.5 mg/dL

6.2 Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	6.3 Recommended Dose Modifications any time during a cycle of therapy
Serum phosphorus >7.0 – 10.0 mg/dL despite phosphate lowering therapy Serum Pi > 10.0 mg/dL	• if resolved by ≤ 14 days after suspending BGJ398 (infigratinib), ↓ 1 dose level • if does not resolve within 14 days of suspending BGJ398 (infigratinib), discontinue patient from the study. Discontinue patient from the study
Hypercalcemia Serum calcium grade 2 Serum calcium ≥ grade 3	Hold BGJ398 (infigratinib) dose until resolved to grade 1 or baseline: • if resolved ≤ 7 days after suspending BGJ398 (infigratinib), maintain dose level • if resolved > 7 days after suspending BGJ398 (infigratinib), ↓ 1 dose level Discontinue patient from the study
Nervous system disorders	
Neurotoxicity Grade 2 Grade ≥ 3	Omit dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398 (infigratinib) Discontinue patient from study drug treatment
GI disorders	
Pancreatitis Grade ≥ 2	Discontinue patient from study drug treatment

6.2 Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	6.3 Recommended Dose Modifications any time during a cycle of therapy
Diarrhea	
Grade 1	Maintain dose level of BGJ398 (infigratinib), but initiate anti-diarrheal treatment
Grade 2	• Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment, maintain dose level of BGJ398 (infigratinib). • For reoccurrence of diarrhea CTCAE Grade 2, hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1, ↓ BGJ398 (infigratinib) by 1 dose level
Grade 3	• Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment • ↓ BGJ398 (infigratinib) by 1 dose level • For reoccurrence of diarrhea CTCAE Grade 3, despite optimal anti-diarrheal treatment, discontinue patient from study treatment.
Grade 4	Discontinue patient from study treatment. Note: Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt diarrhea
Vomiting Grade 2 not controlled by optimal anti-emetic therapy	Hold BGJ398 (infigratinib) doses until ≤ grade 1, ↓ 1 dose level
Grade 3 not controlled by optimal anti-emetic therapy or Grade 4	Discontinue patient from study
Eye Disorders (confirmed by ophthalmologic examination)	
Retinal disorders Grade 2 CSR and CSR-like events	Hold BGJ398 (infigratinib) until resolved to ≤ grade 1 but refer the patient to a retinal specialist for evaluation • If resolved in ≤ 14 days, ↓ BGJ398 (infigratinib) by 1 dose level • If resolved in > 14 days, discontinue BGJ398 (infigratinib)
Grade 3 CSR and CSR-like events and any other grade 3 eye disorders	Hold BGJ398 (infigratinib) until resolved to grade ≤ 1. • If resolved in ≤ 14 days, ↓ BGJ398 (infigratinib) by 1 dose level • If resolved in > 14 days, discontinue BGJ398 (infigratinib)

6.2 Worst Toxicity CTCAE v4.03 Grade (unless otherwise specified)	6.3 Recommended Dose Modifications any time during a cycle of therapy
≥ grade 1 retinal vein occlusion, grade 4 CSR and CSR-like events, and grade 4 other eye disorders	Discontinue BGJ398 (infigratinib)
Other ocular/visual toxicity ≥ grade 3	Hold BGJ398 (infigratinib) until resolution to ≤ grade 1 If resolution in ≤14 days, ↓ 1 dose level, otherwise discontinue BGJ398 (infigratinib)
General disorders	
Fatigue Grade 3	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1 • If resolved in ≤ 7 days, maintain dose level of BGJ398 (infigratinib). • If resolved in > 7 days, discontinue patient from study treatment.
Other clinically significant AEs	
Grade 3 Grade 4	Hold dose of BGJ398 (infigratinib) until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of BGJ398 (infigratinib). 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 (infigratinib) will be discontinued from study drug treatment. If a patient requires a dose delay of > 14 days from the intended day of the next scheduled dose of BGJ398 (infigratinib) then study treatment must be stopped.	

Table 6-4 Toxicity – Follow-up evaluation

TOXICITY	FOLLOW-UP EVALUATION
Metabolic (hyperphosphatemia)	Serum phosphorus lowering therapy consisting of dietary phosphate intake restriction and oral phosphate binders should be applied as follows: Calcium-containing phosphate binders are not recommended. Starting Cycle 1 Day 1 (beginning with the midday or evening meal onC1D1): - Restriction of dietary phosphate intake to 600 - 800 mg/day, if BMI ≥ 21kg/m^2. -Sevelamer 1 tablet (800mg) per meal; i.e. 3 x 800 mg/day.

TOXICITY	FOLLOW-UP EVALUATION
	Serum Pi > 5.5 – 7.0mg/dL: - Increase the dose of sevelamer up to 1200mg tid with meals Serum Pi > 7.0mg – 9.0mg/dL - Increase the dose of sevelamer up to 1600mg (2 tablets per meal) tid with meals If serum phosphorus increases > 7.0mg/dL despite phosphorus lowering therapy given for at least 14 days, the BGJ398 (infigratinib) dose should be held and then dose subsequently reduced. All patients will continue to be followed until resolution to serum phosphorus ≤ 5.5 mg/dL or baseline or stabilization.
Renal	If serum creatinine CTCAE Grade ≥ 1 has been demonstrated in conjunction with hyperphosphatemia, this parameter must be repeated at least weekly until resolution. 24-hour urine collection should also be obtained for total phosphate, calcium, protein and creatinine clearance within weekly intervals. Ultrasound examination of the kidneys should be performed as indicated to evaluate *de-novo* calcifications until resolution or stabilization of creatinine.

6.4 Follow up for dose modifications/treatment interruptions

Patients whose treatment is interrupted or permanently discontinued due to an 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, whichever comes first. If a patient requires a dose delay of > 14 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. However, the patient will continue to be followed for toxicity as previously described. All patients will be followed for adverse events and serious adverse events for 30 days following the last dose of BGJ398 (infigratinib).

6.5 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 physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications.

6.5.1 Permitted concomitant therapy requiring caution and/or action

Drugs that alter the pH of the GI tract

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

Corticosteroids

Chronic dosing of corticosteroids such as dexamethasone and prednisone is known to induce CYP3A enzymes, thereby increasing the risk of reducing drug exposure to sub-therapeutic levels. In addition BGJ398 (infigratinib) is an in vitro inhibitor of CYP3A4 and has the potential to increase the systemic exposure of corticosteroids that are metabolized by CYP3A4.

Systemic corticosteroid treatment can be used with caution.

Substrates and inhibitors

CYP substrates and inhibitors

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

Caution is advised when BGJ398 (infigratinib) is co-administered with opioid analgesics. Inhibition of opioid metabolism by CYP3A4 can lead to opioid toxicity, including fatal respiratory depression, or an enhanced risk for QTc prolongation. Patients receiving BGJ398 (infigratinib) and opioid analgesics should be carefully monitored. Synthetic opioids with clinically relevant interactions with CYP3A4 inhibitors include, but are not limited to, propoxyphene, fentanyl, alfentanyl and sufentanil. Use of alfentanyl, a sensitive CYP3A4 substrate with narrow therapeutic window, should be 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 (infigratinib) is a reversible inhibitor of CYP2C8, CYP2C9 and CYP2C19. Permitted medications to be used with caution in this study include those that are sensitive substrates of CYP2C8, CYP2C9, CYP2C19, or those substrates that have a narrow therapeutic index. BGJ398 (infigratinib) is a substrate of CYP3A4. Therefore moderate inhibitors and inducers should be used with caution if no other alternative is available.

Transporter substrates

In vitro data show that BGJ398 (infigratinib) is an inhibitor of BCRP. CQM157, a metabolite of BGJ398 (infigratinib), is an inhibitor of transporters P-gp, BCRP, OATP1B1, and OATP1B3 (IC_{50} 2-4 μM). 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.

Anti-emetics

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

QT/QTc interval prolongation or torsade de pointes medications

Medications that have the potential to prolong the QT/QTc interval or induce torsade de pointes are allowed with caution. Treating 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)

6.5.2 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 or radiation therapy (that includes > 30% of the bone marrow reserve), and surgery) other than the study treatment 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 the study.

CYP inhibitors

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

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

Patient on strong or moderate CYP3A4 inducers or inhibitors or medications that rely on CYP3A4 for metabolism, should switch whenever possible to a product with less interaction with/reliance on the pathway or patient should be on a stable dose of the medication prior to enrollment.

CYP inducers

Strong inducers of CYP3A4 are prohibited because their usage would likely decrease the exposure of BGJ398 (infigratinib). Caution should be used during administration of moderate inhibitors.

Phosphorus and calcium

Medications that increase the serum levels of phosphorus and/or calcium are prohibited. 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 first dose of study drug.

6.6 Criteria for removal from study

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

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

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the treating and/or lead investigator.
- Patient refusal
- Patient withdrawal
- Administrative reasons after discussion/approval by the Lead Investigator
- Lost to follow-up/Non-compliance
- Study termination

6.7 Study drug(s)

6.7.1 Packaging and labeling

BGJ398 (infigratinib) will be supplied by Novartis as 25mg and 100mg-mg hard gelatin capsules for oral use, packaged in bottles, and will be administered on a flat scale.

Medication will be labeled for Clinical Trial use and will include storage conditions for the drug and the medication number but no information about the patient.

Table Packaging and labeling

Study drugs	Packaging	Labeling
BGJ398 (infigratinib)	hard gelatin capsules in bottles (25mg, 100mg)	Labeled as "BGJ398 (infigratinib)"

6.7.2 Supply, receipt and storage

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 site investigator and designated study staff have access. Upon receipt, BGJ398 (infigratinib) 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 (infigratinib) for self-administration at home until at least their next scheduled study visit.

6.7.3 Drug compliance and accountability

Patients will be required to keep a pill diary (see Section 11.3 Appendix C for sample medication diary). Pill count will be performed at the end of each cycle to confirm drug compliance.

Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation.

At the conclusion of the study, and, as appropriate during the course of the study, the Site Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Novartis.

6.7.4 Disposal and destruction

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

6.7.5 Study drug discontinuation

Patients who discontinue study treatment should be scheduled for an End of Study Visit within 14 days after discontinuing study treatment, at which time all of the assessments listed for the End of study visit will be performed. Patients lost to follow up should be recorded as such.

All patients who discontinue study treatment (or a knowledgeable informant), including those who refuse to return for the final 14-day Follow up Visit, should be contacted for safety evaluations, anti-neoplastic therapies received after discontinuation of study drug, and overall survival $\leq$ 30 days following the last dose of study treatment.

Patients whose treatment is interrupted or permanently discontinued due to a study-related adverse event or abnormal laboratory value must be followed 30 days post study discontinuation until all toxicities have resolved to CTCAE $\leq$ 1 or until stabilization.

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 completely resolved or until the toxicity is considered to have stabilized after at least 6 months of follow-up. Refer to section on Clinical Safety.

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.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

The table below lists all of the assessments and indicates with an "X" the visits when they are performed.

End of treatment/end of study visit to occur within 14 days after discontinuing study treatment.

End of post-treatment follow-up to occur up to 30 days post study discontinuation until all toxicities have resolved to CTCAE ≤ 1 or until stabilization.

Table 7-1 Visit evaluation schedule

	Screening	**Treatment**								**Subsequent cycles**	**End of treatment / End of study visit**	**End of Post-treatment follow-up**	**Survival**
		Cycle 1				**Cycle 2**				**Cycle 3+** *Visits on day 1 of each cycle unless more frequent visits are clinically indicated*			
Visit no.	**1**[1]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**			
Day of cycle	**Screening / Baseline**	**1**	**8**	**15**	**21**	**1**	**8**	**15**	**21**	**1**	**EOT***	**End of Post-treatment follow-up**	**Survival****
Informed consent	**X**												
Demography	**X**												
Inclusion/ exclusion criteria[1]	**X**												
Relevant medical history	**X**												
Physical exam*	**X**	**X**		**X**		**X**		**X**		**X**	**X**	**X**	
Vitals*	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**	**X**	**X**	
Ophthalmic assessment**	**X**									**X (only cycle 3)**			
ECG[2]	**X**	**X**				**X**				**X**			
Performance Status ECOG*	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**	**X**	**X**	
Archival tissue (≥10 unstained slides)[3]	**X**												
Blood for banking of normal DNA	**X**												

	Screening	**Treatment**								**Subsequent cycles**	**End of treatment / End of study visit**	**End of Post-treatment follow-up**	**Survival**
		Cycle 1				**Cycle 2**				**Cycle 3+** *Visits on day 1 of each cycle unless more frequent visits are clinically indicated*			
Visit no.	**1**[1]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10+**			
Day of cycle	**Screening / Baseline**	**1**	**8**	**15**	**21**	**1**	**8**	**15**	**21**	**1**	**EOT***	**End of Post-treatment follow-up**	**Survival****
Radiological tumor assessment/ response assessment (CT Scans)[4]	**X**									**Every uneven treatment cycle and +/- 8 days of D1 of respective cycle**	**X**		
Hematology[5]	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**	**X**		
Serum Chemistry[6]	**X**	**X**	**X**	**X**	**X**	**X**		**X**		**X**	**X**		
Pregnancy Test[7]	**X (blood)**	**X**				**X**				**X**	**X**		
LVEF assessment[10]	**X**	**To be repeated every 4-6 months in asymptomatic patients. In symptomatic patients, LVEF assessment should be done every 2-4 months and more frequently as needed if symptoms occur/clinically indicated**											
BGJ398 (infigratinib) dosing[8]		**Continuous (21 days with 7 days of rest)**											
Tumor biopsy[9]		**In responders with progressive disease**											
Prophylactic phosphate-lowering therapy		Daily											
Concomitant medications		**Continuous monitoring**											
Adverse events		**Continuous Monitoring (up to 30 days post study discontinuation)**											
Overall Survival		**Overall survival [days] = date of death – date of randomization + 1**											**X**

[1] Baseline clinical/laboratory evaluations must be done within 2 weeks prior to start of protocol therapy. Imaging must be done within 28 days of start of therapy.

[2] ECG should be performed as a standard12 lead resting ECG (with QTc Interval report) - done at screening or baseline, then prior to the first administration of BGJ398 (infigratinib), on Day 1 of Cycle 1 and subsequently at day 1 of every cycle, pre-dose and at the end of treatment. Test should be performed within ±8 days of the scheduled day of assessment. In patients with clinical evidence of heart failure (NYHA≥2) an assessment of cardiac function (e.g. MUGA) should be considered.

[3] Can be substituted with tissue from the fresh biopsy (if sufficient material available).

[4] Radiological tumor assessment should be performed at baseline within 28 days before start of treatment and subsequently every 8 weeks from initiation of study drug, until progression of disease or end of treatment. All assessments should be performed within ±8 days of the scheduled day of assessment. The assessment at the EOT visit is only to be performed if the prior assessment occurred ≥ 21 days before. Comparable alternative imaging modalities may be used (MRI/PET) if indicated.

[5] Hematology – WBC plus differential (neutrophil including bands, lymphocyte, monocyte, eosinophil, basophil and other counts, hemoglobin and platelets. Should be performed on D1, D8, and D15 of cycle 1 and 2. For subsequent cycles, day 1 and day 15 hematology assessments are acceptable. Test should be performed within ±8 days of the scheduled day of assessment.

[6] Serum chemistry: K+, Na+, chloride, bicarbonate, BUN, creatinine, Ca++, phosphorus, Mg++, ALT, AST, total bilirubin, alkaline phosphatase. Test should be performed within ±8 days of the scheduled day of assessment.

[7] All women of child bearing potential (pre-menopausal or less than 1 year after the onset of menopause, and intact uterus) must have a serum pregnancy test (β-hCG) ≤ 72 hours before the first dose of study treatment. Additionally, a urine pregnancy test should be performed at Day 1 of each cycle and at the End of Treatment visit (serum test is acceptable as an alternative). A positive pregnancy test requires immediate interruption of study drug treatment until serum β-hCG is performed and found to be negative. If positive, the patient must be discontinued

Pregnancy testing is only required in woman with child bearing potential (pre-menopausal women with intact uterus)

[8] BGJ398 (infigratinib) is taken daily (21 days on with 7 days of rest) and self-administered by the patient. Medication cannot be administered through G tube. Treatment courses continue until disease progression or unacceptable drug intolerance. Patient is supplied a new bottle of study drug on days 1 of each cycle (each bottle contains 30 tablets).

[9] Patients who demonstrate initial clinical and/or radiographic response (e.g. tumor shrinkage) to therapy, followed by subsequent progressive disease by RECIST, should proceed with mandatory tissue biopsy for biomarker correlative studies in event of accessible tumor tissue.

[10] LVEF assessment can be done by MUGA scan or Echocardiogram. A prior normal LVEF assessment in the past 6 months in the absence of cardiac symptoms is acceptable as a baseline assessment.

[*] A scan performed for clinical reasons mid-cycle (e.g., for clinical symptoms of possible disease progression) which confirms progressive disease and which results in the patient being taken off study, will count as the end of treatment radiologic evaluation.

[**] Patients will be followed for survival status, and time of death, though this is not a primary endpoint of the study. See section 4.5 and 10.6.

***** Tests should be performed within ±8 days of the scheduled day of assessment during treatment period with BGJ398 (infigratinib)..

****Ophthalmic exam should** include: visual acuity testing, slit lamp examination of the anterior eye segment, IOP, and fundoscopy. Additional examination methods such as specular microscopy (that enables a magnified, direct view of the corneal epithelium), corneal pachymetry, and dilated fundoscopy. Ophthalmic exams should be done at baseline and after two cycles (=beginning of cycle 3). In addition ophthalmic exams should be done as clinically indicated.

7.2 Screening Examination

Baseline evaluations are to be conducted within 14 days prior to start of protocol therapy. Scans and x-rays must be done < 28 days prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. The screening examination must start with the Informed Consent procedure. The treating investigator is obliged to give the patient thorough information about the study and the study related assessments, and the patient should be given ample time to consider his or her participation. The treating investigator must not start any study related procedure before ICF is signed and dated by both patient (and impartial witness, if applicable) and investigator.

7.3 Assessment types

7.3.1 Efficacy

Efficacy will be assessed through RECIST 1.1 defined objective response rate (e.g. ORR, complete or partial response).

Per RECIST 1.1, investigators are to obtain confirmatory scans greater than 4 weeks after objective response (Eisenhauer EA et al, Eur J Ca, 2009).

For the purposes of this study, patients should be reevaluated for response every 8 weeks. Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer EA et al, Eur J Ca, 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with BGJ398 (infigratinib).

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received any therapy with BGJ398 (infigratinib), and have had their disease re-evaluated (= at least one post-baseline scan is available) will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 2 (i.e. clinically indicated scan ahead of schedule shows progressive disease) will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received any therapy with BGJ398 (infigratinib), and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease is defined per RECIST 1.1 (Eisenhauer et al Eur J Cancer 2009)

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes are defined per RECIST 1.1 (Eisenhauer et al Eur J Cancer 2009)

Non-measurable disease is defined per RECIST 1.1 (Eisenhauer et al Eur J Cancer 2009)

Target lesions nodes are defined per RECIST 1.1 (Eisenhauer et al Eur J Cancer 2009)

Non-target lesions nodes are defined per RECIST 1.1 (Eisenhauer et al Eur J Cancer 2009)

Methods for Evaluation of Measurable Disease

Analogous to outlined methods in RECIST 1.1 nodes are defined per RECIST 1.1 (Eisenhauer et al Eur J Cancer 2009). Briefly:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Response Criteria

Evaluation of Target Lesions

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

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters and not qualifying for progressive disease criteria.

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

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

Evaluation of Non-Target Lesions

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

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

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

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

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

Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation*
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation*
CR	NE	No	PR	
PR	Non-PD/NE	No	PR	
SD	Non-PD/NE	No	SD	Documented at least once ≥4 wks. from treatment start*
Not all evaluated	Non-PD	No	NE	--
PD	Any	Yes or No	PD	--
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript (Eisenhauer et al Eur J Cancer 2009) for further details on what is evidence of a new lesion.

Only for non-randomized trials with response as primary endpoint.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

NE = non evaluable

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

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

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

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

NE = non evaluable

Confirmatory Measurement/Duration of Response

Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed ≥4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at an interval of ≥4 weeks).

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease or death due to study indication (whichever happens first) objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression or death due to study indication (whichever happens first) are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

7.3.2 Safety

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the monitoring of hematology, blood chemistry, ECG and the regular monitoring of vital signs, and physical exam including weight and performance status.

These assessments should be performed within ±8 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NCI CTCAE v4.

BGJ398 (infigratinib) has been well tolerated in its phase I, expansion, and phase II studies to date.

Post-biopsy patients will be followed closely for any evidence of complications. Dose delay rules will be closely followed as outlined (Section 6.1.5). In addition the Treating Investigator may elect to further delay treatment if any serious concerns about wound healing or unexpected events should occur.

7.3.3 Pharmacokinetics

BGJ398 (infigratinib) will be dosed at the established phase II dose, 125 mg PO daily. No specific pharmacokinetics will be obtained.

7.3.4 Correlative Analysis

For Details on FGFR aberration testing please see Section 4.1.1

FGFR profiling will be performed in the following two scenarios:

1. Genomic profiling to identify FGFR altered tumors and correlation of specific genetic changes with efficacy.

2. Tumors that respond and subsequently developed resistance (acquired resistance) will be biopsied to explore mechanisms of resistance to FGFR inhibition. Analysis of such tumors may be broader and include exome sequencing, RNA-seq analysis or similar tests.

While requirements for tissue and correlational studies are clearly stated and are to be implemented stringently, medical necessity, e.g. in the case of potential harm to the patient, or other extenuating circumstances may trigger a review and possible waiver per the PI on rare occasions.

Archival Tissue and Blood:

In addition to FGFR testing all patients are required to provide ≥10 unstained FFPE slides. This requirement can be waived only if a fresh tumor biopsy provides adequate tissue or per discussion with the Lead Investigator (Dr. Seiwert).

All patients are required to collect blood for banking of normal DNA

→ See Appendix B for tissue collection form

7.3.5 Tumor Biopsies

1) If no archival tissue for FGFR genetic aberration testing is available a fresh tumor biopsy is encouraged, and should typically be processed as a fresh frozen biopsy with OCT embedding. Please contact the Lead Investigator (Dr. Seiwert at tseiwert@medicine.bsd.uchicago.edu or 773-702-2452 for more details).

2) Tumors that showed benefit from therapy (= RECIST response, or prolonged disease stabilization ≥ 6 months) and subsequently progress are required to undergo a fresh biopsy.

Biopsy should be performed preferentially by a surgeon (excisional biopsy or core needle biopsy (3-4 cores) or via interventional radiology (core biopsy (3-4 cores)). A large (several pass) bronchoscopic biopsy is potentially also acceptable, but a discussion about the amount of required tissue between the Treating Investigator and the pulmonary attending performing the procedure is required prior to biopsy. An FNA is not acceptable.

Biopsy in the above two scenarios is mandatory.

Typically a biopsy should be done in a lesion that is not the **only lesion** for RECIST measurement. A waiver of this requirement can be obtained after discussion with the Lead Investigator (Dr. Seiwert; tseiwert@medicine.bsd.uchicago.edu or 773-702-2452).

7.3.6 Biopsy safety considerations

Biopsies (core biopsies and small excisional biopsies) are generally considered safe during administration of treatment. Nevertheless in difficult to assess/high risk locations the treatment may be held for 2 days prior to biopsy and 3-5 days afterwards. For larger scale surgeries or should bleeding or wound healing complications arise the treating investigator should contact the Lead Investigator in order to get approval to continue holding therapy and will assess how long to hold treatment on a cases by case basis.

8 Data Reporting

Data reporting will be performed utilizing the eVelos electronic data capture system. The University of Chicago CRA will provide applicable user registration information.

All required data must be recorded in the eVelos database at the completion of each cycle. AEs are to be entered in real time. SAEs are to be entered on the Serious Event Form within 24 hours of the site's knowledge of the event and sent via email (preferred) or fax to the University of Chicago (PhaseIICRA@medicine.bsd.uchicago.edu or qaccto@bsd.uchicago.edu; Fax: 773-702-4889). All case report forms must be completed by designated study personnel. Each screened (consented) patient is to be entered into eVelos within 48 hours of patient registration. In addition to direct data entry, you may be required to provide supporting source documentation. Source records are original documents, data, and records (e.g., medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. Each site will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form.

9 Registration Procedures

9.1 General Guidelines

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-treatment evaluations. Patients must meet all of the eligibility requirements listed in Section 5. Eligible patients will be entered on study centrally by the University of Chicago study coordinator. All sites should call the study coordinator at (773) 834-3095 or PhaseIICRA@medicine.bsd.uchicago.edu to verify availability of a slot.

Following registration, patients (must/should) begin protocol treatment within 7-10 business days. Issues that would cause treatment delays should be discussed with the Lead Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study will be canceled. The study coordinator/CRA should be notified of cancellations as soon as possible.

9.2 Registration Process

When a potential patient has been identified, notify the CRA via phone or email to ensure a reservation on the study ((773) 834-3095 or PhaseIICRA@medicine.bsd.uchicago.edu). Reservations for potential subjects will only be held for subjects who have signed consent for that particular study.

When registering a subject, the following must occur:

- Confirm that the institution has a current IRB approval letter for the correct version of protocol/consent and has an annual update on file, if appropriate.
- Submit all required materials (Eligibility Checklist, Source documentation, & signed consent form) to confirm eligibility and required pre-study procedures to the CRA a minimum of 48 hours prior to the subject's scheduled therapy start date.
- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.
- Communicate with the above CRA to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the PI. PI may clarify, but not overturn, eligibility criteria.
- Affiliate sites must confirm registration of subjects by obtaining a subject study ID number from the CRA via phone, fax or email.
- If a subject does not start on the scheduled day 1 treatment date, promptly inform the CRA as the delay in start may deem the subject ineligible and/or require further or repeat testing to ensure eligibility.
- The date the patient is randomized if randomization is involved or receives treatment for the first time will be considered the patient's "OnStudy Date." The patient's subject ID will be assigned and a confirmation of registration will be issued by the CRA on this date. Subjects that sign consent and do not go "OnStudy" will be recorded in the database with the date they signed consent and the reason for not going "OnStudy" (e.g., Ineligible, Screen Failure or Withdrawn Consent).

10 Safety monitoring and reporting

10.1 Adverse Events

10.1.1 Definitions and reporting

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs expected by the investigational agent (Section 10.1.2) and the characteristics of an observed AE (Section 10.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

10.1.2 Adverse event list

Adverse reactions are listed below by MedDRA body system organ class.
The following convention has been utilized for the classification of frequency:

Very common ≥ 1 in 10

Common ≥ 1 in 100 and < 1 in 10

Uncommon ≥ 1 in 1,000 and < 1 in 100

Categories have been assigned based on absolute frequencies in the clinical trial data.

ADVERSE EVENT CATEGORY	VERY COMMON	COMMON	UNCOMMON	EXPEDITED REPORTING IF GRADE > 2
Blood and lymphatic system disorders			X	
Endocrine disorders			X	X
Metabolism and nutrition disorders			X	
Nervous system disorders			X	
Cardiac disorders			X	X
Vascular disorders			X	
Hemorrhages			X	
Gastrointestinal disorders			X	
Hepatobiliary disorders			X	
Skin and subcutaneous tissue disorders			X	
Renal and urinary disorders			X	

General disorders and administration site conditions			X	
Corneal/ophthalmic disorders			X	

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Special AE expedited reporting:**
  AEs in the table under section 10.1.2 should undergo expedited reporting if the grade is above the grade provided in column labeled "Expedited Reporting if Grade > 2".

- **Attribution** of the AE:
  Definite (5) – The AE *is clearly related* to the study treatment.
  Probable (4) – The AE *is likely related* to the study treatment.
  Possible (3) – The AE *may be related* to the study treatment.
  Unlikely (2) – The AE *is doubtfully related* to the study treatment.
  Unrelated (1) – The AE *is clearly NOT related* to the study treatment.

10.3 Adverse Event Definitions

10.3.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

At each evaluation patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms, and review of the patient's own record of adverse events.

Adverse events will be followed until resolution while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization of the adverse event, or until the patient starts a new treatment regimen, or death, whichever comes first.

10.3.2 Serious Adverse Event

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

1) Death
2) Life-threatening (e.g. places subject at immediate risk of death, this does not include events that might have caused death if they occurred a greater severity)
3) Results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) 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.

10.3.3 Unexpected Events

Unexpected events are those not listed at the observed specificity or severity in the protocol, informed consent, or investigator brochure. An event is considered unexpected if it is listed as occurring within the class of drugs or otherwise expected from the drug's pharmacological properties but which has not been previously observed with this specific investigational agent.

10.3.4 Adverse Reactions

An adverse event is considered to be an adverse reaction if there evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater than expected frequency.

10.4 Adverse Event Reporting Requirements

10.4.1 Routine adverse event reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported using the Serious Event Reporting Form and/or MedWatch Form discussed below must also be reported in routine study data submissions.**

All adverse events (except grade 1 and 2 laboratory abnormalities that do not require an intervention), regardless of causal relationship, are to be recorded in the case report form and source documentation. The Site Investigator must determine the intensity of any adverse events according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and their causal relationship.

10.4.2 Serious adverse event reporting to the Coordinating Center

Use the UC CCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

All serious adverse events (as defined in sections 10.3.2) and all adverse events that have been specified to require expedited reporting in the section 10.1.2 table occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UC CCC) Clinical Trials Office (CCTO). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the CCTO by the end of the business day when s/he becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day.

Reports should be made using the 'Serious Event Report' Form. Please scan and send via email (preferred) or fax to the following:

University of Chicago Phase II CRA General:
PhaseIICRA@medicine.bsd.uchicago.edu
Phone: 773-834-3095
Fax: 773-702-4889

UC CCC Cancer Clinical Trials Office Quality Assurance:
qaccto@bsd.uchicago.edu

All unexpected adverse reactions must be reported to the IND holder so that the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu, within the specified timelines below regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Participating sites should not forward any adverse event reports directly to the FDA. The CCTO will report all events to the FDA as per the current FDA guidelines.

Fatal or Life-threatening Events: within 4 calendar days from treating investigator knowledge of the event

All Other Reportable Events: within 10 calendar days of treating investigator knowledge of the event

All serious adverse events should also be reported to the local IRB of record according to their policies and procedures.

10.4.3 Serious and Unexpected Adverse Event reporting by the Coordinating Center

The designated UC CCC Regulatory Manager will notify all participating sites of all unexpected and serious adverse reactions that occur on this clinical trial and which are reported to the FDA and/or UC Institutional Review Board (IRB). When reported to the FDA, a copy of the completed Form 3500A (MedWatch) will be provided to the responsible Regulatory Manager by the CCTO IND Coordinator for distribution to all participating sites.

10.4.4 Reporting Requirements for the Institutional Review Board

At the University of Chicago: Events meeting current IRB reporting criteria must be submitted by the principal investigator via the IRB's electronic submission system within **the IRB's designated reporting timeframes**. Details of the IRB's current reporting policy and timelines can be found on their website at: http://bsdirb.bsd.uchicago.edu/forms-guidelines/up.html

At other centers: the local regulations for reporting to the IRB overseeing clinical research should be followed by the individual sites.

10.4.5 Novartis instructions for rapid notification of serious adverse events

All serious adverse events must be reported to Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E) and reporting will be done via the coordinating center (Univ. of Chicago). . Applicable events will be reported to the IRB and FDA as per their current policies.

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All events must be reported, by FAX (877-778-9739) **to Novartis Pharmaceuticals DS&E Department within 24 hours of learning of its occurrence.** This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours.

Any serious adverse event occurring after the patient has provided informed consent 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).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

10.5 Pregnancies

Any pregnancy that occurs during study participation should be reported by the site. 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.

10.6 Duration of Follow up

Patients will be followed for any medical issues for a minimum of **8 weeks** (**6 months** is recommended) after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. In addition patients will be followed ≤ **every 1-3 months** for **survival until 5 years post treatment or until death**, whichever occurs first. Information on progression (as defined in this protocol) or death will be collected even if the patient has been removed from the study previously.

11 Statistical methods and data analysis

This phase IIa open label, proof-of-concept trial, that will be a arm study across several centers through the University of Chicago Personalized Cancer Care Consortium (PCCC) in which all eligible patients with histologically-confirmed recurrent/metastatic HNSCC and FGFR alteration will receive BGJ398 (infigratinib) at 125 mg PO daily.

20 patients will be enrolled on the study. Accrual of 20 patients is estimated to occur over 18-24 months.

Primary objective will be to assess efficacy of BGJ398 (infigratinib) in FGFR altered HNSCC (regardless of HPV status) using objective response rate (e.g. complete and partial response per RECIST 1.1 measurement).

11.1 Sample size calculation

Based on TCGA and our U Chicago cohort, FGFR2-3 mutations are estimated to occur in 5-8% of HPV (-) HNC and 10-15% of HPV (+) HNC. High level FGFR1 amplification (defined as copy number ≥ 4) is estimated to occur in 7-10% of HPV (-) HNC. FGFR3-TACC3 translocation is estimated to occur in 3-5% of either HPV (+) or HPV (-) head and neck cancers (in TCGA two TACC3-FGFR3 translocations occurred in HPV (+) HNC). It is expected that FGFR aberration will be mutually exclusive. The primary endpoint will be objective response rate (ORR; complete or partial response) in each of the two treatment arms (HPV(+) and HPV(-)).

With a Simon Two Stage Design (Minimax), a preset one-sided alpha level of 0.1 and power of 80%, we determined the minimum sample size required to detect the hypothesized response rate of 21% for BGJ398 (infigratinib) in each Cohort: A sample of 20 FGFR alteration (+) patients will be large enough to detect a response rate of 20% for BGJ398 (infigratinib) compared to a null response rate of 5% (Williamson et al. 2010, de Souza et al 2012) with 80% power and one-sided type I error rate of 0.10.

An interim analysis for futility will be conducted after 11 response evaluable patients without interruption of enrollment. If 0/11 responses are seen, the study will be stopped prematurely for futility. If at least one response is seen, an additional 9 patients will be enrolled. The results of the study will be deemed negative if ≤2 responses are seen in 20 patients.

Response rate of BGJ398 (infigratinib) in FGFR subgroups (as defined by certain genetic changes in FGFR1-3) will be reported if relevant as the grouping of genetic aberration as well as the size each group may not be sufficient for statistical analysis. The following grouping is suggested, but may be adapted as new information becomes available:

1. FGFR3 translocations
2. Other FGFR translocations
3. FGFR1 amplification
4. FGFR1 mutations
5. FGFR2 mutations
6. FGFR3 mutations
7. Other rare FGFR aberrations such as FGFR2 amplification, or FGFR3 amplification.

Kaplan-Meier estimates and 90% confidence intervals, using Greenwood's standard error estimate, will be tabulated at planned imaging intervals for progression-free survival (at 8 weeks, 16 weeks, 24 weeks, and every 8 weeks thereafter). Also, median PFS and 90% CI will be determined. We will perform similar analysis for Overall survival (OS) for up to 5 years.

We will report on duration of response and duration of stable disease and may consider a landmark analysis in responders versus non-responders.

12 Ethical considerations and administrative procedures

12.1 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.

12.2 Discontinuation of the study

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

12.3 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.

12.4 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.

12.5 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.

13 Study Management and Regulatory Affairs

13.1 Multicenter guidelines

The specific responsibilities of the Lead Investigator and the Coordinating Center are presented in Appendix B. Clinical studies coordinated by The University of Chicago must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements

The Study Lead Invesgiator/Coordinating Center is responsible for distributing all official protocols, amendments, and IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

13.2 Institutional Review Board (IRB) Approval and Consent

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.

Unless otherwise specified, each participating institution must obtain its own IRB approval. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

The treating investigator (or their designee) must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

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

Fertile men and women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement as outlined in this protocol for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study

13.3 Food and Drug Administration (FDA) Approval

This study will be conducted under an IND held by Tanguy Seiwert at the University of Chicago. The University of Chicago CCTO will be responsible for facilitating all communications with the FDA on behalf of the IND holder. Participating sites should not communicate directly with the FDA.

13.4 Required Documentation

Prior to the selection of a study site that is not a full member of the Personalized Cancer Care Consortium, the audit and trial oversight processes for the site must be reviewed and approved by the UC CCC Clinical Research Advisory Committee.

Before the study can be initiated at any site, the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the University of Chicago Comprehensive Cancer Center.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

13.5 Data and Safety Monitoring

This study will be remotely monitored by the designated University of Chicago Clinical Research Associate (CRA) in accordance with the University of Chicago, Section of Hematology/Oncology standard operating procedure titled Monitoring of Multi-Institutional Investigator Initiated Clinical Trials.

Prior to subject recruitment, and unless otherwise specified, a participating site will undergo a Site Initiation Teleconference to be conducted by the designated University of Chicago research team. The site's principal investigator and his or her study staff must attend the site initiation meeting.

Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and to ensure that the site Investigator is aware of his/her ongoing responsibilities.

Unless otherwise specified, this protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan. The conference will review:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented using the Protocol Deviation Form in the eVelos clinical trial management system. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported into the eVelos system within 7 days.

13.6 Auditing

In addition to the clinical monitoring procedures, the University of Chicago Cancer Clinical Trials Office (CCTO) will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UC CCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, they ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements by performing annual quality assurance audits. The CCTO will review subjects enrolled at the University of Chicago and at institutions who are formal members of the Personalized Cancer Care Consortium (PCCC) in accordance with audit procedures specified in the Data and Safety Monitoring plan.

Auditing procedures for participating sites that are not full members of the PCCC must be specified and approved by the UC CCC Clinical Research Advisory Committee. In general, for sites that are not full members of the PCCC, auditing responsibility will be delegated to the participating center, with the annual audit report forwarded to the University of Chicago for review.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

13.7 Amendments to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by Novartis and the Lead Investigator before implementation. Following this review, all modifications to the protocol, consent form will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead Investigator can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form (if applicable) to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.

- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment **must** be IRB approved by the institution **within 3 months** from the date that it was received.

- **The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter.** The version dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.

- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

13.8 Annual IRB Renewals, Continuing Review and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the participating institutions' IRBs at least once a year for the duration of the study. The annual IRB renewal approvals for participating institutions should be forwarded promptly to the Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

13.9 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

13.10 Obligations of Study Site Investigators

The Study Site Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Study Site Principal Investigator is responsible for personally overseeing the treatment of all study patients. He/she must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Study Site Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

14 Appendices

14.1 Appendix A: Performance Status Criteria

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

14.2 Appendix B: Multicenter Guidelines

Responsibility of the Study Lead PI

- The Study Lead PI will be the single liaison with regulatory and data management staff, outside sponsor/s, FDA, and funding agencies The Study Lead PI is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Study Lead PI. There will be only one version of the protocol, and each participating institution will use that document. The Study Lead PI is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Study Lead PI is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements are the responsibility of the Study Lead PI.
- The Study Lead PI is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Study Lead PI will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- The Coordinating Center is responsible for maintaining copies of IRB approvals from each participating site.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Study Lead PI.
- The Coordinating Center will maintain documentation of AE reports. The Coordinating Center will submit AE reports to the Study Lead PI for timely review.

14.3 Appendix C: Tissue Sample Collection Form

BGJ398 (infigratinib) – HNC

Clinician/Research Nurse: Please Fill Out

Tissue Samples

Patient Name: _____ MRN# (if applicable): _____

Patient Protocol ID #: _____ Date Tissue Obtained: _____

Institution: _____ Attending Physician: _____

Site of Biopsy: _____Site of Primary Tumor: _____

Did Surgical Pathology review tissue for presence of tumor (please circle)? **Yes No**

Number of unstained slides (≥10 slides (5 μm thick), 12-18 ideal):_____

Frozen Sample from biopsy: [ ] Pre-treatment

[ ] Re-biopsy (acquired resistance)

Blood collection (please check):

2 EDTA tubes (purple top, serum), 2x10ml: ___ 1 SST tube 7.5ml (gold top):_____

Date of blood draw: _____ Time of blood draw:_____

Contact Person's Phone Number/pager/email address:

Dept. of Pathology (University of Chicago)
Tissue Bank Intake Coordinator
5841 S Maryland, MC 3083
Chicago, IL 60637
***Phone* 773-834-8392 or 773-702-0119**

Please notify Dr. Seiwert once the sample was submitted:

Email: **tseiwert@medicine.bsd.uchicago.edu**; or call tissue bank Tel: 773-599-7501

14.4 Appendix D: Tumor Response Assessment RECIST 1.1

Response criteria for target lesions

1. Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10mm)
2. Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions taking as reference the baseline sum diameters and does not meet PD criteria
3. Progression (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (note: the appearance of one or more new lesions is also considered progression).
4. Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as references the smallest sum diameters while on study

Response criteria for non-target lesions

1. Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10mm short axis)
2. Non-CR/ Non-PD:	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
3. Progression (PD):	Unequivocal progression of existing non-target lesions (Note: the appearance of one or more new lesions is also considered progression)

Overall response

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks. Confirmation*
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation*
CR	NE	No	PR	
PR	Non-PD/NE	No	PR	

SD	Non-PD/NE	No	SD	Documented at least once ≥4 wks. from treatment start*
Not all evaluated	Non-PD	No	NE	--
PD	Any	Yes or No	PD	--
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript (Eisenhauer et al Eur J Cancer 2009) for further details on what is evidence of a new lesion.

Only for non-randomized trials with response as primary endpoint.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

NE = non evaluable

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

14.5 Appendix E: Drug Accountability - Sample Medication Diary

Site Number	Subject Number	Subject Initials	Cycle

Subject Drug Diary

Bring your diary and study drug bottles (containing unused drug and empty bottles) to EACH appointment with the research nurse.

Please complete the diary every day. Write the date and time of each dose of study drug you take. If you did not take your daily dose, or did not take your full dose, please write down the actual amount taken. If you experience any health/medical complaints, please record this information on the back of this card.

Day	Date	time of dose	# of _____
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
21			
22-28	Treatment Break (restart BGJ398 (infigratinib) on Day 1 of next cycle (=Day 29))		

Health / Medical Complaints

Please describe what you experienced	Date started	Dated stopped

Other Medications

Record only medications (prescription and/or over-the counter, including herbal medications and vitamins) taken other than study drug.

Name of Medication	Why did you take the medication?	Date started	Dated stopped

15 References

- Chaturvedi AK, Engels EA, Pfeiffer RM, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. Journal of Clinical Oncology. 2011 Nov 10;29(32):4294-301.
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