OSU 19041
Version Date: 5/23/2024
Approval Date: 6/20/2024

A phase II study of oral Infigratinib in adult patients with advanced or metastatic solid tumors with *FGFR1-3* gene fusions or other *FGFR* genetic alterations

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Protocol Summary:

Protocol number	OSU 19041
Title	A phase II study of oral Infigratinib in adult patients with advanced or metastatic solid tumors with *FGFR1-3* gene fusions or other *FGFR* genetic alterations
Brief title	Infigratinib in treatment of advanced solid tumors with *FGFR* fusions or mutations
Industry Partner and Clinical Phase	QED Therapeutics, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study is designed to evaluate the efficacy of the targeted, selective pan-FGFR inhibitor Infigratinib when administered as a single agent to patients with genetically selected advanced or metastatic solid tumors through assessment of the overall response rate. Molecular characterization such as genomic profiling of these tumors at baseline (i.e. prior to FGFR inhibitor therapy), on-treatment, and at the time of progression may lead to increased understanding of primary and acquired resistance mechanisms, as well as rationale treatment combinations.
Primary Objectives	1. To evaluate the efficacy of single agent Infigratinib in patients with advanced or metastatic solid tumors of any histologic classification with *FGFR1-3* gene fusions/translocations or other *FGFR* genetic alterations as measured by overall response rate assessed by investigator according to RECIST v1.1. 2. To understand response rate and potential for Infigratinib to benefit patients who have *FGFR* alterations such as point mutations/insertions/deletions in different solid tumor types.
Secondary Objectives	1. To further evaluate the efficacy of single agent Infigratinib as measured by progression free survival, best overall response, disease control rate, overall survival assessed by investigator as per RECIST v1.1 2. To characterize the safety and tolerability of single agent Infigratinib by type, frequency, and severity of AEs and SAEs 3. To evaluate benefit of Infigratinib in patients who have received one prior FGFR inhibitor
Study design	This is a multi-center, open label, single arm phase II study evaluating Infigratinib anti-tumor activity in advanced or metastatic solid tumor patients with *FGFR* genetic alterations including gene

	fusions/translocations, point mutations, insertions/deletions, and amplifications. Oral, monotherapy Infigratinib will be administered once daily for the first 3 weeks (21 days) followed by one week break of each 28-day cycle. Treatment period will begin on Cycle 1 Day 1 and will continue until disease progression, unacceptable toxicity, withdrawal of informed consent, or death. Patients will be evaluated for tumor response radiographically every 8 weeks until disease progression or discontinuation from study using RECIST v1.1.
Population	Up to fifty adult patients with histologically or cytologically confirmed advanced or metastatic solid tumors of any type with *FGFR1-3* gene fusion/translocation or other *FGFR* genetic alterations who have evidence of radiologic progression following standard of care (SOC) treatment regimens or who are intolerant of SOC will be enrolled to this study. The fifty adult male and female patients over age 18 are from the three following cohorts: 1. Cohort 1: Solid tumor patients with *FGFR1-3* fusion/translocation (**n, up to 30**) who have progressed on or are intolerant to SOC therapies. Prior therapy with a different FGFR inhibitor is not permitted. Cholangiocarcinoma patients are excluded from this cohort (there are multiple competing studies and opportunities for patients to get treatment in other trials). 2. Cohort 2: Solid tumor patients with *FGFR1-3* fusion/translocation **(n=10)** who have progressed on or are intolerant to SOC therapies and received treatment with a different FGFR inhibitor. Cholangiocarcinoma patients are permitted in this cohort. 3. Cohort 3: Solid tumor patients with genetic alterations such as point mutations, insertions/deletions, or amplifications in any FGFR gene family member **(n=10)**. Prior therapy with a different FGFR inhibitor is not permitted. Cholangiocarcinoma patients are permitted in this cohort.
Inclusion criteria	• Patients with histologically or cytologically confirmed solid tumors of any type at the time of diagnosis. • Written documentation of any CLIA-certified assay for determination of *FGFR1-3* gene fusions/translocations or other *FGFR* genetic alterations is required for eligibility. • Patients must have received at least one prior standard of care regimen for advanced or metastatic disease. Patients should have had evidence of progressive disease following prior regimen, or if prior treatment discontinued due to toxicity must have continued evidence of measurable or evaluable disease. Patients who have received prior treatment with a

	different FGFR inhibitor will be evaluated in a separate cohort on study (i.e. Cohort 2). • ECOG performance status ≤ 1 (Patients with ECOG performance status of 2 may be considered on a case-by-case basis after discussion with Principal Investigator at Ohio State University).
Exclusion criteria	• Patients who have therapies available that are known to confer a clinical benefit will be excluded. • Current evidence of clinically significant corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjuctivitis, confirmed by ophthalmologic examination. • History and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, and asymptomatic coronary calcification. • Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral Infigratinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome). • History and/or current evidence of endocrine alterations of calcium/phosphate homeostasis, e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis etc. • Concurrently receiving treatment with agents that are known strong inhibitors or inducers of CYP3A4. Medications which increase serum phosphorus and/or calcium concentration are excluded (See Appendix 2 for list of prohibited medications).
Investigational therapy	Infigratinib administered as oral mono-therapy
Efficacy assessments	Tumor response according to RECIST Version 1.1 assessed by Investigator
Safety assessments	Adverse event (AE) reporting and changes from baseline in laboratory parameters, vital signs, ophthalmic assessment, cardiac imaging
Other assessments	Biomarker assessment and additional correlative studies: 1. <u>Tumor-normal sequencing for biomarker detection:</u> Archival or newly obtained tumor samples will be collected to explore mechanisms of resistance to Infigratinib treatment through analysis of next generation sequencing data from tumor sample at baseline, on-treatment (after completion of 2 cycles), and after the development of disease progression (whenever available). 2. <u>Circulating tumor DNA (ctDNA) sequencing:</u> Blood samples will be

	collected at screening and throughout the study for ctDNA analysis to explore correlation with genetic alterations in tumor tissue at baseline, clinical response and development of resistance.
Data analysis	Data will be collected and analyzed centrally by the Clinical Trials Office at The Ohio State University. It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of patients will be available for analysis. Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety observations. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented. For all analyses, data from patients with *FGFR1-3* gene fusions/translocations and from patients with other *FGFR* genetic alterations will be summarized separately, unless otherwise stated. The estimated ORR along with the corresponding 90% confidence interval will be presented for each cohort. OS and PFS will be estimated using the Kaplan Meier method. For Cohort 1, a Simon optimum two-stage design is used to detect an ORR of at least 25% vs. ORR $\leq$ 5% in this patient population. After evaluating 9 patients in the first stage, the trial will be terminated if 0/9 patients demonstrate a response. If at least 1 of 9 patients has CR or PR, a total of 30 evaluable patients in Cohort 1 will be enrolled.
Key words	Infigratinib, advanced solid tumors, *FGFR1-3* gene fusion/translocation, *FGFR* genetic alterations, RECIST v1.1

1. Background

1.1 Overview of FGFR genetic alterations in human cancers

The fibroblast growth factor receptor (FGFR) protein family consists of four highly conserved transmembrane receptor tyrosine kinases (FGFR1-4). Receptor activation by the fibroblast growth factor (FGF) ligands leads to intracellular signaling to ultimately promote cell growth, proliferation and survival. The FGFR signaling pathway is aberrantly activated in multiple types of human cancers through various genomic alterations including point mutations, copy number amplifications, and chromosomal translocations or fusions. Both the overall frequency of FGFR alterations and the relative distribution of the types of alterations vary by cancer type (Helsten et al. 2016; Wu et al. 2013; Babina and Turner 2017).

1.1.1 FGFR gene fusions

Activating FGFR gene fusions have been detected in different types of human cancers. Common fusion partners of *FGFR* include *CCDC6*, *BICC1*, *TACC3* and *AHCYL1* (Babina and Turner 2017; Wu et al. 2013). FGFR fusion partners frequently contain dimerization or oligomerization domains. For example, the transforming acidic coiled-coil containing protein 3 (TACC3), when fused to the C-terminus of FGFR3 (replacing FGFR3's final exon), leads to constitute kinase activity, localization of the fused protein to spindle poles and chromosomal segregation defects to result in aneuploidy; the fused protein has been shown to activate MAPK-ERK and JAK-STAT signaling pathways (Babina and Turner 2017). Whereas *TACC3* is a common 3' fusion partner of *FGFR3*, *FGFR2* fusions with different partners, first reported in 2013 (Wu et al. 2013), have been detected in approximately 15% of intrahepatic cholangiocarcinomas and with lower frequencies in thyroid, prostate, and lung cancers. FGFR2 fusion partners such as coiled coil domain-containing protein 6 (CCDC6) and BicC family RNA-binding protein 1 (BICC1) also fuse to the cytoplasmic tail of FGFR2, resulting in deletion of its C-terminal exon, which as previously described is also deleted in a subset of *FGFR2* amplified cancers. The fusion protein exerts oncogenic properties likely through enhanced fusion receptor dimerization and ligand-independent signaling. **Table 1** below contains *FGFR* fusions that have been detected to date in different human cancers (Babina and Turner 2017).

1.1.2 FGFR activating mutations

Somatic or acquired activating mutations including point mutations and small insertions/deletions (indels) have been detected in *FGFR1-4* genes both within and outside the tyrosine kinase domain (Babina and Turner 2017). Overall, these mutations occur more commonly in *FGFR2* and *FGFR3*. For instance, *FGFR2* mutations have been reported in 10-12% of endometrial cancers, 4% of NSCLCs and gastric cancers, and 2% of urothelial cancers. Mutations in *FGFR3* occur in up to 75% of non-muscle invasive urothelial cell carcinomas, 15% of invasive urothelial carcinomas, and 2% of cervical cancers. Interestingly, unlike *EGFR* mutations that cluster within the receptor kinase domain, many *FGFR2/3* mutations occur in the extracellular immunoglobulin and transmembrane domains of the receptor. These mutations lead to increased receptor dimerization and ligand-independent receptor activation and signaling to promote oncogenesis. Finally, mutations in the kinase domain of FGFR1, FGFR2 and FGFR4 constitutively activate the receptors but are detected at lower frequencies in human cancers. For example, the FGFR2 N549H/K mutation, which can transform cell lines, has been detected in 1.4% of endometrial cancers and less than 1% if invasive breast cancer.

Table 1. FGFR fusions and gene partners in different human cancers

Cancer Type	5'-gene	3'-gene
Bladder	*FGFR3*	*TACC3*
Breast	*FGFR1*	*ADAM18*
	RHOT1	*FGFR1*
	NSD3	*FGFR1*
	FGFR2	*CCDC6*
Cholangiocarcinoma	*FGFR2*	*AHCYL1*
	FGFR2	*BICC1*
	FGFR2	*CCDC6*
	FGFR2	*VCL*
	FGFR2	*CLIP1*
	FGFR2	*POC1B*
	FGFR2	*KIAA1598*
Glioblastoma	*FGFR3*	*TACC3*
Head and neck squamous cell carcinoma	*FGFR3*	*TACC3*
	FGFR3	*TPRG1*
Lung squamous cell carcinoma	*BAG4*	*FGFR1*
	FGFR2	*CCAR2*
	CCAR2	*FGFR2*
	FGFR3	*TACC3*
Ovarian cancer	*FGFR2*	*USP10*
Prostate adenocarcinoma	*SLC45A3*	*FGFR2*
	FGFR3	*AES*
	FGFR2	*KLK2*
Thyroid carcinoma	*FGFR2*	*OFD1*
	VCL	*FGFR2*

Note: This Table provides a representative list of gene fusions and cancers and is not comprehensive. Additional FGFR gene fusions and cancer types continued to be discovered.

In summary, given the significant contribution of deregulated FGFR signaling to tumorigenesis and progression through various genetic alterations including amplifications, mutations, and gene fusions, small molecule inhibitors targeting this pathway have been developed and their anti-tumor activities are currently being evaluated in clinical trials. Treatment with pan-FGFR inhibitors in patients with cholangiocarcinoma and urothelial cancer having *FGFR* fusions has led to overall response rates of 14.8% and 25.4% as well as disease control rate of 64.2% and 75.4%, respectively (Javle et al. 2018; Pal et al. 2018). These clinical data strongly support research and development of FGFR inhibitors for additional types of human cancers with *FGFR* fusions as well as cancers that contain non-fusion alterations.

1.2 Introduction to investigational treatment

1.2.1 Overview of Infigratinib

Infigratinib is an orally bio-available, selective and ATP-competitive pan-fibroblast growth factor receptor (FGFR) kinase inhibitor, which has demonstrated anti-tumor activity in preclinical, *in vitro,* and *in vivo* tumor models harboring FGFR genetic alterations. Infigratinib belongs to the pyrimidinyl aryl urea chemical class and its chemical name is 3-(2,6-Dichloro3,5- dimethoxyphenyl)-1-{6-[4-(4-ethyl-1-piperazin-1-yl)phenylamino]-pyrimidinyl-4-yl}-1methylurea phosphate(1:1).

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

1.2.1.1 Non-clinical experience

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

Consistent with inhibition of FGFR autophosphorylation, 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, Infigratinib shows anti-tumor activity in multiple models bearing FGFR genetic alterations (Guagnano 2012; Konecny 2013).

1.2.1.2 Animal drug metabolism and pharmacokinetics

In all species tested, 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. Infigratinib is widely distributed to tissues in the rat and has a high affinity to melanin containing tissues. *In vitro* hepatic systems metabolize Infigratinib predominantly to 2 pharmacologically active metabolites: BHS697 and BQR917. Biotransformation of 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 0.21 μM. In addition, in vitro data indicate that Infigratinib is primarily a CYP3A4 substrate.

Infigratinib is a potent reversible inhibitor of CYP3A4 (Ki 0.26 μM). The compound also reversibly inhibits CYP2C9 and CYP2C19 with Ki of 6.09 μM and 4.1 μM, respectively and CYP2C8 with IC50 of 12 μM. 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).

1.2.1.3 Safety pharmacology and toxicology

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 Infigratinib revealed a decrease in human Ether-à-go-go-related gene (hERG) channel activity with an IC50 of 2.0 μM (1121 ng/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, 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 Infigratinib treatment consisting of irreversible, slight bilateral opacity with dose-dependent incidence, as assessed by *in vivo* ophthalmology. The clinical/ophthalmoscopic finding was associated with reversible, diffuse epithelial keratopathy at the highest dose of 10 mg/kg. In the 2-week rat toxicity study, doses of 20 mg/kg/day did lead to vasculopathy associated with moribundity after 6 administrations.

In a dog toxicity study, minimal, fully reversible retention of the primary spongiosa and minimal increase in mineralization in lung and kidney without observed functional impairment were observed.

1.2.1.4 Clinical experience

1.2.1.4.1 Clinical safety

As of the cutoff for the Investigator's Brochure v10, 453 patients and 134 healthy volunteers have received infigratinib, alone or in combination, in 4 healthy volunteer, two phase 1, one phase 1b, and three phase 2 trials. All trials have completed with the exception of the ongoing phase 2 CBGJ398X2204 study of infigratinib in patients with advanced or metastatic cholangiocarcinoma with FGFR2 gene fusions/translocations or other FGFR genetic alterations.

The treatment emergent adverse events, regardless of relationship to infigratinib, reported for the CBGJ398X2204 study as of 01 June 2017, that occurred in ≥ 20% of subjects were: hyperphosphatemia (82.5%), 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%), and hypercalcemia (20.6%).

Grade 3 or 4 events that occurred in ≥ 5% of subjects were hyperphosphatemia (15.9%), hypophosphatemia (6.3%), hyponatremia (12.7%), lipase increased (7.9%), and stomatitis (7.9%).

Hyperphosphatemia is a pharmacodynamic marker of on-target FGFR pathway inhibition seen in the majority of subjects treated at doses of ≥ 100 mg/day. Renal tubular phosphate secretion and reabsorption are controlled through the FGFR1 pathway. Inhibition of this pathway leads to inability to secrete phosphate and secondary elevations in fibroblast growth factor 23. The hyperphosphatemia has been managed by dietary phosphate restrictions, phosphate lowering therapy, and drug interruptions and dose reductions, which led to the introduction of the alternate 3 weeks on/1 week off drug schedule.

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

No effect of infigratinib on electrocardiogram (ECG) intervals, including QTc, has been noted. Reversible and largely asymptomatic decreases in left ventricular ejection fraction (LVEF) have been noted in subjects enrolled on study, as measured by serial transthoracic echocardiography or multiple gated acquisition (MUGA) scans.

Please refer to the infigratinib Investigator Brochure for additional information.

1.2.1.4.2 Clinical efficacy

Preliminary anti-tumor activity was seen in the phase 1 first-in-human trial in subjects treated at doses of >100 mg of infigratinib in *FGFR1*-amplified squamous non-small cell lung cancer and urothelial carcinoma with *FGFR3* genetic alterations. In a phase 1 expansion cohort of sixty-seven patients with previously treated metastatic urothelial carcinoma harboring *FGFR3* genetic alterations (fusions and mutations), an overall response rate of 25.4% was observed in patients treated with Infigratinib. An additional 38.8% of patients had stable disease, leading to a disease control rate of 64.2% (Pal et al. 2018).

Sixty-one subjects with advanced or metastatic cholangiocarcinoma containing *FGFR2* fusions (n = 48), *FGFR* mutation (n = 8), or amplification (n = 3) whose disease had progressed while receiving prior therapy (35 women; median age, 57 years) were enrolled into the BGJ398X2204 study as of 30 Jun 2016 (Javle et al. 2018). At the pre-specified data cutoff, 50 subjects had discontinued study drug. All responsive tumors contained *FGFR2* fusions. The ORR was 14.8% (18.8% FGFR2 fusions only), the disease control rate was 75.4% (83.3% FGFR2 fusions only), and the estimated median PFS was 5.8 months (95% CI, 4.3 to 7.6 months).

1.2.1.2.3 Clinical pharmacokinetics

The pharmacokinetics (PK) of Infigratinib and active metabolites have been evaluated following single and repeat daily doses in the ongoing phase I study (CInfigratinibX2101).

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. The 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 Infigratinib, PK parameters on Day 28 should be viewed with caution. The interpatient variability was high for Infigratinib.

Concentration data from active metabolites BHS697 (desethyl metabolite) and BQR917 (Noxide) was available across all cohorts. CQM157 (aniline metabolite) was analyzed in a few patients following Amendment 6 of the InfigratinibX2101 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 Infigratinib varied across patients (3% -300%). CQM157 (N=4) did not appear to accumulate on daily dosing, whereas accumulation was observed for Infigratinib and metabolites BHS697 and BQR917. Please refer to Investigator's Brochure for more details.

2. Rationale

2.1 Study rationale and purpose

The FGFR signaling pathway has critical roles in development, cell proliferation, metabolism and survival (Turner and Grose 2010). Deregulation of FGFR signaling has been implicated in the development of many types of human cancers by resulting in cellular programs that promote tumor progression or resistance to anti-cancer therapies. Furthermore, molecular studies have shown that FGFR signaling exhibits cross-talk with the RAS-MAPK-ERK and PI3K-AKT pathways (Babina and Turner 2017).

The results from two recent clinical studies provide additional support for using Infigratinib in treating patients with solid tumors harboring *FGFR* genetic alterations. In a phase 1 expansion cohort of 67 patients with previously treated metastatic urothelial carcinoma harboring *FGFR3* genetic alterations (fusions and mutations), an overall response rate of 25.4% was observed in patients treated with Infigratinib. An additional 38.8% of patients had stable disease, leading to a disease control rate of 64.2% (Pal et al. 2018). In CInfigratinibX2204 a single-arm, multi-center phase 2 study of 61 patients with advanced cholangiocarcinoma with *FGFR* genetic alterations (n=48 fusions; n=8 mutations; n=3 amplifications) having progression on first-line gemcitabine-containing chemotherapy, Infigratinib treatment produced an overall response rate of 14.8% and a disease control rate of 75.4% (Javle et al. 2018). Progression free survival (PFS) of patients treated with Infigratinib was 5.8 months, which is on par with first-line chemotherapy. Based on the results in these 61 patients, enrollment has been increased to a total of 120 patients to more precisely define response rate, duration of response and PFS.

In summary, genetic alterations in the FGFR gene family occur frequently in different types of human cancers (**Table 1**). To date, the results of pre-clinical and clinical studies support further evaluation of the efficacy of Infigratinib in treating patients with various cancer types, in addition to cholangiocarcinoma and urothelial carcinoma, driven by oncogenic FGFR signaling that result from structural alterations such as fusions as well as other types of activating mutations.

2.2 Rationale for study design

Based on the existing pre-clinical and clinical data described in Section 2.1, the current tissue-agnostic study is designed to evaluate efficacy of Infigratinib when administered as a single agent to patients with genetically selected advanced or metastatic solid tumors through assessment of the overall response rate. The presence of oncogenic *FGFR* fusions or other FGFR genetic alterations in cancers are likely to confer sensitivity to Infigratinib. A single arm study evaluating response to Infigratinib and durability of response is an appropriate design in this cancer type-agnostic patient population, which is defined by the presence of a specific targetable genetic alteration (e.g. *FGFR* fusion or activating mutation) rather than histologic classification of cancer (Simon et al. 2016). One of the aims of this study is to further evaluate the efficacy of Infigratinib in solid tumor patients who have had treatment with an alternate FGFR inhibitor. Numerous secondary mutations in *FGFR* after treatment with an FGFR inhibitor have been reported that confer resistance to therapy (Katoh 2018). It would be important to determine the efficacy of Infigratinib in patients who may have acquired mutations induced by different FGFR inhibitors.

In summary, the current study is designed to evaluate the efficacy of Infigratinib in the following patients:

- Patients with different solid tumor types containing *FGFR* fusions
- Patients with different solid tumor types containing other activating mutations in *FGFR*
- Patients with different solid tumor types having received prior therapy with FGFR inhibitors

2.3 Rationale for dose and regimen selection

Patients enrolled in this study will receive 125 mg qd of Infigratinib on a 3 week on (21 day) /1 week off (7 day) schedule in 28-day cycles. This dose level and regimen is based on experiences from the CInfigratinibX2101 trial.

The MTD/RP2D from the CInfigratinibX2101 study was identified as 125 mg administered once daily (qd) in continuous 28-day cycles. While dose levels of 100 mg qd and higher were tolerated by patients, the majority of the patients experienced reversible hyperphosphatemia, which led to study drug interruptions. An evaluation of the drug administration records for patients prior to receiving prophylactic phosphate-lowering therapy, indicated that the median time until first dose interruption was approximately 23 days and the median duration of interruption was 7 days. This observation led to the introduction of an expansion arm in the ongoing CInfigratinibX2101 study to evaluate the administration of 125 mg qd on a 3 week on (21 days) / 1 week off (7 days) schedule in 28-day cycles. To date, the majority of patients enrolled in this arm have completed their first cycle of therapy without hyperphosphatemia induced dose interruptions, while maintaining anti-tumor activity.

3. Objectives and endpoints

3.1 Table 2. Primary objectives and endpoints

Primary objectives	Primary endpoints
1. To evaluate the efficacy of single agent Infigratinib in patients with advanced or metastatic solid tumors of any histologic classification with	Overall response assessed by investigator as per RECIST v1.1

	FGFR1-3 gene fusions/translocations or other *FGFR* genetic alterations (with and without prior therapy with different FGFR inhibitor)	
2.	To understand response rate and potential for Infigratinib to benefit patients who have *FGFR* alterations including point mutations, insertions/deletions and amplifications in different solid tumor types.	Overall response assessed by investigator as per RECIST v1.1

3.2 Table 3. Secondary objectives and endpoints

Secondary objectives	Secondary endpoints
1. To further evaluate the efficacy of single agent Infigratinib	Progression free survival, best overall response, disease control rate, overall survival assessed by investigator as per RECIST v1.1
2. To characterize the safety and tolerability of single agent Infigratinib	Safety: Type, frequency, and severity of AEs and SAEs Tolerability: dose interruptions, reductions and dose intensity
3. To evaluate benefit of Infigratinib in patients who have received one prior FGFR inhibitor	Progression free survival, best overall response, disease control rate, overall survival assessed by investigator as per RECIST v1.1

3.3 Exploratory objectives:

Exploratory objective 1: To detect biomarkers of resistance to Infigratinib treatment through tumor sequencing.

- Method: Archival or newly obtained tumor samples will be collected to explore mechanisms of resistance to Infigratinib treatment through analysis of next generation DNA sequencing data from tumor sample at baseline, on-treatment (after completion of 2 cycles) and after the development of disease progression (whenever available). Detailed protocol for tissue acquisition and sequencing is in Section 7.3.2 “Biomarkers and correlative studies”.

Exploratory objective 2: To develop a circulating tumor DNA (ctDNA) or liquid biopsy assay optimized for monitoring response to Infigratinib and detecting emerging resistance mutations to Infigratinib

- Method: Blood samples will be collected at screening and throughout the study for ctDNA analysis to explore correlation with genetic alterations in tumor tissue at baseline, clinical response and development of resistance. Detailed protocol for the development of *FGFR* liquid biopsy assay in Section 7.3.2 “Biomarkers and correlative studies”.

4. Study design

4.1 Description of study design

This is a multi-center, open label, single arm phase 2 study evaluating Infigratinib anti-tumor activity in advanced or metastatic solid tumor patients with *FGFR* genetic alterations including gene fusions/translocations, point mutations, and insertions/deletions. Oral, monotherapy Infigratinib will be administered once daily for the first 3 weeks (21 days) followed by one week break of each 28-day cycle. Treatment period will begin on Cycle 1 Day 1 and will continue until disease progression, unacceptable toxicity, withdrawal of informed consent, or death. Patients will be evaluated for tumor response radiographically every 8 weeks until disease progression or discontinuation from study using RECIST v1.1.

As depicted in Figure 1, patient accrual for the current study will occur at The Ohio State University and through clinical sites from institutions that are members of the Oncology Research Information Exchange Network (ORIEN, http://oriencancer.org/). OSU is a founding member of ORIEN, which includes eighteen large academic hospital systems with patients who have consented to a common study that includes tumor profiling by next generation sequencing (whole exome and RNAseq), collection of clinical data, and re-contact for potential clinical trials offering therapies that match the genetic alterations in their cancers. Thus, ORIEN provides a mechanism for pre-screening to identify candidate patients with *FGFR* genetic alterations and can help accelerate patient accrual to this study.

Clinical subsites to be determined based on populations of *FGFR*+ patients and interest from ORIEN members. Additional non-ORIEN clinical sites may be identified as well. Regardless of prior research screening, all patients must have had CLIA-certified assay with requisite *FGFR* gene alterations. Additional subsites with active molecular testing for *FGFR* may also be recruited as a clinical subsite.

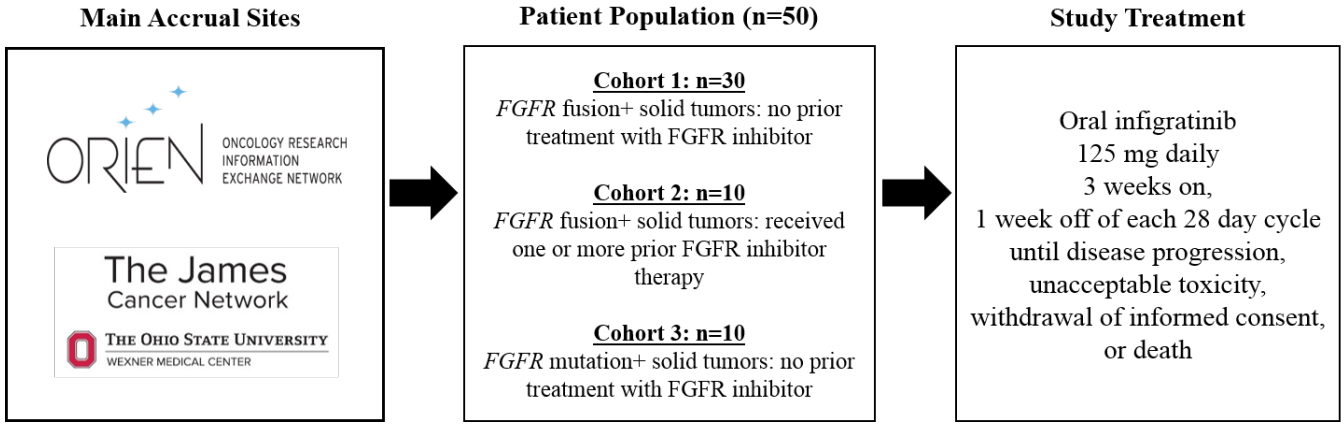

Figure 1. Study schema for phase 2 trial evaluating Infigratinib efficacy in patients with advanced *FGFR*-altered solid tumors with and without prior exposure to alternate FGFR inhibitor therapy.

Molecular Eligibility

Documented evidence of *FGFR* genetic alterations with a CLIA-certified assay is required in order to begin study related screening procedures. Evidence can be demonstrated by locally available data (local laboratory or institution-designated sequencing facility). If local data or the results of the central analysis meet inclusion criteria, the patient can proceed with the screening procedures.

Screening
Screening assessments must be completed within 21 days prior to the first dose of study treatment except for the radiological tumor assessment which should be performed within 28 days prior to the first dose.

Treatment period
Treatment period will begin on Cycle 1 Day 1 and will continue until disease progression, unacceptable toxicity, withdrawal of informed consent, or death.

End of treatment (EOT)
The EOT visit occurs within 14-28 days after of the decision to discontinue study treatment. All participating patients must complete this visit even if they had to discontinue prematurely.

Follow-up
All patients will be followed up as described in Section 7.1.6.

30-day safety follow-up period
At a minimum, all patients must complete the safety follow-up assessments 30 days after their last dose of Infigratinib.

Disease progression follow-up period
All patients enrolled in the study who discontinue study treatment for any reason other than disease progression will have a tumor assessment every 8 weeks, until disease progression or the initiation of subsequent anticancer therapies, or death, whichever occurs first.

Survival follow-up period
All patients enrolled in the study will be followed for survival every 4 months for one year after discontinuation of treatment.

4.2 Timing of interim analyses and design adaptations

No formal interim analysis is planned for this study. Safety and efficacy data will be continuously monitored by QED Therapeutics in conjunction with the investigators for decision-making purposes. This is a signal finding study and early stopping rules for efficacy will not be applicable. Substantial safety data is already available for existing Infigratinib study, but will be monitored.

4.3 Assessment of potential mechanisms of resistance

Patients will have mandatory tumor tissue and blood samples collected at baseline, on-treatment (after completion of 2 cycles), and at disease progression to study the mechanisms of drug treatment resistance.

4.4 Definition of end of the study

End of study is defined as the time when the last patient completes the survival follow-up as described in Section 7.1.6 or when the last patient on study has expired, been lost to follow-up, or withdraws consent, whichever occurs first or when the study is terminated early.

The analysis of study data will be based on all patients' data up to the time when all patients have completed at least 6 cycles of treatment or discontinued the study. This will be the cutoff point for the primary clinical study report (CSR). The additional data for any patients continuing to receive Infigratinib, or remain in safety or survival follow-up beyond the cut-off point will be summarized in a final CSR that will be prepared once all patients have either discontinued or completed the study i.e. end of survival follow-up period which is defined as the time when all patients have discontinued study and at least 80% of the patients have died, withdrawn consent, or been lost to follow-up.

4.5 Early study termination

The study can be terminated at any time for any reason by the Principal Investigator for reasons related to efficacy or safety. Should this be necessary, the patient should make every effort to complete their final visit. The same assessments should be performed as described in Section 7.1.4 and Section 7.1.5 for a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5. Study population

5.1 Patient population

Adult patients with histologically or cytologically confirmed advanced or metastatic solid tumors with *FGFR1-3* gene fusions/translocations or other *FGFR* genetic alterations will be enrolled (**Figure 1**, Section 4.1). Patients must have received at least one prior regimen and therapies available that are known to confer a clinical benefit consisting of standard of care (SOC) therapy for cancer of a given histology classification or have demonstrated intolerance of SOC therapy. Patients should have had evidence of progressive disease following their prior regimen or if prior treatment was discontinued due to toxicity must have continued evidence of measurable or evaluable disease.

This trial plans to enroll a total of fifty patients, divided into the following 3 cohorts:

- Cohort 1: n=30, *FGFR1-3* fusion+ solid tumors, no prior treatment with FGFR inhibitor
- Cohort 2: n=10, *FGFR1-3* fusion+ solid tumors, must have received prior FGFR inhibitor therapy
- Cohort 3: n=10, *FGFR* mutation+ solid tumors, no prior treatment with FGFR inhibitor

Evidence of *FGFR* genetic alterations must be documented (refer to Section 7.1.1 for further details).

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies. Patients who do not initially meet all of the inclusion or exclusion criteria may be re-screened for consideration in the trial. If a patient is rescreened, the same patient ID number should be used (see Section 7.1.2.2).

Only patients who have documented evidence *FGFR* genetic alterations will be allowed to enter screening. The investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered treatment in the study.

5.2 Inclusion criteria

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

1. Patients with histologically or cytologically confirmed advanced or metastatic solid tumors of any histologic classification at the time of diagnosis.
2. Written documentation of local or central CLIA-certified laboratory determination of *FGFR* gene fusions/translocations or activating mutations.
3. The study is open to solid tumors in the following cohorts:
    a. Cohort 1: Solid tumor patients with *FGFR1-3* fusion/translocation (**n, up to 30**) who have progressed on or are intolerant to SOC therapies. Prior therapy with a different FGFR inhibitor is not permitted. Cholangiocarcinoma patients are excluded from this cohort (there are multiple competing studies and opportunities for patients to get treatment in other trials).
    b. Cohort 2: Solid tumor patients with *FGFR1-3* fusion/translocation **(n=10)** who have progressed on or are intolerant to SOC therapies and received treatment with a different FGFR inhibitor. Cholangiocarcinoma patients are permitted in this cohort.
    c. Cohort 3: Solid tumor patients with genetic alterations such as point mutations, insertions/deletions, or amplifications in any FGFR gene family member **(n=10)**. Prior therapy with a different FGFR inhibitor is not permitted. Cholangiocarcinoma patients are permitted in this cohort.
4. Evidence of measurable or evaluable disease according to RECIST Version 1.1.
5. Patients must have received at least one prior SOC regimen for advanced/metastatic cancer. Patient should have had evidence of progressive disease following their prior regimen, or if prior treatment was discontinued due to toxicity must have continued evidence of measurable or evaluable disease. Patients who have received prior treatment with an alternate FGFR inhibitor are still eligible for the study.
6. Patients with primary CNS cancer or CNS metastases are excluded (because it is unclear how much CNS penetration the drug has). However, asymptomatic patients with history of successfully treated CNS metastases with surgery or radiation and follow up imaging showing stability, can be eligible.
7. Patients ≥ 18 years of age of either gender.
8. ECOG performance status ≤ 1 (Patients with ECOG performance status of 2 may be considered on a case-by-case basis after discussion with QED Therapeutics).
9. Able to read and/or understand the details of the study and provide written evidence of informed

consent as approved by IRB/EC.

10. Recovery from adverse events of previous systemic anti-cancer therapies to baseline or Grade 1, except for:
    a. Alopecia
    b. Stable neuropathy of ≤ Grade 2 due to prior cancer therapy
11. Able to swallow and retain oral medication.
12. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

5.3 Exclusion criteria

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

1. Patients who have therapies available that are known to confer a clinical benefit will be excluded from the study.
2. Neurological symptoms related to underlying disease requiring increasing doses of corticosteroids. Note: Steroid use for management of CNS tumors is allowed but must be at a stable dose for at least 2 weeks preceding study entry.
3. 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 is not expected to require treatment for recurrence during the course of the study or affect survival.
4. Any other medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures.
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. History and/or current evidence of extensive tissue calcification including, but not limited to, the soft tissue, kidneys, intestine, myocardium and lung with the exception of calcified lymph nodes, minor pulmonary parenchymal calcifications, and asymptomatic coronary calcification.
7. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral Infigratinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
8. Current evidence of endocrine alterations of calcium/phosphate homeostasis, e.g., parathyroid disorders, history of parathyroidectomy, tumor lysis, tumoral calcinosis etc.
9. Treatment with any of the following anti-cancer therapies prior to the first dose of Infigratinib within the stated timeframes:
    a. Cyclical chemotherapy (intravenous) within a period of time that is shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C)
    b. Biological therapy (e.g., antibodies – including bevacizumab) within a period of time that is ≤ 5 t1/2 or ≤ 4 weeks, whichever is shorter, prior to starting study drug
    c. Continuous or intermittent small molecule therapeutics within a period of time that is ≤ 5 t1/2 or ≤ 4 weeks (whichever is shorter) prior to starting study drug
    d. Any other investigational agents within a period of time that is ≤ 5 t1/2 or less than the cycle length used for that treatment or ≤ 4 weeks (whichever is shortest) prior to starting study drug
    e. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) ≤ 4 weeks or limited field radiation for palliation ≤ 2 weeks prior to starting study drug
10. Patients who are currently receiving treatment with agents that are known strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration are excluded. (Refer to Appendix 2 for list of prohibited medications). Patients are not permitted to receive enzyme-inducing anti-epileptic drugs.
11. Consumption of grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, 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 (TdP) 7 days prior to first dose.
13. Use of amiodarone within 90 days prior to first dose.
14. Current use of therapeutic doses of warfarin sodium or any other coumadin-derivative anticoagulants. Heparin and/or low molecular weight heparins are allowed.

15. Insufficient bone marrow function:
    a. ANC ≤ 1,000/mm3 [1.0 x 10^9/L]
    b. Platelets ≤ 75,000/mm3 [75 x 10^9/L]
    c. Hemoglobin ≤ 9.0 g/dL
16. Insufficient hepatic and renal function:
    a. Total bilirubin ≥ 1.5x ULN unless associated with patient's primary cancer and/or metastases and with Principal Investigator's approval
    b. AST and ALT ≥ 3x ULN unless associated with patient's primary cancer and/or metastases and with Principal Investigator's approval
    c. Alkaline phosphatase ≥ 2.5x ULN unless associated with patient's primary cancer and/or metastases and with Principal Investigator's approval
    d. Calculated or measured creatinine clearance of < 40 mL/min
17. Calcium-phosphate homeostasis:
    a. Inorganic phosphorus outside of institutional normal limits
    b. Total serum calcium (can be corrected) outside of institutional normal limits
18. Clinically significant cardiac disease including any of the following:
    a. Congestive heart failure requiring treatment (NYHA Grade ≥ 2), LVEF < 50% as determined by MUGA scan or ECHO, or uncontrolled hypertension (refer to WHOISH guidelines)
    b. History or presence of clinically significant ventricular arrhythmias, atrial fibrillation, resting bradycardia, or conduction abnormality
    c. Unstable angina pectoris or acute myocardial infarction ≤ 3 months prior to starting study drug
    d. QTcF > 470 msec (males and females)
    e. History of congenital long QT syndrome
19. 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.
20. Women of child-bearing potential (WOCBP), 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. Highly effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    b. 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.
    c. Male sterilization (at least 6 months prior to screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.
    d. Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine systems (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

    In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

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 6 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.

21. 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 as well as during intercourse with a male partner in order to prevent delivery of the drug via seminal fluid.

6. Treatment

The investigational drug will be Infigratinib as an oral formulation.

6.1 Study treatment

The pharmacist will dispense the correct number and dose strength of capsules to ensure that each patient receives sufficient drug until the next scheduled visit.

6.1.1 Dosing regimen

Table 4: Dose and treatment schedule

Study treatment	Formulation	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
Infigratinib	FMIv3	Capsule(s) for oral use	125 mg (administered as one 100 mg capsule and one 25 mg capsule)	Daily (3 weeks on, 1 week off schedule in 28-day cycles)

6.1.1.1 Instructions for administration of Infigratinib

- Patients should be instructed to take the daily dose of Infigratinib in the morning, at approximately the same time each day (24 ± 2 hour interval).
- Infigratinib should be administered in the fasted state at least 1 hour before or 2 hours after a meal.
- 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.
- 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 Infigratinib, 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, Infigratinib should be dosed at least 2 hours before or 10 hours after dosing with a gastric protection agent.

- Patients must avoid consuming grapefruits, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or juice within 7 days prior to the first dose of study medication, through the end of study participation. This is due to a potential CYP3A4 interaction with study medication. Normal oranges and orange juice are allowed.
- The investigator or responsible site personnel should instruct the patient to take the study drug exactly as prescribed to promote compliance. All dosages prescribed and dispensed to the patient and all dose changes or missed doses during the study must be recorded on the Dosage Administration Record eCRF.
- Drug accountability must be performed on a regular basis. Patients will be instructed to return unused study drug to the site at the end of each cycle. The site personnel will ensure that the appropriate dose of each study drug is administered at each visit and will provide the patient with the correct amount of drug for subsequent dosing.
- Patients will be given a drug diary to complete with each cycle.

6.1.2 Ancillary treatments

Phosphate-lowering treatment, including low phosphate diet and phosphate binding therapy such as sevelamer hydrochloride, should be implemented prophylactically with meals on the first day of study drug initiation and modified as clinically indicated throughout Infigratinib administration. Recommendations for treatment are provided in **Table 6**, but should be modified as per country or institutional guidelines.

6.1.3 Treatment duration

All patients will receive Infigratinib daily on a three week on (21 days), one week off (7 days) schedule in 28-day cycles. Patients may continue treatment with Infigratinib until the patient experiences unacceptable toxicity, disease progression, treatment is discontinued at the discretion of investigator or withdrawal of consent, or death.

6.2 Dose modifications

6.2.1 Dose modifications 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. All dose modifications should be based on the worst preceding toxicity (**Table 6**). Dosage changes must be recorded on the Dosage Administration Record CRF.

The following guidelines should be applied.

Each patient will be allowed 3 dose reductions. Patients should discontinue Infigratinib if toxicities persist following 3 dose reductions (**Table 5**).

Following resolution of toxicity to baseline or ≤ Grade 1, treatment is resumed at either the same or lower dose of study drug as per the criteria in **Table 6**. If treatment is resumed at the same dose of study drug, and the same toxicity recurs with the same or worse severity regardless of duration, dose must be reduced to the next lower dose level. If treatment is resumed at the lower dose of study drug, and the same toxicity recurs with the same or worse severity, the patient should have a second dose reduction.

Patients who discontinue the study for a study related adverse event or an abnormal laboratory value must be followed as described in Section 8.

In exceptional situations, study treatment may continue even if the patient experienced one of the treatment stopping rules. The decision to allow for continuation of treatment will be made on a case-by-case basis following discussion with the Principal Investigator (Sponsor).

Situations that may allow for continuation of treatment include the following:

- A dose delay of > 14 days has occurred, but the patient is clearly benefiting from study treatment (i.e., stable disease, partial response, or complete response) and it is the investigator's opinion that no safety concerns are present. If the patient is clearly benefiting from the study treatment (i.e. stable disease, partial response, or complete response), and in the opinion of the investigator no safety concerns are present, after discussion with QED Therapeutics Medical Monitor, the patient may remain on the study treatment.

- 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 5: Dose reduction table

	Dose reduction			
	Starting dose level 0	Dose level -1	Dose level -2	Dose level -3
Infigratinib	125 mg	100 mg	75 mg	50 mg

Table 6: Criteria for interruption and re-initiation of Infigratinib treatment

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	**Recommended Dose Modifications any time during a cycle of therapy**
Cardiac disorders	

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Cardiac - Prolonged QTcF interval Grade 1 and 2: QTcF ≥ 481msec and ≤ 500 msec (asymptomatic)	Maintain dose level of Infigratinib ECG (Electrocardiogram) assessments should be performed for 2 additional cycles at the same frequency as in cycle 1, or as clinically indicated • If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule. • If ECG assessments are still abnormal (QTcF ≥ 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 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 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 ○ If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed as per visit schedule. ○ If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤500 msec), then ECG monitoring must continue at the same frequency as in cycle 1 or as clinically indicated, for all subsequent cycles • Patients who experience recurrent QTcF ≥ 500msec after one dose reduction will be discontinued from study. NB: If ventricular arrhythmia or Torsades de Pointes is observed in a patient, he/she will be discontinued from the study. Whenever QTcF > 500msec is observed, a plasma sample for determination of Infigratinib concentration

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
	should be obtained with the time of sample collection noted.
Cardiac disorders - others Grade ≥ 3, or congestive heart failure ≥ 2	 Discontinue patient from study treatment.
Investigations-Hematology	
ANC decreased (Neutropenia) Grade 3 (ANC < 1.0 - 0.5 x 10^9/L) Grade 4 (ANC < 0.5 x 10^9/L)	 Hold dose of Infigratinib until resolved to CTCAE Grade ≤ 1 or baseline, then: • If resolved within ≤ 7 days, maintain dose level of Infigratinib • If resolved within > 7 days, ↓ 1 dose level of Infigratinib. Hold dose of Infigratinib until resolved to CTCAE ≤ Grade 1, ↓ 1 dose level of Infigratinib.
Febrile neutropenia Grade 3 (ANC < 1.0 x 10^9/L, single temperature of > 38.3°C or 101F, or a sustained temperature of ≥ 38.0°C, or 100.4F) Grade 4	 Hold dose of Infigratinib until resolved to CTCAE Grade ≤ 1, then: • If resolved within ≤ 7 days, ↓ 1 dose level of 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, transfusion indicated) Grade 4 (Life-threatening consequences; urgent intervention indicated)	 Hold dose of Infigratinib until resolved or corrected to CTCAE Grade ≤ 1 or baseline, then maintain dose level Hold dose of Infigratinib until resolved or corrected to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	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 Infigratinib until resolved to CTCAE Grade ≤ 1 or baseline • If resolved within ≤ 7 days, maintain dose level of Infigratinib. • If resolved within > 7 days, ↓ 1 dose level of Infigratinib
Grade 3 (PLT < 50 - 25 x 10^9/L) with bleeding or Grade 4 (PLT < 25 x 10^9/L)	Hold dose of Infigratinib until resolved to CTCAE Grade ≤ 1 or baseline, then ↓ 1 dose level
Investigations – Renal	
Serum creatinine ≥ Grade 2	If serum creatinine CTCAE Grade ≥ 2 has been demonstrated in conjunction with hyperphosphatemia, serum creatinine levels must be repeated at least weekly until resolution. 24-hour urine collection should be obtained as clinically indicated for total phosphate, calcium, protein, and creatinine clearance. Ultrasound examination of the kidneys should be performed as indicated to evaluate *de-novo* calcifications until resolution or stabilization of creatinine.
Grade 2 (> 1.5 - 3.0 x ULN or baseline)	Hold dose of Infigratinib until resolved to Grade ≤1 or baseline: • If resolved within ≤ 7 days, maintain dose level of Infigratinib. • If resolved within > 7 days, ↓ 1 dose level of Infigratinib.
Grade ≥ 3 (> 3.0 x baseline; >3.0-6.0 x ULN)	Discontinue patient from study treatment.
Investigations – Hepatic	

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Blood bilirubin (patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only)	
Grade 2 (>1.5 – 3.0 x ULN if baseline was normal; >1.5-3.0 x baseline if baseline was abnormal)	Hold dose of Infigratinib until resolved to CTCAE Grade ≤ 1 • If resolved within ≤ 7 days, maintain dose level of Infigratinib. • If resolved within > 7 days, ↓ 1 dose level of Infigratinib.
Grade ≥ 3 (> 3.0 – 10.0 x ULN if baseline was normal; >3.0 – 10.0 x baseline if baseline was abnormal)	Discontinue patient from study treatment. Note: If CTCAE Grade 3 or 4 hyperbilirubinemia is due to hemolysis, then ↓ 1 dose level of Infigratinib and continue treatment at the discretion of the Investigator.
AST or ALT	
Grade 3 (> 5.0 - 20.0 x ULN if baseline was normal; >5.0 – 20.0 x baseline if baseline was abnormal) without bilirubin elevation > 2.0 x ULN	Hold dose of Infigratinib until resolved to CTCAE Grade ≤ 1 or baseline • If resolved within ≤ 7 days, maintain dose level of Infigratinib. • If resolved within > 7 days, ↓ 1 dose level of Infigratinib.
Grade 4 (> 20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal) 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 Infigratinib until resolved to CTCAE Grade ≤ 1 • If resolved within ≤ 7 days, ↓ 1 dose level of Infigratinib. • If resolved within > 7 days, discontinue patient from study treatment.
AST or ALT > 5.0 x ULN and total bilirubin > 2.0 x ULN; no evidence of biliary obstruction or other causes that can reasonably explain the concurrent elevation	Discontinue patient from study treatment.

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Laboratory / Metabolic disorders	
Asymptomatic amylase and/or lipase elevation Grade 3 (> 2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic) Grade 4 (>5.0 x ULN and with signs and symptoms)	• Hold dose of Infigratinib until resolved to CTCAE Grade ≤ 2. • ↓ 1 dose level of Infigratinib For recurrent Grade 3 asymptomatic lipase or amylase elevation despite dose reduction, drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤ Grade 2. For any Grade 4 asymptomatic lipase or amylase elevation, drug should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤ Grade 2. Note*:* A CT scan or other imaging study to assess the pancreas, liver, and gallbladder should be performed as clinically indicated within 1 week of the first occurrence of any CTCAE ≥ Grade 3 amylase and/or lipase.
Hyperphosphatemia Grade 1: Laboratory finding only and intervention not indicated Grade 2: Noninvasive intervention indicated Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated Grade 4: Life-threatening consequences; urgent intervention indicated (e.g. dialysis)	Maintain dose level of Infigratinib and optimize phosphate lowering therapy as clinically indicated. Maintain dose level of Infigratinib and optimize phosphate lowering therapy as clinically indicated. Hold Infigratinib until resolved ≤ Grade 2. Restart at same dose level with maximal phosphate binder dosing. Hold Infigratinib until resolved ≤ Grade 2. Reduce one dose level dose level with maximal phosphate binder dosing. It is recommended that phosphate binder dosing continues during Infigratinib dose interruptions for hyperphosphatemia and that serum phosphorus values be monitored frequently, e.g. every 2-3 days. Phosphate binder dosing should be held during the week off Infigratinib therapy each cycle (Days 22-28) and during Infigratinib dose interruptions for non-hyperphosphatemia adverse events.

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Hypercalcemia	
Serum calcium Grade 2 or 3	Hold Infigratinib dose until resolved to Grade 1 or baseline: • if resolved within ≤ 7 days after suspending Infigratinib, maintain dose level • if resolved within > 7 days after suspending Infigratinib, ↓ 1 dose level
Serum calcium ≥ Grade 4	Discontinue patient from the study
Nervous system disorders	
Neurotoxicity	
Grade 2	Omit dose of Infigratinib until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of Infigratinib
Grade ≥ 3	Discontinue patient from study drug treatment
GI disorders	
Pancreatitis	
Grade 2 (Enzyme elevation; radiologic findings only)	Hold Infigratinib dose until resolved to Grade 1 or baseline: • if resolved within ≤ 7 days after suspending Infigratinib, maintain dose level • if resolved within > 7 days after suspending Infigratinib, ↓ 1 dose level
Grade ≥ 3 (Severe pain; vomiting; medical intervention indicated)	Discontinue patient from study drug treatment
Diarrhea	
Grade 1	Maintain dose level of Infigratinib, initiate anti-diarrheal treatment
Grade 2	• Hold dose of Infigratinib until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment, maintain dose level of Infigratinib. • For reoccurrence of diarrhea CTCAE Grade 2, hold dose of Infigratinib until resolved to CTCAE Grade ≤ 1, ↓ Infigratinib by 1 dose level

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Grade 3	• Hold dose of Infigratinib until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment • ↓ Infigratinib by 1 dose level • For reoccurrence of diarrhea CTCAE Grade 3, despite optimal antidiarrheal 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 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 central serous retinopathy and central serous retinopathy -like events	Hold Infigratinib until resolved to ≤ Grade 1 and continue ophthalmologic evaluation • If resolved within ≤ 14 days, ↓ Infigratinib by 1 dose level • If resolved within > 14 days, discontinue Infigratinib
Grade 3 central serous retinopathy and central serous retinopathy-like events and any other Grade 3 eye disorders	Hold Infigratinib until resolved to Grade ≤ 1. • If resolved within ≤ 14 days, ↓ Infigratinib by 1 dose level • If resolved within > 14 days, discontinue Infigratinib
≥ Grade 1 retinal vein occlusion, Grade 4 central serous retinopathy and central serous retinopathy-like events, and Grade 4 other eye disorders	Discontinue Infigratinib
Other ocular/visual toxicity	
≥ Grade 3	Hold Infigratinib until resolution to ≤ Grade 1 If resolution within ≤14 days, ↓ 1 dose level, otherwise discontinue Infigratinib
General disorders	

Worst Toxicity CTCAE v5.0 Grade (unless otherwise specified)	Recommended Dose Modifications any time during a cycle of therapy
Fatigue Grade 3	Hold dose of Infigratinib until resolved to CTCAE Grade ≤ 1. If resolved within ≤ 7 days, maintain dose level of Infigratinib.
Other clinically significant AEs	
Grade 3 Grade 4	Hold dose of Infigratinib until resolved to CTCAE Grade ≤ 1, then ↓ 1 dose level of Infigratinib. Discontinue patient from study treatment.
All dose modifications should be based on the worst preceding toxicity. Once a dose reduction has occurred dose re-escalation may be allowed on a case by case basis after discussion with the Principal Investigator/Sponsor. Patients who require more than two dose reductions of Infigratinib will be generally discontinued from study drug treatment.	

6.2.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. Clinical experts or specialists, such as ophthalmologist, endocrinologist, dermatologist, should be consulted as deemed necessary. Further guidelines and recommendations for the management of specific study drug induced toxicities (hyperphosphatemia, diarrhea) are provided in **Table 6**. All patients must be followed up for adverse events and serious adverse events for 30 days following the last doses of Infigratinib.

6.2.3 Anticipated risks and safety concerns for the study drug

Eligibility criteria as well as specific dose modification and stopping rules are included in this protocol. Guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced adverse events, i.e. hyperphosphatemia, renal toxicities are provided in **Table 6**. Refer to preclinical toxicity and or clinical data found in the Infigratinib Investigator Brochure.

6.3 Concomitant medications

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 eCRF page. A concomitant medication is considered prohibited if it appears on any of the prohibited medication lists for any clinical pharmacology property of the drug (e.g. CYP, BCRP).

6.3.1 Permitted concomitant therapy

Any palliative and supportive care for disease related symptoms, including any medication for a concurrent medical condition are permitted, except as specifically prohibited below.

Hematopoietic growth factors

Hematopoietic growth factors (e.g. erythropoietin, G-colony stimulating factor (CSF) and GM-CSF) are not to be administered prophylactically or to be used to meet eligibility criteria. However, these drugs may be administered as per the label of these agents or as dictated by local practice or guidelines established by the American Society of Clinical Oncology (ASCO).

Hormone replacement therapies

Hormone replacement therapies such as thyroid and growth hormones are allowed, as well as estrogen replacement hormone treatment.

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 Infigratinib administration. Recommendations for treatment are provided in **Table 6**, but should be modified as per country or institutional practice.

6.3.2 Permitted concomitant therapy requiring caution and/or action

Details for specific medications which require action and/or caution while on study are provided in Appendix 1. The rationale for these medications is provided below.

Drugs that alter the pH of the GI tract
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 Infigratinib, and limit bioavailability.

Substrates and inhibitors

CYP substrates and inhibitors
Infigratinib was shown to inhibit the CYP3A4 in in-vitro assays, thus, suggesting an increased risk of drug interactions with concomitant medications that are metabolized by CYP3A4.

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 Infigratinib is an inhibitor of BCRP (Breast Cancer Resistance Protein). Medications which are BCRP substrates 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 de Pointes, and therefore need to be used with caution. See Appendix 1 for list of drugs that 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.

Medications with a possible or conditional risk of QT/QTc interval prolongation or torsade de pointes
Preliminary data have shown that Infigratinib has no effect on cardiac conduction or ECG intervals (see current version of the Infigratinib Investigator Brochure). However, medications that have the potential to prolong the QT/QTc interval or induce Torsade de Pointes (possible and conditional risk of TdP/QT prolongation) are allowed with caution. Investigators at their discretion may co-administer such medications, but patients should be carefully monitored. See Appendix 1 for list of drugs that need to be used with caution. Please note that the list might not be comprehensive.

6.3.3 Prohibited concomitant therapy

Details for specific medications prohibited while on study are provided in Appendix 2. The rationale for the restricted medications is provided below.

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 such as the ones listed in Appendix 2 are prohibited because Infigratinib is a likely substrate of this isoenzyme.

CYP inducers
Strong inducers of CYP3A4 are prohibited because their usage may decrease the exposure of Infigratinib. Therefore, agents such as those listed in Appendix 2 are prohibited. Please note that the list may not be exhaustive.

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

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

Preliminary data have shown that Infigratinib has no effect on cardiac conduction or ECG intervals (See current version of the Infigratinib Investigator Brochure). However, medications that are known to prolong the QT/QTc interval or induce Torsade de Pointes (Risk of TdP/QT prolongation) are prohibited. List of these medications is given in Appendix 2. Please note that the list might not be comprehensive.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

Each patient is identified in the study by a Subject Number (Subject No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by The Ohio State University to the investigative site) with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Subject No. available to the investigator through The Ohio State University Multi-Site Clinical Trial Team.

6.4.2 Treatment assignment or randomization

This is an open-label, single arm study. There will be no randomization required for this study.

6.4.3 Treatment blinding

Treatment is not blinded in this study.

6.5 Study drug preparation and dispensation

The investigator or responsible site personnel must instruct the patient or caregiver to take the study drugs as per protocol. Study drug(s) will be dispensed to the patient by authorized site personnel only. All dosages prescribed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

Infigratinib will be supplied as hard gelatin capsules for oral use of dosage strengths 25 mg, and 100 mg.

6.5.1 Study drug packaging and labeling

Infigratinib capsules are packaged in HDPE bottles with child resistant closures.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient.

6.5.2 Drug supply and storage

Study treatments must be received by designated personnel at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, the study treatment should be stored according to the instructions specified on the drug labels and in the Investigator’s Brochure.

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

6.5.3.2 Study drug accountability

The investigator or designee will maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation. During the course of the study, the investigator will maintain accurate records of used and unused study treatment, packaging, drug labels, and drug accountability log.

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 Disposal and destruction

The study drug can be destroyed at the site if permitted by local regulations. Alternatively, the study drug can be destroyed at a third-party depot.

7. Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7 lists all of the assessments and indicates with an "X" the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) ("Category" column).

- Baseline imaging assessments can be conducted within 28 days prior to 1st day of study treatment.
- All other baseline/screening assessments must be performed within 21 days prior to 1st treatment.
- Baseline/screening assessments that are conducted within 3 days prior to 1st treatment can be used to satisfy the day 1 requirement. Every effort must be made to follow the schedule outlined in **Table 7**.

For all visits, there is a ± 3-day window on assessments to take into account scheduling over weekends and holidays, if not explicitly specified otherwise. For post baseline imaging assessments, a ±7 day window is allowed, except for the first post baseline assessment (+7 day window permitted).

All assessments should be performed as outlined in **Table 7** and as clinically indicated.

Table 7: Visit evaluation schedule

	Category	Screening	Cycle 1				Cycle 2		Cycle 3		Subsequent cycles	End of study treatment	30-day follow-up (end of study)	Disease Progression follow-up every 8 weeks	Survival follow-up (every 4 months after EOT for 1 year)
Study Period		**Treatment**										**EOT**	**Follow-up**		
Day of Cycle		**-28 to -1**	**1**	**8**	**15**	**21**	**1**	**15**	**1**	**15**	**1**	**≤14 days of decision to discontinue treatment**			
Study Informed Consent (ICF)	D	X													
Demography	D	X													
Inclusion/exclusion criteria	D	X													
Relevant medical history/current medical conditions	D	X													
Diagnosis and extent of cancer	D	X													
Prior antineoplastic therapy	D	X													
Prior/concomitant medications	D	X	Continuous									X	X		
Physical examination	S	X	X	X	X	X	X	X	X	X	X	X			
Height	D	X													
Weight	D	X	X				X		X		X	X			
Vital signs	D	X	X	X	X	X	X	X	X	X	X	X			
Performance status	D	X	X				X		X		X	X			
Ophthalmic assessment	D	X			X		X		X		X	X			
Hematology	D	X	X	X	X	X	X	X	X		X	X			
Chemistry	D	X	X	X	X	X	X	X	X		X	X			
Coagulation	D	X	If clinically indicated												
Urinalysis (microscopic or macroscopic)	D	X	If clinically indicated												
Pregnancy test	D	X	X				X		X		X	X			
Tumor response per RECIST 1.1	D	X							X		Day 1 of every odd cycle	X (if not done within 28 days prior)		X (only for pts. who discontinue	

	Category	Screening	Cycle 1				Cycle 2		Cycle 3		Subsequent cycles	End of study treatment	30-day follow-up (end of study)	Disease Progression follow-up every 8 weeks	Survival follow-up (every 4 months after EOT for 1 year)
Study Period		**Treatment**										**EOT**	**Follow-up**		
Day of Cycle		**-28 to -1**	**1**	**8**	**15**	**21**	**1**	**15**	**1**	**15**	**1**	**≤14 days of decision to discontinue treatment**			
														for any reason other than progression of disease	
Study drug administration			Continuous on a 3 weeks on 1 week off schedule												
12-lead ECG	D	X	X		X		X		X		X	X			
Cardiac imaging (ECHO or MUGA)	D	X					X					X			
Adverse Events	D	Continuously throughout the study													
Collection of archival paraffin blocks/slides or a newly obtained tumor sample AND pathology report	D	X													
Newly obtained tumor sample (if medically feasible)	D	X[a]	X (mandatory on-treatment biopsies occurring at the end of Cycle 2 and upon disease progression)												
Blood sample for assessment of circulating tumor DNA (ctDNA)	D	X	X		X		X	X	X	X	Day 1 of every cycle	X (if not done within 28 days prior)			
Survival follow-up	D														X
Antineoplastic therapies since discontinuation of study treatment	D												X	X	
Disease progression follow-up														X	

[a] Sample will not be collected if a fresh tumor sample has already been collected at baseline for the purpose of DNA sequencing.

7.1.1 Molecular Eligibility

Evidence of *FGFR* genetic alterations can be obtained from any CLIA-certified assay including but not limited to local testing of samples at an institution-designated or preferred laboratory or an institution-designated sequencing facility.

A copy of the corresponding pathology report for each patient will be sent to the Lead Site (The Ohio State University Multi-Site Clinical Trial Team).

FGFR genetic alterations must be captured on the appropriate eCRF upon enrollment onto the study after the patient has signed the study's main Informed Consent.

In addition, all patients will provide a pre-treatment tumor specimen, preferably a tumor biopsy, so that subsequent central testing and analysis can be completed.

7.1.2 Screening

The IRB study approved informed consent form (ICF) must be signed and dated before any study-specific screening procedure is performed. Procedures which are part of the clinical routine during the initial diagnostic work-up of the patient may be obtained before obtaining the ICF. A copy of the ICF must be given to the patient or to the person signing the form. The investigator or designee must record the date when the study informed consent was signed in the medical records of the patient.

Patients will be evaluated against study inclusion and exclusion criteria and safety assessments. Screening assessments must be completed within 21 days prior to the first dose of treatment except for the radiological tumor assessment which should be performed within 28 days prior to the first dose. Screening assessments must be repeated if outside of screening windows.

7.1.2.1 Eligibility screening

After a patient signs the study Informed Consent Form, the investigator or clinical site should determine patient eligibility.

7.1.2.2 Information to be collected for screen failures

The reason for not being started on study treatment will be entered on the screening phase disposition page. For all screening failure patients, demography, inclusion/exclusion and informed consent information along with the reason for screen failure will be collected. No other data will be entered in the database for patients who are screen failures, unless the patient experienced a Serious Adverse Event during the screening phase (see Section 8 for SAE reporting details).

7.1.2.3 Patient demographics and other baseline characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, prior concomitant medications, diagnosis and extent of tumor, baseline tumor

mutation status (FGFR gene fusions/translocation or other FGFR genetic alterations) and details on prior antineoplastic treatments.

7.1.3 Treatment period

The treatment period commences on the first day of the first cycle of Infigratinib and ends after the last dose of Infigratinib.

During the study treatment period, patients will be regularly monitored to assess the safety and early anti-tumor activity of treatment. For purpose of scheduling and evaluations, a treatment cycle will consist of 28 days.

During the treatment period, the patient is obliged to follow the investigators instructions with regards to contraception, concomitant medications and dosing regimen. There is no fixed duration; patients may continue treatment with the study drug until the development of an unacceptable toxicity that precludes any further treatment, disease progression, and/or treatment is discontinued at the discretion of the Investigator or by patient refusal.

7.1.4 Discontinuation of study treatment

Patients may voluntarily discontinue from the study treatment for any reason at any time. If a patient decides to discontinue from the study treatment, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision and record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

Study treatment must be discontinued under the following circumstances:

- Adverse events, that results in a significant risk to the patient's safety.
- The following deviation from the prescribed dose regimen for study treatment: dose interruption of > 14 days from the intended day of the next scheduled dose, unless otherwise specified in Section 6.1.3
- Pregnancy
- Any other protocol deviation that results in a significant risk to the patient's safety
- Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in **Table 7** (end of study treatment visit) and then enter the follow-up epoch. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them (Lost to follow-up).

For patients who discontinue treatment for reasons other than documented disease progression, death, lost to follow-up, or withdrawal of consent, tumor assessments must continue to be performed every 8 weeks until documented disease progression, death, lost to follow-up, or withdrawal of consent.

7.1.4.1 Replacement policy

No replacements will be needed.

7.1.5 Withdrawal of consent

Patients may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact.

The Lead Investigative Site (The Ohio State University) will continue to retain and use all research results that have already been collected for the study evaluation. All biological samples that have already been collected may be retained and analyzed at a later date (or as required by local regulations).

If a patient withdraws consent, the investigator must make every effort (e.g. dates of telephone calls, e-mail, letter) to determine the primary reason for this decision and record this information.

Study treatment must be discontinued, and no further assessments conducted.

Further attempts to contact the patient are not allowed unless safety findings require communication or follow-up.

7.1.6 Follow-up period

Patients lost to follow-up should be recorded as such on the eCRF. For patients who are lost to follow-up, the Investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

30-day safety follow-up period

All patients must complete the safety follow-up assessments 30 days after the last dose of the study treatment. Information relating to antineoplastic therapies taken since discontinuation of study treatment and AEs (including concomitant medication taken for ongoing AEs) will be collected for 30 days after the last dose of the study treatment.

All AEs suspected to be related to study drug should be followed up weekly, or as clinically indicated, until resolution or stability.

Disease progression follow-up period

All patients enrolled in the study who discontinue study treatment for any reason other than disease progression will have a tumor assessment every 8 weeks (± 7 days), until disease progression or the initiation of subsequent anticancer therapies, or death, whichever occurs first. Any newly started antineoplastic therapies during the follow-up period must be recorded on the Antineoplastic therapy since discontinuation eCRF.

Survival follow-up period

All patients enrolled in the study will be followed for survival every 4 months for one year after discontinuation of treatment. Survival follow-up will continue until all patients have discontinued study and at least 80% of the patients have died, withdrawn consent, or been lost to follow-up.

7.1.7 Lost to follow-up

For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the investigator should show "due diligence" by contacting the patient, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the patient (e.g. dates of telephone calls, emails, letters, etc.). A patient should not be considered lost to follow-up until due diligence has been completed.

7.2 Assessment types

7.2.1 Efficacy assessment

Tumor response will be evaluated locally by the investigator according to the guideline (see Appendix 3) based on the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer et al 2009). Each patient will be evaluated for all potential sites of tumor lesions at screening/baseline and every 8 weeks after starting study treatment until disease progression.

CT (Computed Tomography) /MRI (Magnetic Resonance Imaging) scans will be performed at baseline within 28 days before start of treatment and subsequently every 8 weeks from treatment start until progression of disease.

After baseline, the first assessment should be performed at Cycle 3 Day 1 (+7 day window) and all subsequent assessments should be performed within ±7 days of the scheduled day of assessment. The same method of assessment and the same technique should be used to characterize each individual and reported lesion at baseline and during follow-up. If a patient discontinues treatment for reasons other than radiological documentation of progression of disease, an efficacy assessment should be performed at the time of End of Treatment unless a CT/MRI for tumor measurement was performed ≤ 4 weeks earlier.

Chest, abdomen, and pelvis CT scans are required for all patients at baseline. If at baseline, a patient is known to have a contraindication to CT i.v. contrast media or develops a contraindication during the trial, a contrast-enhanced MRI (if possible) of chest, abdomen, and pelvis should be performed.

For the patients with skeletal lesions suspected at baseline, a whole-body bone scan (e.g. TC 99, NaF PET, etc.) should be performed. Skeletal lesions which are identified on a whole body bone scan at baseline, which are not visible on the chest, abdomen or pelvis CT/MRI scan, should be re-imaged at baseline with localized CT, MRI or x-ray, and followed at scheduled visits (every 8 weeks).

Partial Response (PR) and Complete Response (CR) should be confirmed by repeat assessments performed at least 4 weeks and no later than 6 weeks after the criteria for response are first met.

PET/CT may be used only if it is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and intravenous contrast media. While FDG-PET may complement CT scans in assessing progression per RECIST 1.1 (Appendix 3) FDG-PET assessments should be disregarded for this protocol.

If possible, a single radiologist should perform all tumor response evaluations for an individual patient.

Any lesion that has been previously treated with radiotherapy should be considered as a nontarget lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a target lesion.

All radiological assessments obtained for patients enrolled during the study will be sent to The Ohio State University Multi-Site Clinical Trial Team.

7.2.2 Safety and tolerability assessment

Safety and tolerability assessments will include adverse event reporting and changes from baseline in laboratory parameters and vital signs. Tolerability will be assessed by the incidence of AEs leading to study drug delay or discontinuation. Safety will be monitored by assessing the procedures listed below as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination must be performed as indicated in **Table 7**.

Physical examination will be performed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information about the physical examination must be present in source documentation at the study site. Significant findings that are present prior to signing of informed consent form for the study must be included in the Relevant Medical History/Current Medical Conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent for the study must be recorded on the AE eCRF.

7.2.2.2 Vital signs

Vital signs (body temperature, pulse rate, blood pressure) must be performed in the same position, either sitting or supine, before dosing and as indicated in **Table 7**.

Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

7.2.2.3 Height and weight

Weight will be measured as indicated in **Table 7**. Height will be collected at screening only. More frequent examinations may be performed at the discretion of the Investigator and if medically indicated.

7.2.2.4 Performance status

The ECOG performance status will be assessed as indicated in **Table 8**.

Assessments of performance status will be performed on the scheduled day, even if study treatment is being withheld.

Table 8: ECOG performance status

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

7.2.2.5 Ophthalmologic assessments

Ophthalmologic examination will be performed as indicated in **Table 7** which includes: 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 will be performed as clinically indicated.

7.2.2.6 Laboratory evaluations

Clinical laboratory analyses are to be performed by the local laboratory as indicated in **Table 7** and **Table 9**. Laboratory tests will be collected and analyzed on the scheduled day, even if study treatment is being withheld. More frequent assessments may be performed at the discretion of the Investigator and if medically indicated and should be recorded on the Unscheduled Visit eCRFs.

At any time during the study, abnormal laboratory parameters which are clinically relevant (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require

therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the Adverse Events eCRF page. Laboratory data will be summarized using the CTCAE (version 5.0).

The Ohio State University Multi-Site Clinical Trial Team must be provided with a copy of the laboratory's certification, and normal ranges for each parameter measured. In addition, if at any time a patient has laboratory parameters obtained from a different outside laboratory, a copy of the certification and normal ranges for that laboratory will be required.

Hematology
Hematology tests are to be performed by the local laboratory according to the visit schedule outlined in **Table 7**. For details on the hematology panel refer to **Table 9**.

Clinical chemistry
Clinical chemistry tests are to be performed by the local laboratory according to the visit schedule outlined in **Table 7**. For details on the biochemistry panel refer to **Table 9**.

Coagulation
International normalized INR, pro-thrombin time (PT), partial thromboplastin time will be measured according to the visit schedule in **Table 7** and **Table 9**.

Urinalysis
Urinalysis includes dipstick analysis will be performed according to the visit schedule in **Table 7** and **Table 9**. Microscopic urinalysis will be performed only if macroscopic urinalysis result is abnormal.

Pregnancy and assessments of fertility
All WOCBP (pre-menopausal or less than 1 year after the onset of menopause) must have a serum pregnancy test (β-hCG) ≤ 72 hours before the first dose of study treatment. Additionally, a serum pregnancy test should be performed at Day 1 of each cycle and at the End of Treatment visit.

Table 9: Clinical laboratory parameters collection plan

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

Pregnancy Test	Serum hCG at screening; day 1 of each cycle, EOT and other times points

7.2.2.7 Cardiac assessments

ECG evaluations will be conducted centrally. For all patients prior to the first administration of Infigratinib, a minimum of 3 sequential 12-lead ECGs, separated by at least 5-10 minutes, must be performed on Day 1 of Cycle 1. This is necessary to get an accurate baseline QTcF calculation. 12-lead ECGs are to be performed at the following time-points:

- At screening and/or baseline
- Cycle 1 Day 1: pre-dose and 2-hr post-dose, ± 15 min. (3 sequential)
- Cycle 1 Day 15: pre-dose (3 sequential)
- All Subsequent cycles, day 1: pre-dose (3 sequential)
- At the end of treatment

Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with the The Ohio State University Principal Investigator (Sponsor) prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the AE eCRF page.

7.2.2.8 Cardiac imaging

MUGA scans or echocardiogram to assess LVEF will be performed as outlined in Table 7. A MUGA scan or echocardiogram will be performed at end of study treatment only if an assessment of LVEF has not been performed ≤ 14 days prior to study completion.

7.2.3 Biomarkers and correlative studies

Infigratinib biomarker assessments are required to confirm patient eligibility and potentially aid in understanding the effects of Infigratinib treatment on molecular markers of disease and FGFR pathway regulation as related to clinical outcome. This study will attempt to investigate three exploratory objectives through correlative studies proposed in this section.

- Exploratory objective 1: To detect biomarkers of resistance to Infigratinib treatment through tumor-normal sequencing (Section 7.2.3.4.2).

- Exploratory objective 2: To develop a circulating tumor DNA (ctDNA) or liquid biopsy assay optimized for monitoring response and detecting emerging resistance mutations to Infigratinib (Section 7.2.3.4.2).

7.2.3.1 Tumor samples for tumor-normal sequencing

Screening: Collection of an archival tumor sample (tissue blocks or 15-20 unstained slides) is mandatory and will be collected from all patients during screening. A corresponding pathology report should be included along with the archival sample. If an archival tumor sample is not available, a newly obtained tumor sample should be obtained and provided as a formalin-fixed, paraffin-embedded block. Archival or newly obtained tumor samples will be used to explore mechanisms of resistance to cancer treatment through analysis of next generation sequencing data from tumor samples at baseline, on-treatment (after completion of 2 cycles) and after the development of disease progression (whenever available). Additional archival sample may be requested if the original sample sent is of insufficient quantity or quality to complete the planned analysis. For detailed protocol, see Section 7.2.3.4.

On treatment and post-progression: A newly obtained tumor sample should be collected on treatment at the end of Cycle 2 (mandatory) and at progression (mandatory, end of treatment) for patients if safe and feasible, as it will provide a unique opportunity to investigate the potential mechanisms of resistance to Infigratinib. This will be performed using potentially a combination of genomic, transcriptomic and proteomic technology, which may include profiling of mutation, amplification and/or modification in DNA, RNA, or protein levels in tumor tissue. For detailed protocol, see Section 7.2.3.4.

Sample collections must be captured on the appropriate eCRF and requisition page(s). Detailed instructions for the collection, handling, labeling, and shipment of samples are outlined in The Ohio State University Tumor and Blood Laboratory Manuals.

7.2.3.2 Analysis of plasma circulating tumor DNA (ctDNA) for *FGFR* alterations

Blood (approximately 10 ml) will be collected at screening and Day 1 and Day 15 of Cycles 1-3, and Day 1 of every subsequent cycle, and at the time of disease progression (EOT). These samples will be used for analysis of ctDNA to explore whether genetic alterations found in tumor samples may also be observed in blood, and if any alterations found are predictive of response and/or associated with development of resistance. For detailed protocol on liquid biopsy, see Section 7.2.3.4.

7.2.3.4 Procedures and protocols of correlative studies

7.2.3.4.1 Precision Cancer Medicine for Advanced Cancer Through High-throughput Sequencing

Patients enrolled in the current study will have mandatory research biopsies and tumor sequencing upon disease progression. At The Ohio State University, research biopsies and sequencing (DNA and RNA) will be carried out in a companion tissue collection study, Precision Cancer Medicine for Advanced Cancer Through High-throughput Sequencing (**NCT02090530**, PI: Sameek Roychowdhury, MD PhD). This IRB approved tissue collection and cancer profiling study, **OSU-13053**, enrolls eligible patients who have advanced or refractory metastatic cancer of any histologic classification, to undergo mandatory tumor biopsies pre-treatment and post-progression, integrated sequencing, bioinformatics analysis, and return of clinically significant sequence results to the treating oncologists and patients. Patients enrolled at other clinical subsites will complete biopsies that will be collected, banked, and then shipped to The

Ohio State University and processed per protocol in The Ohio State University Tumor and Blood Laboratory Manual.

Collection of Biospecimens in NCT02090530

Consent and tissue management is supervised by the OSU-13053 Precision Cancer Study. Specimens that will be collected include serial blood, pre-treatment and on-treatment tumor biopsies, and progressive tumor biopsy. Tumor biospecimens included in this protocol may be fresh, frozen or formalin-fixed tumor specimens. Biospecimens may be collected through the clinical site's outpatient and inpatient facilities. Generally, most procedures will occur through the Department of Radiology (Interventional procedures). However, some procedures could occur through other areas such as dermatology (skin biopsy) or operating rooms (undergoing a standard of care procedure that is anticipated to yield excess tissue). Previously collected tissue blocks, can also be used for sequencing. The OSU-13053 Precision Cancer Study uses a secure Custom Database/LIMS to catalog, store, and track specimens.

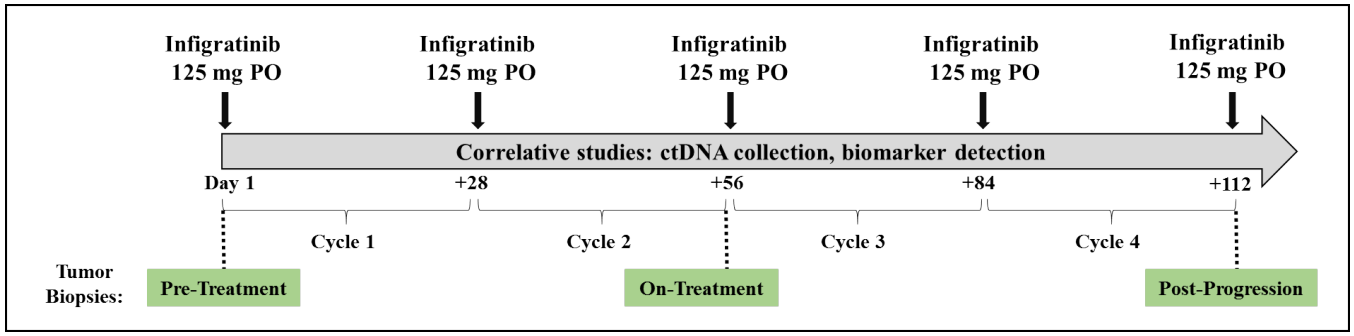

Figure 2. Example of proposed schedule of mandatory tumor biopsies on the study: before initiation of Infigratinib (pre-treatment), after completion of 2 cycles of therapy (on-treatment), and upon confirmed disease progression (post-progression).

Blood and Tissue Procurement in NCT02090530

A) Serial blood samples: Blood samples will be drawn on Day 1 of each treatment cycle (except for Cycle 1-3 in which blood is obtained on Days 1 and 15) from patients coinciding with study visits or scheduled to have venipuncture for routine clinical purposes. Generally, blood draws for research purposes will be 4-5 10mL tubes.

Blood Processing: Generally, the processing and storage of blood samples will involve the following protocol. Blood will be drawn into one or more tubes that contain EDTA, heparin or citrate for the collection and stored as serum, white blood cells or whole blood. To preserve patient and donor confidentiality, samples are given a specimen ID number. Serum and white blood cells will be separated from other cellular components by centrifugation, allocated into tubes, catalogued, and frozen at –80° C or viably in liquid nitrogen freezers. Samples may be processed for DNA, RNA, and/or protein.

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

D) Mandatory tumor tissue biopsy: Patients will undergo mandatory pre-treatment, on-treatment (after completion of 2 cycles) and post-progression tumor biopsies. The inclusion/exclusion criteria list circumstances where a pre-treatment biopsy is not possible**.** Tumor tissue or fluids will be collected from patients through the least invasive approach. Patients will receive informed consent detailing risks and benefits of the specific procedure. The list of possible procedures includes but is not limited to: percutaneous needle biopsy (liver, lung, breast, soft tissue mass), lymph node biopsy, bone marrow biopsy and aspirate, thoracentesis for pleural fluid and paracentesis for peritoneal fluid. When patients undergo tumor biopsy, they will receive a routine clinical consent as provided by the health care professional who performs the procedure. Generally, this will be staff from the Department of Radiology. This consent process will describe the procedure, risks, benefits, and alternatives.

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

7.2.3.4.2 Research Laboratory Correlative Studies

The Roychowdhury Lab/Cancer Genomics Lab Team will supervise all correlative studies. As described above, tumor and blood samples collection and profiling would be performed as part of the OSU Precision Cancer Study, a companion study to this trial supervised by the Roychowdhury Lab Team. This study supervises research tumor biopsies, germline tissue collection (blood and buccal swabs), comprehensive molecular profiling such as genomics, transcriptomics, and proteomics.

A) Research Characterization of Tumor DNA and RNA

Tumor DNA and RNA profiling with NGS: For research sequencing, we would use whole exome capture and RNAseq protocols to prepare libraries for sequencing as previously described (Reeser et al. 2017; Samorodnitsky et al. 2015). Libraries will be submitted to a vendor for sequencing on an Illumina HiSeq4000 instrument. Bioinformatics analysis will be performed in the Roychowdhury lab to derive annotated single nucleotide variation, copy number alteration, microsatellite status, and gene expression using existing tools as previously described (Kautto et al. 2017; Bonneville et al. 2017; Reeser et al. 2017; Samorodnitsky et al. 2015).

The overexpression of *FGFR1-3* has been correlated with response to FGFR inhibition in selected head and neck cancer patients, raising the possibility that *FGFR* mRNA may be a biomarker in appropriate patient populations. Therefore, it would be of interest to perform quantitative measurements of *FGFR* mRNA in tumor samples collected from patients on this study. One mechanism of *FGFR* overexpression is through gene amplification, as *FGFR1* and *FGFR3* amplifications have been detected frequently in cancers of the lung (squamous), head and neck and bladder. Interestingly, cancers without demonstrable *FGFR* amplifications can also exhibit mRNA overexpression, which can be attributed to alternate mechanisms that increase *FGFR* transcription (e.g. epigenetic modifications of gene promoters). Regardless of the mechanisms leading to increased *FGFR* expression, the CLIA-validated NGS assay SpARKFuse would be utilized to measure *FGFR* mRNA levels in cancers with any *FGFR* genomic alteration including amplification and fusions (Reeser et al. 2017) to determine the utility of mRNA as a predictive biomarker. This assay has been optimized for clinical grade sequencing of tumor RNA; a customized RNASeq analysis pipeline has also been developed to detect presence of fusions and expression of 93 kinase genes (including *FGFR1-4*). Methods for calculating gene expression utilizing FPKM (fragments per kilobase of transcript per million mapped reads) from SpARKFuse data have been published (Reeser et al. 2017)

B) Research Sequencing of ctDNA: A liquid biopsy for detection of *FGFR* genetic alterations

ctDNA sequencing. We will evaluate pre-treatment and serially collected blood samples for *FGFR* alterations through plasma ctDNA sequencing. We will use a custom hybridization-based capture for *FGFR1-4* exons and introns. Samples will be sequenced on an Illumina-based sequencing platform and analyzed to detect point mutations, insertions/deletions, copy changes, and gene fusions.

C) Tumor archiving for future use in Companion Diagnostics and Bridging Studies.

As the Lead site for this study, Dr. Roychowdhury and Ohio State University will provide central tumor archiving for all patients accrued at all subsites. This will include pre-treatment and post-progression tumor samples. Our CLIA-certified Cancer Genomics Lab will accession, store, review histology, and coordinate samples for future use in Companion Diagnostics or Bridging Studies as needed.

7.3 Central Radiology Review

Treatment and management decisions will be made based on local Investigator review of clinical, exam, lab, and imaging findings. In addition, we will contract with Biotel Research for central radiology review for the study (https://www.gobio.com/clinical-research/medical-imaging/). Similar to the Investigators, they will provide assessments based on RECIST v1.1. Each site will provide imaging to Biotel accordingly with appropriate privacy protections and controlled access.

8. Safety monitoring and reporting

8.1 Adverse events

8.1.1 Adverse Event (AE) definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product. Any worsening of a preexisting condition, which is temporally associated with the use of the study drug (i.e., occurs after the first dose of study drug), is also an AE.

AEs include:

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

Additionally, AEs may include signs or symptoms resulting from:

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

8.1.2 Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms that are considered clinically significant in the opinion of the investigator.
- Test result requires additional diagnostic testing (other than merely repeating an abnormal test) or medical/surgical intervention.
- Test result leads to a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Test result is considered to be an AE by the investigator or sponsor.

8.1.3 Performing adverse events assessments

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to the investigational product(s), will be reported, as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious AE requiring immediate notification to QED Therapeutics or its designated representative.

8.1.4 Reporting adverse events

For all enrolled patients, AEs should be recorded on the eCRF beginning with signing of the informed consent form and concluding 30 days following the last dose of the assigned study treatment, or the investigator/patient decision to discontinue treatment, whichever occurs later.

AEs ongoing after the reporting period: Any ongoing AEs thought to be at least possibly study-drug related after this time should be followed and reported to the sponsor's medical monitor until they resolve to baseline (or CTCAE grade ≤1), stabilize, or are considered to be chronic/irreversible.

8.1.5 Adverse event severity

The severity of AEs will be assessed according to the NCI CTCAE, v5.0. If the AE is not defined in the CTCAE, the investigator will determine the severity of the AE based on the following definitions:

- *Mild (grade 1):* The AE is noticeable to the patient but does not interfere with routine activity;
- *Moderate (grade 2):* The AE interferes with routine activity but responds to symptomatic therapy or rest;
- *Severe (grade 3):* The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy;
- *Life-Threatening (grade 4):* The patient is at immediate risk of death;
- *Death (grade 5):* The patient dies as a direct result of the complication or condition induced by the AE.

8.1.6 Causality

The investigator's assessment of causality must be provided for all AEs (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to the AE. In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and on the SAE form and report such an assessment in accordance with the SAE reporting requirements. The investigator will use medical consideration and use the following categories of causality to determine the relatedness of an AE with the study drug based on the following definitions. Not all criteria in each category of relatedness must be present.

- **Definitely Not Related (not drug related)**
  - The patient did not receive study drug OR
  - The temporal sequence of the AE onset relative to the administration of the study drug is not reasonable OR
  - There is another obvious cause of the AE

- **Probably Not Related (not drug related)**
  - There is evidence of exposure to study drug
  - There is another more likely cause of the AE

- Dechallenge (if performed) is negative or ambiguous
- Rechallenge (if performed) is negative or ambiguous

- **Possibly Related (drug related)**
  - There is evidence of exposure to study drug
  - The temporal sequence of the AE onset relative to administration of the study drug is reasonable
  - The AE could have been due to another equally likely cause
  - Dechallenge (if performed) is positive

- **Probably Related (drug related)**
  - There is evidence of exposure to study drug
  - The temporal sequence of the AE onset relative to administration of the study drug is reasonable
  - The AE is more likely explained by the study drug than by another cause

- **Definitely Related (drug related)**
  - There is evidence of exposure to study drug
  - The temporal sequence of the AE onset relative to administration of the study drug is reasonable
  - Dechallenge is positive
  - Rechallenge (if feasible) is positive
  - The AE shows a pattern consistent with previous knowledge of the test drug or a test drug class

8.2 Serious adverse event

8.2.1 Serious adverse event definition

The Investigator will determine the seriousness of an AE based on the following.

An AE is considered a SAE if at least one (1) of the following conditions applies:

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

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

- *Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions:* Any substantial disruption of a person's ability to conduct normal life functions.

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

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

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

- *Cancer:* Occurrence or diagnosis of a new cancer during the study is considered an SAE; a new cancer is a cancer that is histopathologically different than the cancer under study in the clinical trial (i.e., does not include metastatic or progressive disease).

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

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

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

8.2.1.1 Hospitalizations

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

- Social admission (e.g. patient has no place to sleep)
- Protocol-specified admission during a clinical trial (e.g. for a procedure required by the trial protocol)
- Optional admission not associated with a precipitating AE (e.g. for elective cosmetic surgery that was planned prior to study enrollment [appropriate documentation is required for these cases])
- Hospitalization or prolongation of hospitalization for scheduled therapy of the target malignancy

of the study is not considered an SAE

8.2.1.2 Progression of malignancy under study (including signs and symptoms of progression)

Worsening signs and symptoms of the malignancy under study should be reported as AEs. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as an AE.

8.2.2 Reporting serious adverse events

Serious AEs require immediate notification by the investigator or designee to QED Therapeutics Corporation beginning from the time the patient provides informed consent (ie, prior to undergoing any study-related procedure and/or receiving investigational product), through and including 30 days after the last administration of study treatment, or the investigator/patient decision to discontinue treatment, whichever occurs later. Any SAE occurring any time after the reporting period must be promptly reported to QED Therapeutics immediately after becoming aware of the SAE if a causal relationship to the investigational product is suspected. All SAEs ongoing 30 days or more after last dose of study drug is administered should be followed at least every 4 weeks until they resolve to baseline (or CTCAE grade ≤1), stabilize, or are considered to be chronic/irreversible. Should the FDA or national regulatory authorities require that the sponsor submit additional event data, the investigator will be asked to provide those data to the sponsor in a timely fashion.

8.2.2.1 Serious adverse event reporting period

The Ohio State University will be solely responsible for reporting serious adverse events to the OSU IRB, FDA, and QED Therapeutics. Participating subsites report directly to OSU and must report serious adverse events to the OSU PI and Multi-Site Coordinator within 24 hours of knowledge of the event. Serious adverse events are to be reported to the OSU IRB (per policy), FDA (per 21CFR312.32), and the appropriate monitor or subcommittee or task force within QED Therapeutics or its designated representative beginning from the time the patient is first administered investigational product through and including 30 days after permanent discontinuation of the investigational product. Any SAEs occurring any time after the reporting period must be promptly reported to the OSU IRB (per policy), FDA (per 21CFR312.32) and QED Therapeutics if a causal relationship to the investigational product is suspected.

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

8.2.2.2 Immediate reporting of serious adverse events

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

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

All SAEs should be reported to the OSU IRB using the most current version of the Event Reporting Form (available at http://go.osu.edu/Buck-IRB) within 10 days of the Investigator's or research staff member's learning of the event (per IRB policy). Events resulting in temporary or permanent interruption of study activities by the Investigator or funding organization to avoid potential harm to participants should be reported immediately (within 48 hours) whenever possible. SAEs reported from participating institutions will be reported to the IRB by the Multi-Site Coordinator. Participating institutions are responsible for reporting to their local IRB per their institutional guidelines.

8.2.2.3 Information to be provided by the Investigator for a serious adverse event

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

- Investigator identification
- Patient identification (e.g., study assigned sequence ID)
- Information on study drug and concomitant therapies (e.g., start/stop date, dose and frequency of study drug)
- Description of event
- Severity of the SAE
- Relationship of the SAE to the study drug, the patient's disease, or other contributing factors
- Outcome of the SAE

8.2.2.4 Follow-up information on a serious adverse event

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

8.2.2.5 Required follow-up for serious adverse events

There should be routine follow-up for 30 days after permanent discontinuation of study drug in all patients in order to monitor for the occurrence of SAEs. If an SAE continues after the 30-day evaluation period,

then the patient must be followed until the event resolves or stabilizes. The medical monitor may specify a longer period of time, if required to assure the safety of the patient.

8.2.2.6 QED Therapeutics responsibility for expedited safety reports

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

QED Therapeutics: All serious adverse events that are considered related or unrelated to Infigratinib treatment will be recorded on the SAE Report Form and sent within **24 hours** upon learning of the event to: Email: SAEIntake@fortrea.com; FAX: 1-888-726-8416

Exchange of safety information

a) From The Ohio State University to QED Therapeutics:

- Serious adverse events, as defined in FDA regulations 21 CFR 312.32 are to be reported to QED Therapeutics or QED Therapeutics's designee no later than at time of submission to the FDA per the time frames outlined in 21 CFR 312.32.
- Reports of all adverse events related to the study that have been submitted to the appropriate regulatory authorities in accordance with Applicable Law would be sent to QED Therapeutics within 24 hours after reporting including the submission documents.
- Reports of pregnancies in female subjects and female partners of male subjects and pregnancy outcomes will be promptly provided to QED Therapeutics.
- Study institution will promptly respond to QED Therapeutics queries on SAE and make available Medical Records or Study Data as QED Therapeutics may deem necessary to investigate and/or report on an adverse event.
- Reports of non-serious adverse events will be routinely collected during the trial in an appropriately configured database and provided to QED Therapeutics with dedicated outputs.

b) From QED Therapeutics to The Ohio State University:

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

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

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

8.3 Pregnancy and other safety issues

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

If a patient is confirmed pregnant during the trial, study drug administration must be discontinued immediately. Information regarding a pregnancy must be immediately forwarded to the OSU PI, who will report the information to QED Therapeutics.

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

8.3.1 Adverse Error Monitoring and Reporting

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

8.3.2 Data Safety Monitoring Plan

Continuous evaluation of safety, data quality and data timeliness will be carried out. The PI will conduct continuous review of data and patient safety at their regular disease group meetings (at least monthly) and the discussion will be documented in the minutes. The PI of the trial will review toxicities and responses of the trial where applicable at these disease group meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with QED Therapeutics, to determine if the trial should be terminated before completion.

Serious adverse events and responses will also be reviewed by the OSUCCC –James Data and Safety Monitoring Committee (DSMC). The PI will also submit a progress report (quarterly) that will be reviewed by the committee per the DSMC plan. All reportable serious adverse events will also be

reported to the Institutional Review Board (IRB) of record as per the policies of the IRB.

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

9. Data collection and management

9.1 Data confidentiality

Information about study subjects will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect follow-up safety information (e.g. has the subject experienced any new or worsened AEs) at the end of their scheduled study period.

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

Prior to entering key sensitive personally identifiable information (Subject Initials and exact Date of Birth), the system will prompt site to verify that this data is allowed to be collected. If the site indicates that country rules or ethics committee standards do not permit collection of these items, the system will not solicit Subject Initials. Year of birth will be solicited (in the place of exact date of birth) to establish that the subject satisfies protocol age requirements and to enable appropriate age-related normal ranges to be used in assessing laboratory test results.

9.2 Source documents

Before study initiation, at a clinical site initiation visit or at an investigator's meeting, The OSU PI and Multi-Site Team will review the protocol and CRFs with the investigators and their staff.

The investigator teams will maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information recorded on CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator teams will be responsible for confirming consistency between relevant source documents and the CRF entries. This includes full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs.

9.3 Data collection

For studies using Electronic Data Capture (EDC), the designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and, allow modification or verification of the entered data by the investigator staff.

The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

Biomarker (blood and tissue) samples obtained during the course of the study will be collected from the Investigator sites and sent to The Ohio State University Study Team (Tumor and Blood Manual). Designated investigational site staff will enter the information required by the protocol into the appropriate eCRF and/or designated laboratory requisition forms. Remote or field monitors may review the eCRFs and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample(s) by a remote or field monitor or by the designated investigational site staff; and one copy will be retained at the investigational site.

9.4 Database management and quality control

For studies using eCRFs, The Ohio State University Multi-Site Clinical Trial Team will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

10. Statistical methods and data analysis

The primary objective of this open label phase II study is to evaluate the efficacy of single agent Infigratinib in terms of overall response rate (ORR) in three cohorts of patients with solid tumor, FGFR fusions/mutations and failed standard of care (SOC):

- Cohort 1: Solid tumor patients with *FGFR1-3* fusion/translocation (**n, up to 30**) who have progressed on or are intolerant to SOC therapies. Prior therapy with a different FGFR inhibitor is not permitted.
- Cohort 2: Solid tumor patients with *FGFR1-3* fusion/translocation **(n=10)** who have progressed on or are intolerant to SOC therapies and received treatment with a different FGFR inhibitor.
- Cohort 3: Solid tumor patients with genetic alterations such as point mutations, insertions/deletions, or amplifications in any FGFR gene family member **(n=10)**. Prior therapy with a different FGFR inhibitor is not permitted.

The data from participating centers in this protocol will be combined. Data will be summarized with respect to demographic and baseline characteristics, efficacy and safety observations. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

For all analyses, data from patients from each cohort will be analyzed separately, unless otherwise stated.

10.1 Sample size and power calculation

For Cohort 1, the Simon optimum two-stage design is used to evaluate the primary endpoint of overall response rate in this patient population (Simon 1989; Simon et al. 2016). In this relapsed/refractory population of advanced solid tumor patients identified as having genomic fusion in *FGFR1-3*, our null hypothesis is that if the treatment is not active then the overall response rate will be at most 5%, reflecting a response by chance alone. We hypothesize that for this treatment, an ORR of at least 25% would be considered promising in this patient population. This study is designed to detect an ORR of at least 25% vs. ≤ 5%. After evaluating 9 patients enrolled in the first stage, the trial will be terminated if 0/9 patients demonstrate a response. If the trial goes on to the second stage, a total of 30 evaluable patients will be enrolled. If the total number responding is 4 or more, then the drug demonstrates promising response in this patient population. This design has 90% power and 5% type I error.

For Cohort 2 and 3, with n=10 evaluable patients, the estimated ORR with corresponding 90% Confidence Interval for various number of responses are listed below:

Responses	ORR	90% CI
0	0	(0.0, 0.206)
1	0.1	(0.005, 0.394)
2	0.2	(0.037, 0.507)
3	0.3	(0.087, 0.607)

4	0.4	(0.150, 0.696)
5	0.5	(0.222, 0.778)
6	0.6	(0.304, 0.850)
7	0.7	(0.393, 0.913)
8	0.8	(0.493, 0.963)
9	0.9	(0.606, 0.995)
10	1	(0.794, 1.000)

10.2 Data analysis populations set

Full Analysis Set
The Full Analysis set (FAS) includes all patients who received at least one dose of Infigratinib. The FAS will be used for all listings of raw data. Unless otherwise specified, the FAS will be the default analysis set used for all analyses.

Safety Set
The Safety Set includes all patients who received at least one dose of Infigratinib and have at least one valid post-baseline safety assessment. The statement that a patient had no AE (on the AE eCRF) constitutes a valid safety assessment.

Per-Protocol Set
The Per-Protocol Set (PPS) will consist of a subset of patients in the FAS who are compliant with requirements of the Clinical Study Protocol (CSP) in the following ways:

- Patient had an adequate tumor assessment at baseline
- Patient is evaluable for efficacy or discontinued due to adverse event, Investigator's decision, patient's refusal, disease progression, or died prior to the first evaluation of the primary efficacy variable
- Patient had no major protocol deviations.

Patients will be evaluable for efficacy if they have at least one response assessed differently from 'unknown' or 'not assessed' as per RECIST v1.1. All major protocol deviations leading to exclusion from the PPS will be detailed and summarized.

10.3 Treatments (study treatment, concomitant therapies, compliance)

Study treatment
The actual dose and duration in days of Infigratinib treatment as well as the dose intensity (computed as the ratio of actual dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized by means of descriptive statistics. The summary data will be presented for all study days as a single category. The FAS will be used.

Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug treatment will be listed by patient and summarized.

Compliance
Compliance to the protocol will be assessed by the number and proportion of patients with protocol deviations. These will be identified prior to database lock and will be listed and summarized. Compliance to the study drug will be assessed by the number of dose reductions and dose interruptions.

10.4 Efficacy analysis

10.4.1 Primary endpoint: ORR

Analysis of the efficacy primary endpoint (ORR) will be conducted when all patients have completed at least 6 cycles of treatment or have discontinued from the trial. Any PR or CR until the data cut-off date will be considered as a responder for ORR, irrespective of when it occurred. The following analysis will be done for each cohort of patients.

The estimated ORR will be presented along with the corresponding 90% confidence interval for each cohort, based on a binomial distribution.

10.4.2 Secondary efficacy endpoints

Overall survival
Overall Survival (OS) is defined as the time from the date of start of treatment to the date of death due to any cause. The survival time for patients without documentation of death prior to the data cutoff, will be censored at the last date the patient was known to be alive prior to the cutoff date. Survival time for patients with no post-baseline survival information will be censored at the date of start of treatment. OS will be analyzed using the Kaplan Meier method. Survival rate at 4, 6, 8, 12, 18 and 24 months and median OS will be estimated along with 95% confidence intervals from the Kaplan Meier distribution. The FAS will be used.

Progression Free Survival
Progression free survival (PFS) is defined as the date of the start of treatment to the date of the event defined as the first documented progression or death due to any cause. If patient has not had an event, progression-free-survival is censored at the date of last adequate tumor assessment. Kaplan-Meier analysis of PFS will be conducted for each cohort.

Best Overall Response and Disease Control Rate.
Overall lesion assessments will be listed by patient. Best overall response (BOR) will be summarized for the each cohorts using the Overall Response Rate and the Disease Control Rate which are the proportion of patients having respectively a best overall response of PR or CR, or SD, PR or CR. The estimated ORR and corresponding 90% confidence intervals based on the binomial distribution will be reported.

10.5 Safety analysis

Exposure to study drug and study drug compliance will be tabulated.

Safety analyses will be performed on the Safety population, and safety endpoints will be tabulated and presented. All AEs occurring during the study will be included in by-patient data listings and tabulated by organ class and preferred term. Adverse events will be summarized overall, by relationship and by severity. Events leading to death, SAE, and events resulting in treatment discontinuation will be tabulated.

The actual value and change from Baseline to each on-study evaluation will be summarized for vital sign measurements, as warranted by the data. By-patient listings of vital sign measurements will be prepared. Individual patient laboratory parameter values and summary statistics over time will be prepared using descriptive statistics. Severity of select clinical laboratory measures will be determined using NCI CTCAE v5 criteria and Grade 3 or 4 laboratory values will be presented in a separate patient listing.

The use of concomitant medications, coded using World Health Organization Drug Dictionary, will be included in by-patient listing.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and to further define the safety profile of this drug.

11. Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to OSU Multi-Site Clinical Trial Team, designated agents of QED Therapeutics, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in their CRFs.

OSU Investigator Team will provide to investigators, in a separate document, a proposed informed consent form (ICF) that is considered appropriate for this study and complies with the ICH GCP guideline and regulatory requirements. Any changes to this ICF suggested by the investigator must be agreed to by QED Therapeutics before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the QED Therapeutics monitor after IRB/IEC/REB approval.

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 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.

11.4 Discontinuation of the study

The Ohio State University Principal Investigator and QED Therapeutics reserve the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Publication of study protocol and results

The Ohio State University Principal Investigator and QED Therapeutics assure that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this study will be either submitted for publication and/or posted in a publicly accessible database of clinical study results.

11.5 Publication of study protocol and results

The Ohio State University Principal Investigator and QED Therapeutics are committed to following high ethical standards for reporting study results for its innovative medicine, including the timely communication and publication of clinical trial results, whatever their outcome. The Ohio State University Principal Investigator and QED Therapeutics assure that the key design elements of this protocol will be posted on the publicly accessible database, e.g. www.clinicaltrials.gov before study start. In addition, results of interventional clinical trials will be posted publically per local regulations.

The Ohio State University Principal Investigator and QED Therapeutics follows the ICMJE authorship guidelines (www.icmje.org) and other specific guidelines of the journal or congress to which the publication will be submitted

Authors will not receive remuneration for their writing of a publication, either directly from QED Therapeutics. Author(s) may be requested to present poster or oral presentation at scientific congress.

As part of its commitment to full transparency in publications, QED Therapeutics supports the full disclosure of all funding sources for the study and publications, as well as any actual and potential

conflicts of interest of financial and non-financial nature by all authors, including medical writing/editorial support, if applicable.

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a QED Therapeutics-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection instrument for the study. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the CRFs and all other required reports. Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the CRF must be recorded. Any missing data must be explained. Any change or correction to a paper CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry. For electronic CRFs an audit trail will be maintained by the system. The investigator should retain records of the changes and corrections to paper CRFs.

The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and/or guidelines. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to QED Therapeutics. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

11.8 Audits and inspections

Source data/documents must be available for inspection by QED Therapeutics or designee or Health Authorities.

11.9 Financial disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site - prior to study start.

12. Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact QED Therapeutics or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by QED Therapeutics and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by QED Therapeutics, Health Authorities where required, and the IRB/IEC/REB.

Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, The OSU Multi-Site Clinical Trial Team and QED Therapeutics should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

13. Appendices

13.1 Appendix 1: List of concomitant medications

In general, the use of any concomitant medication deemed necessary for the care of the patient is permitted in this study, except as specifically prohibited below. Combination administration of study drugs could result in drug-drug interactions (DDI) that could potentially lead to reduced activity or enhanced toxicity of the concomitant medication and/or Infigratinib.

The following lists are based on the Oncology Clinical Pharmacology Drug-Drug Interaction Database (release date: 29 Oct 2012), which was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and supplemented with the FDA Draft guidance.

Table 10: Drugs to be used with caution while on study

Category	Drug Names
Sensitive CYP3A Substrates	Alpha-dihydroergocryptine, aplaviroc, aprepitant, atorvastatin, brecanavir, brotizolam, budesonide, buspirone, capravirine, casopitant, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, fluticasone, indinavir, levomethadyl, lopinavir, lovastatin, lumefantrine, lurasidone, maraviroc, midazolam, neratinib, nisoldipine, perospirone, quetiapine, ridaforolimus, saquinavir, sildenafil, simvastatin, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil, vicriviroc
Moderate inhibitors of CYP3A4	Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, imatinib, Schisandra sphenanthera, tofisopam, verapamil
Moderate inducers of CYP3A4	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, talviraline, thioridazine, tipranavir
Medications which alter the pH of the GI tract[1]	Proton-pump inhibitors (e.g., omeprazole), H2antagonists (e.g., ranitidine) and antacids.
Medications that have possible risk of TdP/QT prolongation	Dronedarone, eribulin, lapatinib, sunitinib, nilotinib, tamoxifen, gatifloxacin, gemifloxacin, levofloxacin, ofloxacin, roxithromycin, telithromycin, clozapine, iloperidone, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, dolasetron, granisertron, ondansetron, escitalopram, venlafaxine, Ranolazine, voriconazole, amantadine, foscarnet, isradipine, moexipril, nicardipine, fingolimod, tacrolimus, atazanavir, felbamate, famotidine, fosphenytoin, alfuzosin, chloral hydrate, indapamide, lithium,

Category	Drug Names
	octreotide, pasireotide, oxytocin, ranolazine, tizanidine, vardenafil
Medications that have conditional risk of TdP/QT prolongation	Amisulpride, amiptriptyline, clomipramine, desipramine, doxepin, fluoxetine, imipramine, nortriptyline, paroxetine, protriptyline, sertraline, trazodone, trimipramine, ciprofloxacin, trimethoprim-sulfa, diphenhydramine, fluconazole, itrazonazole, ketoconazole, ritonavir, galantamine, solifenacin
BCRP substrates	Rosuvatstatin, methotrexate, irinotecan, atorvastatin, simvastatin, topotecan, sulfasalazine

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

FDA Guidance for Industry, Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. Accessed 10 November 2013 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm2923 62.pdf.

Indiana University School of Medicine's "Clinically Relevant" table (2009). Accessed 14-Jul-2011 http://medicine.iupui.edu/clinpharm/ddis/clinicalTable.aspx.

University of Washington's Drug Interaction Database (2013). http://.druginteractioninfo.org

Drug-Drug Interactions (DDI) Database: Novartis Oncology Clinical Pharmacology Internal Memorandum, Final (v04), 12-Oct-2012

13.2 Appendix 2: List of prohibited medications

Table 11: List of prohibited medication while on study

Category	Drug Names
Strong inducers of CYP3A4	Avasimibe, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort
Strong Inhibitors of CYP3A4	Clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, voriconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, grapefruit juice, juice from Seville oranges
Medications which increase serum phosphorus and/or calcium	Calcium, phosphate, vitamin D, parathyroid hormone (PTH)
Narrow Therapeutic index substrates of CYP3A4	Quinidine, astemizole, terfanadine, cyclosporine, sirolimus, tacrolimus, diergotamine, cisapride, ergotamine, pimozide, alfentanil, fentanyl thioridazine, diergotamine, dihydroergotamine, ergotamine
Medications with established potential for QT prolongation or Torsades de pointes	Amiodarone, Anagrelide, Arsenic trioxide, Astemizole (Off US mkt), Azithromycin, Bepridil (Off US mkt), Chloroquine, Chlorpromazine, Cisapride (Off US mkt), Citalopram, Clarithromycin, Cocaine, Disopyramide, Dofetilide, Domperidone (Not on US mkt), Dronedarone, Droperidol, Erythromycin, Escitalopram, Flecainide, Grepafloxacin (Off market worldwide), Halofantrine, Haloperidol, Ibutilide, Levofloxacin, Levomethadyl (Off US mkt), Mesoridazine (Off US mkt), Methadone, Moxifloxacin, Ondansetron, Pentamidine, Pimozide, Probucol (Off US mkt), Procainamide (Oral off US mkt), Quinidine, Sevoflurane, Sotalol, Sparfloxacin (Off US mkt), Sulpiride (Not on US Mkt), Terfenadine (Off US mkt), Thioridazine, Vandetanib

13.3 Appendix 3: Guidelines for response, duration of overall response, TTF, TTP, progression-free survival and overall survival (based on RECIST 1.1) harmonization of efficacy analysis of solid tumor studies

Document status:	Version 3.1: 29-Nov-2011 Version 3.0: 19-Oct-2009 Version 2.0: 18-Jan-2007 Version 1.0: 13-Dec-2002
Release date:	29-Nov-2011
Authors (Version 3.1):	Appanna K, Chen B, Dharan B, Green S, Porshneva D, Subramanian K, Gauthier M, Patel N, Chica S, Vattikola A, Zuber E
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Authors (Version 2):	Capdeville R, Chen B, Gathmann I, Green S, Lebwohl D, Murawsky M, Wang L, Zuber E
Authors (Version 1):	Gathmann I, Mietlowski W, Kiese B, Mellars K, Capdeville R, Dugan M

Glossary

CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed tomography
DFS	Disease-free survival
eCRF	Electronic Case Report Form
FPFV	First patient first visit
GBM	Glioblastoma multiforme
MRI	Magnetic resonance imaging
LPLV	Last patient last visit
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	Stable disease
SOD	Sum of Diameter
TTF	Time to treatment failure
TTP	Time to progression

UNK	Unknown

13.3.1 Introduction

The purpose of this document is to provide the working definitions and rules necessary for a consistent and efficient analysis of efficacy for oncology studies in solid tumors. This document is based on the RECIST criteria for tumor responses (Therasse et al 2000) and the revised RECIST 1.1 guidelines (Eisenhauer et al 2009).

The efficacy assessments described in Section 13.3.2 and the definition of best response in Section 13.3.17 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 13.3.27 of this guideline describes data handling and programming rules.

13.3.2 Efficacy assessments

Tumor evaluations are made based on RECIST criteria (Therasse et al 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16 and revised RECIST guidelines (version 1.1) (Eisenhauer et al 2009) European Journal of Cancer; 45:228-247.

13.3.3 Definitions

13.3.4 Disease measurability

In order to evaluate tumors throughout a study, definitions of measurability are required in order to classify lesions appropriately at baseline. In defining measurability, a distinction also needs to be made between nodal lesions (pathological lymph nodes) and non-nodal lesions.

- **Measurable disease** - the presence of at least one measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

For patients without measurable disease see Section 13.3.25.

Measurable lesions (both nodal and non-nodal):

- Measurable non-nodal - As a rule of thumb, the minimum size of a measurable non-nodal target lesion at baseline should be no less than double the slice thickness or 10mm whichever is greater - e.g. the minimum non-nodal lesion size for CT/MRI with 5mm cuts will be 10 mm, for 8 mm contiguous cuts the minimum size will be 16 mm.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by CT/MRI, can be considered as measurable lesions, if the soft tissue component meets the definition of measurability.

- Measurable nodal lesions (i.e. lymph nodes) - Lymph nodes ≥15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥10 mm and <15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts (i.e., spherical structure with a thin, non-irregular, non-nodular and non-enhancing wall, no septations, and low CT density [water-like] content) should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.
- Non-measurable lesions - all other lesions are considered non-measurable, including small lesions (e.g. longest diameter <10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions e.g., blastic bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

13.3.5 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 13.3.25.

13.3.6 Methods of tumor measurement - general guidelines

In this document, the term "contrast" refers to intravenous (i.v.) contrast.

The following considerations are to be made when evaluating the tumor:

- All measurements should be taken and recorded in metric notation (mm), 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.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.
- For optimal evaluation of patients, the same methods of assessment and technique should be used to characterize each identified and reported lesion at baseline and during followup. Contrast-enhanced CT of chest, abdomen and pelvis should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm. If, at baseline, a patient is known to have a medical

contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow-up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the QED Therapeutics calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with 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 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 CT 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.
- **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.
- **Ultrasound**: When the primary endpoint of the study is overall response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy**: The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- **Cytology and histology**: Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable

tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).

- **Clinical examination**: Clinical lesions will only be considered measurable when they are superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

13.3.7 Baseline documentation of target and non-target lesions

For the evaluation of lesions at baseline and throughout the study, the lesions are classified at baseline as either target or non-target lesions:

- **Target lesions**: All measurable lesions (nodal and non-nodal) up to a maximum of five lesions in total (and a maximum of two lesions per organ), representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Each target lesion must be uniquely and sequentially numbered on the CRF (even if it resides in the same organ).

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 0.
- **Nodal target**: See Section 13.3.11

A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters (SOD). The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

- **Non-target lesions**: All other lesions are considered non-target lesions, i.e. lesions not fulfilling the criteria for target lesions at baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (i.e. multiple liver metastases). Each non-target lesion identified at baseline must be followed at each subsequent evaluation and documented on eCRF.

13.3.8 Follow-up evaluation of target and non-target lesions

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 12)

and non-target lesions (Table 13) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14) as well as the presence or absence of new lesions.

13.3.9 Follow-up and recording of lesions

At each visit and for each lesion the actual date of the scan or procedure which was used for the evaluation of each specific lesion should be recorded. This applies to target and non-target lesions as well as new lesions that are detected. At the assessment visit all of the separate lesion evaluation data are examined by the investigator in order to derive the overall visit response. Therefore, all such data applicable to a particular visit should be associated with the same assessment number.

13.3.10 Non-nodal lesions

Following treatment, lesions may have longest diameter measurements smaller than the image reconstruction interval. Lesions smaller than twice the reconstruction interval are subject to substantial "partial volume" effects (i.e., size may be underestimated because of the distance of the cut from the longest diameter; such lesions may appear to have responded or progressed on subsequent examinations, when, in fact, they remain the same size).

If the lesion has completely disappeared, the lesion size should be reported as 0 mm.

Measurements of non-nodal target lesions that become 5 mm or less in longest diameter are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in longest diameter irrespective of slice thickness/reconstruction interval.

In other cases where the lesion cannot be reliably measured for reasons other than its size (e.g., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

13.3.11 Nodal lesions

A nodal lesion less than 10 mm in size by short axis is considered normal. Lymph nodes are not expected to disappear completely, so a "non-zero size" will always persist.

Measurements of nodal target lesions that become 5 mm or less in short axis are likely to be non-reproducible. Therefore, it is recommended to report a default value of 5 mm, instead of the actual measurement. This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). Actual measurement should be given for all lesions larger than 5 mm in short axis irrespective of slice thickness/reconstruction interval.

However, once a target nodal lesion shrinks to less than 10 mm in its short axis, it will be considered normal for response purpose determination. The lymph node measurements will continue to be recorded

to allow the values to be included in the sum of diameters for target lesions, which may be required subsequently for response determination.

13.3.12 Determination of target lesion response

Table 12: Response criteria for target lesions

Response Criteria	Evaluation of target lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm [1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD.
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.[3]

1. SOD for CR may not be zero when nodal lesions are part of target lesions
2. Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR [3]. Methodology change See Section 13.3.6.

Notes on target lesion response

Reappearance of lesions: If the lesion appears at the same anatomical location where a target lesion had previously disappeared, it is advised that the time point of lesion disappearance (i.e., the "0 mm" recording) be re-evaluated to make sure that the lesion was not actually present and/or not visualized for technical reasons in this previous assessment. If it is not possible to change the 0 value, then the investigator/radiologist has to decide between the following three possibilities:

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in
- Table above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.

- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.
- **Missing measurements**: In cases where measurements are missing for one or more target lesions it is sometimes still possible to assign PD based on the measurements of the remaining lesions. For example, if the sum of diameters for 5 target lesions at baseline is 100 mm at baseline and the sum of diameters for 3 of those lesions at a post-baseline visit is 140 mm (with data for 2 other lesions missing) then a PD should be assigned. However, in other cases where a PD cannot definitely be attributed, the target lesion response would be UNK.
- **Nodal lesion decrease to normal size**: When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size they should still have a measurement recorded on scans. This measurement should be reported even when the nodes are normal in order not to overstate progression should it be based on increase in the size of nodes.
- **Lesions split**: In some circumstances, disease that is measurable as a target lesion at baseline and appears to be one mass can split to become two or more smaller sub-lesions. When this occurs, the diameters (long axis - non-nodal lesion, short axis - nodal lesions) of the two split lesions should be added together and the sum recorded in the diameter field on the case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation.
- **Lesions coalesced**: Conversely, it is also possible that two or more lesions which were distinctly separate at baseline become confluent at subsequent visits. When this occurs a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis - non-nodal lesion, short axis nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the case report form, the diameter of the "merged lesion" should be recorded for the size of one of the original lesions while a size of "0"mm should be entered for the remaining lesion numbers which have coalesced.
- The **measurements for nodal lesions**, even if less than 10 mm in size, will contribute to the calculation of target lesion response in the usual way with slight modifications.
  - Since lesions less than 10 mm are considered normal, a CR for target lesion response should be assigned when all nodal target lesions shrink to less than 10 mm and all non-nodal target lesions have disappeared.
  - Once a CR target lesion response has been assigned a CR will continue to be appropriate (in the absence of missing data) until progression of target lesions.
  - Following a CR, a PD can subsequently only be assigned for target lesion response if either a non-nodal target lesion "reappears" or if any single nodal lesion is at least 10 mm and there is at least 20% increase in sum of the diameters of all nodal target lesions relative to nadir with at least 5 mm increase in the absolute sum of the diameters.

13.3.13 Determination of non-target lesion response

Table 13: Response criteria for non-target lesions

Response Criteria	Evaluation of non-target lesions
Complete Response (CR):	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesions must be non-pathological in size (< 10 mm short axis)

Progressive Disease (PD):	Unequivocal progression of existing non-target lesions.[1]
Non-CR/Non-PD:	Neither CR nor PD
Unknown (UNK)	Progression has not been documented and one or more non-target lesions have not been assessed or have been assessed using a different method than baseline.

[1]. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail and the progression status should be confirmed later on by the review panel (or study chair).

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**NonCR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 13.3.12 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

13.3.14 New lesions

The appearance of a new lesion is always associated with Progressive Disease (PD) and has to be recorded as a new lesion in the New Lesion CRF page.

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion.
- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 13.3.15).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥10 mm for the first time in the study plus 5 mm absolute increase. **FDG-PET**: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 13.3.6.

13.3.15 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table .

Table 14: Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR[1]
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1. This overall lesion response also applies when there are no non-target lesions identified at baseline.
2. Once confirmed PR was achieved, all these assessments are considered PR.
3. As defined in Section 13.3.8.

If there are no baseline scans available at all, then the overall lesion response at each assessment should be considered Unknown (UNK).

If the evaluation of any of the target or non-target lesions identified at baseline could not be made during follow-up, the overall status must be ‘unknown’ unless progression was seen.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the CR.

13.3.16 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 13.3.25 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

13.3.17 Best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the

treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

The best overall response will usually be determined from response assessments undertaken while on treatment. However, if any assessments occur after treatment withdrawal the protocol should specifically describe if these will be included in the determination of best overall response and/or whether these additional assessments will be required for sensitivity or supportive analyses. As a default, any assessments taken more than 30 days after the last dose of study treatment will not be included in the best overall response derivation. If any alternative cancer therapy is taken while on study any subsequent assessments would ordinarily be excluded from the best overall response determination. If response assessments taken after withdrawal from study treatment and/or alternative therapy are to be included in the main endpoint determination, then this should be described and justified in the protocol.

Where a study requires confirmation of response (PR or CR), changes in tumor measurements must be confirmed by repeat assessments that should be performed not less than 4 weeks after the criteria for response are first met.

Longer intervals may also be appropriate. However, this must be clearly stated in the protocol. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- For non-randomized trials where response is the primary endpoint, confirmation is needed.
- For trials intended to support accelerated approval, confirmation is needed
- For all other trials, confirmation of response may be considered optional.

The best overall response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

Overall lesion responses of CR must stay the same until progression sets in, with the exception of a UNK status. A patient who had a CR cannot subsequently have a lower status other than a PD, e.g. PR or SD, as this would imply a progression based on one or more lesions reappearing, in which case the status would become a PD.

Once an overall lesion response of PR is observed (which may have to be a confirmed PR depending on the study) this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status. However, in studies where confirmation of response is required, if a patient has a single PR (≥ 30% reduction of tumor burden compared to baseline) at one assessment, followed by a <30% reduction from baseline at the next assessment (but not ≥ 20% increase from previous smallest sum), the objective status at that assessment should be SD. Once a confirmed PR was seen, the overall lesion response should be considered PR (or UNK) until progression is documented or the lesions totally disappear in which case a CR assignment is applicable. In studies where confirmation of response is not required after a single PR the overall lesion response should still be considered PR (or UNK) until progression is documented or the lesion totally disappears in which case a CR assignment is applicable.

Example: In a case where confirmation of response is required the sum of lesion diameters is 200 mm at baseline and then 140 mm - 150 mm - 140 mm - 160 mm - 160 mm at the subsequent visits. Assuming that non-target lesions did not progress, the overall lesion response would be PR - SD - PR - PR - PR. The second assessment with 140 mm confirms the PR for this patient. All subsequent assessments are considered PR even if tumor measurements decrease only by 20% compared to baseline (200 mm to 160 mm) at the following assessments.

If the patient progressed but continues study treatment, further assessments are not considered for the determination of best overall response.

Note: these cases may be described as a separate finding in the CSR but not included in the overall response or disease control rates.

The best overall response for a patient is always calculated, based on the sequence of overall lesion responses. However, the overall lesion response at a given assessment may be provided from different sources:

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- QED Therapeutics calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

Overall response rate (ORR) is the proportion of patients with a best overall response of CR or PR. This is also referred to as 'Overall response rate' in some protocols or publications.

Disease control rate (DCR) is the proportion of patients with a best overall response of CR or PR or SD. Another approach is to summarize the progression rate at a certain time point after baseline. In this case, the following definition is used:

Early progression rate (EPR) is the proportion of patients with progressive disease within 8 weeks of the start of treatment.

The protocol should define populations for which these will be calculated. The timepoint for EPR is study specific. EPR is used for the multinomial designs of Dent and Zee (2001) and counts all patients who at the specified assessment (in this example the assessment would be at 8 weeks ± window) do not have an overall lesion response of SD, PR or CR. Patients with an unknown (UNK) assessment at that time point and no PD before, will not be counted as early progressors in the analysis but may be included in the denominator of the EPR rate, depending on the analysis population used. Similarly when examining overall response and disease control, patients with a best overall response assessment of unknown (UNK) will not be regarded as "responders" but may be included in the denominator for ORR and DCR calculation depending on the analysis population (e.g. populations based on an ITT approach).

13.3.18 Progression-free survival

Usually in all Oncology studies, patients are followed for tumor progression after discontinuation of study medication for reasons other than progression or death. If this is not used, e.g. in Phase I or II studies, this should be clearly stated in the protocol. Note that randomized trials (preferably blinded) are recommended where PFS is to be the primary endpoint.

Progression-free survival (PFS) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.

13.3.19 Overall survival

All patients should be followed until death or until patient has had adequate follow-up time as specified in the protocol whichever comes first. The follow-up data should contain the date the patient was last seen alive / last known date patient alive, the date of death and the reason of death ("Study indication" or "Other").

Overall survival (OS) is defined as the time from date of randomization/start of treatment to date of death due to any cause. If a patient is not known to have died, survival will be censored at the date of last known date patient alive.

13.3.20 Time to progression

Some studies might consider only death related to underlying cancer as an event which indicates progression. In this case the variable "Time to progression" might be used. TTP is defined as PFS except for death unrelated to underlying cancer.

Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

13.3.21 Time to treatment failure

This endpoint is often appropriate in studies of advanced disease where early discontinuation is typically related to intolerance of the study drug. In some protocols, time to treatment failure may be considered as a sensitivity analysis for time to progression. The list of discontinuation reasons to be considered or not as treatment failure may be adapted according to the specificities of the study or the disease.

Time to treatment failure (TTF) is the time from date of randomization/start of treatment to the earliest of date of progression, date of death due to any cause, or date of discontinuation due to reasons other than 'Protocol violation' or 'Administrative problems'. The time to treatment failure for patients who did not experience treatment failure will be censored at last adequate tumor assessment.

13.3.22 Duration of response

The analysis of the following variables should be performed with much caution when restricted to responders since treatment bias could have been introduced. There have been reports where a treatment with a significantly higher response rate had a significantly shorter duration of response but where this probably primarily reflected selection bias which is explained as follows: It is postulated that there are two groups of patients: a good risk group and a poor risk group. Good risk patients tend to get into response readily (and relatively quickly) and tend to remain in response after they have a response. Poor risk patients tend to be difficult to achieve a response, may have a longer time to respond, and tend to relapse quickly when they do respond. Potent agents induce a response in both good risk and poor risk patients. Less potent agents induce a response mainly in good risk patients only. This is described in more detail by Morgan (1988).

It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. An analysis of responders should only be performed to provide descriptive statistics and even then interpreted with caution by evaluating the results in the context of the observed response rates. If an inferential comparison between treatments is required this should only be performed on all patients (i.e. not restricting to "responders" only) using appropriate statistical methods such as the techniques described in Ellis et al (2008). It should also be stated in the protocol if duration of response is to be calculated in addition for unconfirmed response.

For summary statistics on "responders" only the following definitions are appropriate. (Specific definitions for an all-patient analysis of these endpoints are not appropriate since the status of patients throughout the study is usually taken into account in the analysis).

Duration of overall response (CR or PR): For patients with a CR or PR (which may have to be confirmed the start date is the date of first documented response (CR or PR) and the end date and censoring is defined the same as that for time to progression.

The following two durations might be calculated in addition for a large Phase III study in which a reasonable number of responders is seen.

Duration of overall complete response (CR): For patients with a CR (which may have to be confirmed) the start date is the date of first documented CR and the end date and censoring is defined the same as that for time to progression.

Duration of stable disease (CR/PR/SD): For patients with a CR or PR (which may have to be confirmed) or SD the start and end date as well as censoring is defined the same as that for time to progression.

13.3.23 Time to response

Time to overall response (CR or PR) is the time between date of randomization/start of treatment until first documented response (CR or PR). The response may need to be confirmed depending on the type of study and its importance. Where the response needs to be confirmed then time to response is the time to the first CR or PR observed.

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 13.3.22. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

- at maximum follow-up (i.e. FPFV to LPLV used for the analysis) for patients who had a PFS event (i.e. progressed or died due to any cause). In this case the PFS event is the worst possible outcome as it means the patient cannot subsequently respond. Since the statistical analysis usually makes use of the ranking of times to response it is sufficient to assign the worst possible censoring time which could be observed in the study which is equal to the maximum follow-up time (i.e. time from FPFV to LPLV)
- at last adequate tumor assessment date otherwise. In this case patients have not yet progressed so they theoretically still have a chance of responding

Time to overall complete response (CR) is the time between dates of randomization/start of treatment until first documented CR. Similar analysis considerations including (if appropriate) censoring rules apply for this endpoint described for the time to overall response endpoint.

13.3.24 Definition of start and end dates for time to event variables

Assessment date
For each assessment (i.e. evaluation number), the **assessment date** is calculated as the latest of all measurement dates (e.g. X-ray, CT-scan) if the overall lesion response at that assessment is CR/PR/SD/UNK. Otherwise - if overall lesion response is progression - the assessment date is calculated as the earliest date of all measurement dates at that evaluation number.

Start dates
For all "time to event" variables, other than duration of response, the randomization/ date of treatment start will be used as the start date.
For the calculation of duration of response the following start date should be used:
- Date of first documented response is the assessment date of the first overall lesion response of CR (for duration of overall complete response) or CR / PR (for duration of overall response) respectively, when this status is later confirmed.

End dates
The end dates which are used to calculate 'time to event' variables are defined as follows:
- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no postbaseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 13.3.25).

Example (if protocol defined schedule of assessments is 3 months): tumor assessments at baseline - 3 months - 6 months - missing - missing - PD. Date of next scheduled assessment would then correspond to 9 months.
- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.
- Date of secondary anti-cancer therapy is defined as the start date of any additional (secondary) antineoplastic therapy or surgery.

13.3.25 Handling of patients with non-measurable disease only at baseline

It is possible that patients with only non-measurable disease present at baseline are entered into the study, either because of a protocol violation or by design (e.g. in Phase III studies with PFS as the primary endpoint). In such cases the handling of the response data requires special consideration with respect to inclusion in any analysis of endpoints based on the overall response evaluations.

It is recommended that any patients with only non-measurable disease at baseline should be included in the main (ITT) analysis of each of these endpoints.

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 15.

Table 15: Overall lesion response at each assessment: patients with non-target disease only

Non-target lesions	New Lesions	Overall lesion response
CR	No	CR
Non-CR/Non-PD[1]	No	Non-CR/non-PD
UNK	No	UNK
PD	Yes or No	PD
Any	Yes	PD

[1] As defined in Section 13.3.8.

In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific numbers with the non-CR/non-PD category.

In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

For ORR it is recommended that the main (ITT) analysis includes data from patients with only non-measurable disease at baseline, handling patients with a best response of CR as "responders" with respect to ORR and all other patients as "non-responders".

For PFS, it is again recommended that the main ITT analyses on these endpoints include all patients with only non-measurable disease at baseline, with possible sensitivity analyses which exclude these particular patients. Endpoints such as PFS which are reliant on the determination and/or timing of progression can incorporate data from patients with only nonmeasurable disease.

13.3.26 Sensitivity analyses

This section outlines the possible event and censoring dates for progression, as well as addresses the issues of missing tumor assessments during the study. For instance, if one or more assessment visits are missed prior to the progression event, to what date should the progression event be assigned? And should progression event be ignored if it occurred after a long period of a patient being lost to follow-up? It is important that the protocol and SAP specify the primary analysis in detail with respect to the definition of event and censoring dates and also include a description of one or more sensitivity analyses to be performed.

Based on definitions outlined in Section 13.3.24, and using the draft FDA guideline on endpoints (Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics April 2005) as a reference, the following analyses can be considered:

Table 16: Options for event dates used in PFS, TTP, duration of response

Situation		**Options for end-date (progression or censoring)[1] (1) = default unless specified differently in the protocol or SAP**	**Outcome**
A	No baseline assessment	(1) Date of randomization/start of treatment[3]	Censored
B	Progression at or before next scheduled assessment	(1) Date of progression (2) Date of next scheduled assessment[2]	Progressed Progressed
C1	**Progression or death after exactly one missing assessment**	(1) Date of progression (or death) (2) Date of next scheduled assessment[2]	Progressed Progressed
C2	**Progression or death after two or more missing assessments**	(1) Date of last adequate assessment[2] (2) Date of next scheduled assessment[2] (3) Date of progression (or death)	Censored Progressed Progressed
D	No progression	(1) Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	(1) N/A (2) Date of discontinuation (visit date at which clinical progression was determined)	Ignored Progressed
F	New anticancer therapy given	(1) Date of last adequate assessment (2) Date of secondary anti-cancer therapy (3) Date of secondary anti-cancer therapy(4) N/A	Censored Censored Event Ignored
G	Deaths due to reason other than deterioration of 'Study indication'	(1) Date of last adequate assessment	Censored (only TTP and duration of response)

[1].=Definitions can be found in Section 13.3.24
[2].=After the last adequate tumor assessment. "Date of next scheduled assessment" is defined in Section 14.1.25. [3].=The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death.

The primary analysis and the sensitivity analyses must be specified in the protocol. Clearly define if and why options (1) are not used for situations C, E and (if applicable) F.

Situations C (C1 and C2): Progression or death after one or more missing assessments: The primary analysis is usually using options (1) for situations C1 and C2, i.e.

- (C1) taking the actual progression or death date, in the case of only one missing assessment.
- (C2) censoring at the date of the last adequate assessment, in the case of two or more consecutive missing assessments.

In the case of two or missing assessments (situation C2), option (3) may be considered jointly with option (1) in situation C1 as sensitivity analysis. A variant of this sensitivity analysis consists of backdating the date of event to the next scheduled assessment as proposed with option (2) in situations C1 and C2.

Situation E: Treatment discontinuation due to 'Disease progression' without documented progression: By default, option (1) is used for situation E as patients without documented PD should be followed for progression after discontinuation of treatment. However, option (2) may be used as sensitivity analysis. If progression is claimed based on clinical deterioration instead of tumor assessment by e.g. CT-scan, option (2) may be used for indications with high early progression rate or difficulties to assess the tumor due to clinical deterioration.

Situation F: New cancer therapy given: the handling of this situation must be specified in detail in the protocol. However, option (1), i.e. censoring at last adequate assessment may be used as a default in this case.

Additional suggestions for sensitivity analyses
Other suggestions for additional sensitivity analyses may include analyses to check for potential bias in follow-up schedules for tumor assessments, e.g. by assigning the dates for censoring and events only at scheduled visit dates. The latter could be handled by replacing in Table 16 the "Date of last adequate assessment" by the "Date of previous scheduled assessment (from baseline)", with the following definition:

- **Date of previous scheduled assessment (from baseline)** is the date when a tumor assessment would have taken place, if the protocol assessment scheme was strictly followed from baseline, immediately before or on the date of the last adequate tumor assessment.

In addition, analyses could be repeated using the Investigators' assessments of response rather than the calculated response. The need for these types of sensitivity analyses will depend on the individual requirements for the specific study and disease area and have to be specified in the protocol or SAP documentation.

13.3.27 Data handling and programming rules

The following section should be used as guidance for development of the protocol, data handling procedures or programming requirements (e.g. on incomplete dates).

13.3.28 Study/project specific decisions

For each study (or project) various issues need to be addressed and specified in the protocol or SAP documentation. Any deviations from protocol must be discussed and defined at the latest in the SAP documentation.

The proposed primary analysis and potential sensitivity analyses should be discussed and agreed with the health authorities and documented in the protocol (or at the latest in the SAP documentation before database lock).

13.3.29 End of treatment phase completion

Patients **may** voluntarily withdraw from the study treatment or may be taken off the study treatment at the discretion of the investigator at any time. For patients who are lost to followup, the investigator or designee should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

The end of treatment visit and its associated assessments should occur within 7 days of the last study treatment.

Patients may discontinue study treatment for any of the following reasons:
- Adverse event(s)
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- Progressive disease
- Study terminated by the sponsor
- Non-compliant with study treatment
- No longer requires treatment
- Treatment duration completed as per protocol (optional, to be used if only a fixed number of cycles is given)

13.3.30 End of post-treatment follow-up (study phase completion)

End of post-treatment follow-up visit will be completed after discontinuation of study treatment and post-treatment evaluations but prior to collecting survival follow-up.

Patients may provide study phase completion information for one of the following reasons:
- Adverse event
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol deviation
- Technical problems
- Subject/guardian decision
- Death
- New therapy for study indication
- Progressive disease
- Study terminated by the sponsor

13.3.31 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at QED Therapeutics or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If QED Therapeutics elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the SAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

Any discontinuation due to 'Disease progression' without documentation of progression by RECIST criteria should be carefully reviewed. Only patients with documented deterioration of symptoms indicative of progression of disease should have this reason for discontinuation of treatment or study evaluation.

13.3.32 Programming rules

The following should be used for programming of efficacy results:

13.3.33 Calculation of 'time to event' variables

Time to event = end date - start date + 1 (in days)

When no post-baseline tumor assessments are available, the date of randomization/start of treatment will be used as end date (duration = 1 day) when time is to be censored at last tumor assessment, i.e. time to event variables can never be negative.

13.3.34 Incomplete assessment dates

All investigation dates (e.g. X-ray, CT scan) must be completed with day, month and year.
If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 13.3.24). If all measurement dates have no day recorded, the 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between previous and following assessment. If a previous and following assessment is not available, this assessment will not be used for any calculation.

13.3.35 Incomplete dates for last known date patient alive or death

All dates must be completed with day, month and year. If the day is missing, the 15th of the month will be used for incomplete death dates or dates of last contact.

13.3.36 Non-target lesion response

If no non-target lesions are identified at baseline (and therefore not followed throughout the study), the non-target lesion response at each assessment will be considered 'not applicable (NA)'.

13.3.37 Study/project specific programming

The standard analysis programs need to be adapted for each study/project.

13.3.38 Censoring reason

In order to summarize the various reasons for censoring, the following categories will be calculated for each time to event variable based on the treatment completion page, the study evaluation completion page and the survival page.

For survival the following censoring reasons are possible:
- Alive
- Lost to follow-up

For PFS and TTP (and therefore duration of responses) the following censoring reasons are possible:
- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
  Event documented after two or more missing tumor assessments (optional, see Table)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 13.3.24. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:
- This may be when there has been a definite decision to stop evaluation (e.g. reason="Sponsor decision" on study evaluation completion page), when patients are not followed for progression after treatment completion or when only UNK assessments are available just prior to data cut-off).
- The reason "Adequate assessment no longer available" also prevails in situations when another censoring reason (e.g. withdrawal of consent, loss to follow-up or alternative anticancer therapy) has occurred more than the specified period following the last adequate assessment.
- This reason will also be used to censor in case of no baseline assessment.

13.4 Appendix 4: COVID-19 Precautions

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

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

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

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

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

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

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