A Phase 1B Study of Infigratinib in Combination with Tamoxifen in Hormone Receptor-Positive, HER2-Negative, FGFR-Altered Advanced Breast Cancer

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TABLE OF CONTENTS

Document History

Date	Summary
27 March 2020	Initial version to SRC (approved 6 April 2020)
29 April 2020	• Document History table added • Number of subjects corrected (up to 36 total) • Cohort 1 dose levels clarified • ClinicalTrials.gov outcomes adjusted • Minor typography and syntax
30 July 2020	• Cohort 1 infigratinib dose levels increased from 2 dose levels (100 mg and 125 mg) to 3 dose levels (75 mg, 100 mg, and 125 mg). • Cohort 1 recommended infigratinib dose when 0 of 3 or 1 of 6 subjects experience a DLT in their first 2 cycles at that dose. • Intra-subject dose escalation allowed in Cohort 1 only, such that if a subject starts at infigratinib 100 mg and remains on-study after 2 cycles with no DLTs seen, they will begin receiving infigratinib 125 mg, and the number of DLTs in Cycles 3 and 4 will count toward the primary endpoint in Cohort 1 at this dose. • Number of subjects adjusted for Cohort 1 (minimum 3 total instead of 6 total) and for both Cohorts together (maximum 33 instead of 36). • Clarification for Cohort 2 that expansion to 12 subjects at recommended dose should include N = 6 IC2, and N = 6 IC6. • Multiplexed ion beam imaging (MIBI) mentioned as another possible in situ proteomic method for exploratory analysis, in addition to Digital Spatial Profiling (DSP) • Research tissue biopsies to be sent to the Curtis lab for processing
21 August 2020	• Administrative changes, updates, and corrections
31 August 2020	• Moved ondansetron from Appendix A to Appendix B. • Corrections to the following: o Cohort 2 treatment group numbering as 4 to 6, not 3 to 5 (in Section 2.5). o Table 4 was mislabeled as Figure 1 (in section 2.5). o AE drug relationship are to be determined for infigratinib, tamoxifen (Cohort 1); fulvestrant (Cohort 2); or palbociclib (Cohort 2), removing gemcitabine plus cisplatin (in Section 7.3). o REDCap will be used as data management, rather than OnCore (in Section 11.3). • Administrative changes, updates, and corrections, including the addition of hyperlinks (not highlighted)

23 Sept 2020	• QED Therapeutics will be notified within 24 hours of learning of occurrence of an SAE, Suspected Unexpected Serious Adverse Reactions or pregnancy event (Sections 7.4 and 7.5), instead of within 7 days. • QED Therapeutics will supply the Case Report Forms for SAE and Pregnancy events to be reported to QED. QED may be notified via by email (SAEintake@covance.com) using their provided CRFs or upload to electronic SAE portal (Sections 7.4 and 7.5). • Instead of within 7 days, Suspected Unexpected Serious Adverse Reactions will be submitted to the FDA via an IND amendment within 15 days, and within 7 days for life-threatening conditions and death (Section 7.4), to match with the defined FDA guidance document on reporting. • Eliminating pharmacokinetics assessments per QED Therapeutics, as the data collection is no longer required
1 Oct 2020	Removes Cohort 2 throughout
9 Oct 2020	The frequency of echocardiogram (ECHO) monitoring has been adjusted to Baseline, Cycle 2 Day 1, and End of Treatment.

5 Apr 2021	• Dr. Jennifer Caswell-Jin is assuming the role of IND-holder, Principal Investigator, and Protocol Director.
	• In Section 5.1.2, the allowed dosing time interval for infigratinib was revised to be 24 ± 4 hour for consistency with the Pharmacy Manual (Section 7.0). Clarified that infigratinib should be dosed in the morning when possible, with the understanding that there may be scheduling limitations at times (eg, delay in drug dispense on days with clinic visit).
	• Updated Study Calendar (Section 9).
	  ○ Added Complete Metabolic Panel as an optional assessment in the “Other Follow-up” timepoint.
	  ○ Clarified in footnote 25 that only clinical indicated assessments need to be performed beyond 30 days.
	  ○ Clarified that “End of Treatment/Withdrawal” should be 0 to 14 days from the decision made to discontinue study treatment (previously 0 to 14 days from final dose) to match footnote 23.
	• Administrative changes, updates, and corrections

28 Oct 2021	• Updates regulatory status information for infigratinib (Section 2.2) • Updates Participant Selection and Enrollment Procedures (Section 3) to identify the 3rd reviewer of eligibility to be a member of the study team (eg, investigator or back-up study coordinator) • Specifies / elaborates that the tamoxifen dosing window is 4 to 8 hours after infigratinib administration. • Identifies QED Therapeutic’s partner, the Helsinn Group, throughout the protocol, including for data sharing / access (Section 11.2). • Administrative changes, updates, and corrections.
11 Nov 2021	• Updates safety reporting in sections 7.4 and 7.5, per manufacturer’s request

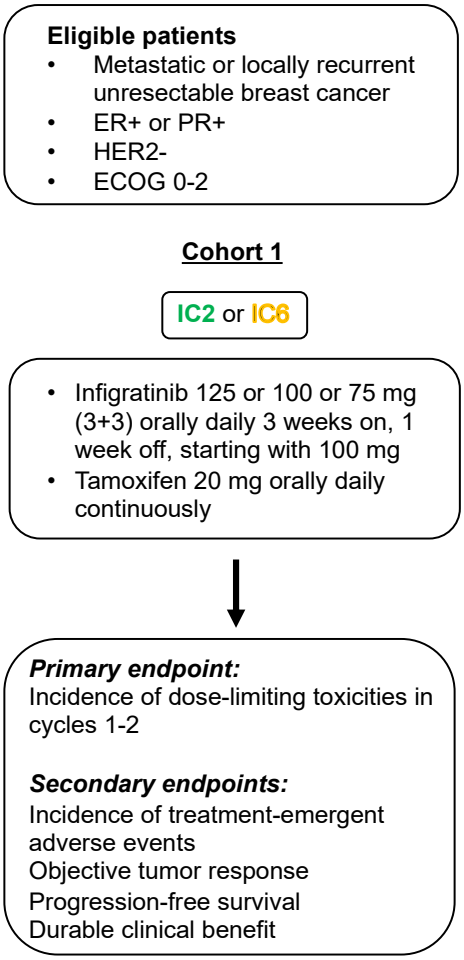
PROTOCOL SYNOPSIS

TITLE	**A Phase 1B Study of Infigratinib in Combination with Tamoxifen in Hormone Receptor-Positive, HER2-Negative FGFR-Altered Advanced Breast Cancer**
STUDY PHASE	1B
INDICATION	Advanced breast cancer, ER and/or PR^{+}, $HER2^{-}$. Additional inclusion and exclusion criteria outlined in n Section 3.1 and Section 3.2.
INVESTIGATIONAL PRODUCT	Cohort 1: Infigratinib + Tamoxifen
PRIMARY OBJECTIVE	Identify the recommended dose of infigratinib to be used in combination with the FDA-approved dose and schedule of tamoxifen.
SECONDARY OBJECTIVES	1. Estimate the incidence of treatment-emergent adverse events. 2. Estimate the objective tumor response rate. 3. Estimate progression-free survival. 4. Estimate the clinical benefit rate.
EXPLORATORY OBJECTIVES	1. Establish viable tumor-derived organoid cultures to study *in vitro* tumor response to combination targeted therapy. 2. Examine cell-free DNA from plasma across therapy to identify markers of therapeutic resistance. 3. Examine tumor and microenvironmental changes across therapy using in situ proteomics.
STUDY POPULATION	Eligible subjects will be adults with ER-positive and/or PR-positive, HER2-negative breast cancer and radiographic evidence of metastatic disease, or locally recurrent unresectable disease. Women must be postmenopausal. Due to length, the Eligibility Criteria are only presented in one instance. See Section 3 Participant Selection and Enrollment Procedures.

PROTOCOL SYNOPSIS

TREATMENT SUMMARY	Infigratinib is an oral selective FGFR1-3 inhibitor that has been tested in phase 1 and 2 clinical trials as a single agent. This phase 1B study will assess the safety and tolerability of infigratinib in combination with the FDA-approved dose and schedule of tamoxifen (Cohort 1). In Cohort 1, up to 3 dose levels of infigratinib will be evaluated: 125 mg; 100 mg; and 75 mg, starting with the middle dose level (100 mg). Infigratinib will be administered orally daily, 3 weeks on, 1 week off. Subjects will also be given tamoxifen 20 mg orally continuously. If toxicity presents, individual subjects may dose-reduce by 25 mg infigratinib per reduction, to a lower limit of 75 mg infigratinib (See Sections 2.5 and 6). Treatment with study drug will continue for 18 months or confirmed disease progression, unacceptable toxicity deemed probably-related to study drug, whichever occurs first, or other reasons outlined in Section 4.3.
SAMPLE SIZE	Up to 12 subjects evaluable (minimum 3), not including subject replacement.

SCHEMA


Eligible patients
• Metastatic or locally recurrent unresectable breast cancer
• ER+ or PR+
• HER2-
• ECOG 0-2
Cohort 1
IC2 or IC6
• Infigratinib 125 or 100 or 75 mg (3+3) orally daily 3 weeks on, 1 week off, starting with 100 mg
• Tamoxifen 20 mg orally daily continuously
Primary endpoint:
Incidence of dose-limiting toxicities in cycles 1-2
Secondary endpoints:
Incidence of treatment-emergent adverse events
Objective tumor response
Progression-free survival
Durable clinical benefit

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
ASCO-CAP	American Society of Clinical Oncology-College of American Pathologists
CBC	Complete blood count
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
CR	Complete Response
CRF	Case report/record form
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
CYP3A	Cytochrome P450 3A
DLT	Dose-limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECHO	Echocardiogram
ER	Estrogen receptor
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
FISH	Fluorescence *in situ* hybridization
HR	Hormone receptor
IC	Integrative Cluster
IHC	Immunohistochemistry
IRB	Institutional Review Board
LLN	Lower limit of normal
MAD	Maximum administered dose
METABRIC	Molecular Taxonomy of Breast Cancer International Consortium
MTD	Maximum tolerated dose
OCT	Optical coherence tomography
ORR	Objective response rate
PFS	Progression-free survival
PD	Progressive Disease
PR	Progesterone receptor
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event
SD	Stable disease
TCGA	The Cancer Genome Atlas
TEAE	Treatment-emergent adverse event

1. OBJECTIVES

1.1. Primary Objective

- Determine the maximum (no greater than 125 mg) dose of infigratinib used in combination with the FDA-approved dose and schedule of tamoxifen (Cohort 1), in terms of the number of dose-limiting toxicities observed in the first 2 cycles of therapy in subjects with hormone receptor-positive, HER2-negative advanced breast cancer.

1.2. Secondary Objectives

- Estimate the incidence of treatment-emergent adverse events (serious and non-serious).
- Estimate the objective tumor response rate (ORR) in subjects with measurable disease.
- Estimate the progression-free survival (PFS).
- Estimate the durable clinical benefit rate.

1.3. Exploratory Objectives

- Establish viable tumor-derived organoid cultures to study *in vitro* tumor response to combination targeted therapy
- Examine cell-free DNA from plasma across therapy to identify markers of therapeutic resistance
- Examine tumor and microenvironmental changes across therapy using in situ proteomics.

2. BACKGROUND

2.1 Study Disease

Advanced-stage, or metastatic, breast cancer remains incurable in the vast majority of cases, with an estimated median survival of approximately 3 years. [1] Hormone receptor-positive (HR^+) disease is generally viewed as less aggressive than triple-negative or $HER2^+$ breast cancer, but recent data from our group suggest that a subset of HR^+ breast cancers are highly aggressive, exhibiting recurrence rates higher than triple-negative breast cancers or $HER2^+$ breast cancers in the era prior to trastuzumab. [2] These high-risk HR^+ breast cancer subtypes classify as one of four integrative clusters (ICs or “IntClusts”), each defined by a characteristic gene amplification as follows. [2,3]

- IC1, defined by *RPS6KB1* (17q23)
- IC2, defined by *FGF3/4/19* and *CCND1* (11q13). IC2 is associated with a poor prognosis amongst ER-positive tumors, with a 10-year disease-specific survival rate of only about 50%.
- IC6, defined by *FGFR1* (8p12). IC6 is associated an intermediate prognosis and a 10-year disease-specific survival of around 60%.
- IC9, defined by *MYC* (8q24)

Notably for IC2, *FGF3/4/19* and *CCND1* are tightly located within the 11q13 genomic region and are almost universally amplified together as a cassette in breast cancer; [2,3] thus amplification of either is generally consistent with amplification of both. *FGFR1* amplifications occur in approximately 10% and *CCND1/FGF3/4/19* amplifications in approximately 6% of early-stage $ER^+/HER2^-$ breast cancers; [2,3] proportions are likely higher in advanced-stage breast cancer given the higher rates of recurrence. While these characteristic amplifications are almost universally present within tumors classifying as the relevant integrative subtype, the converse is not true: in the METABRIC cohort, approximately one quarter of $HR^+/HER2^-$ tumors that carry the *CCND1* amplification classify as integrative subtype 2, and approximately half of those that carry the *FGFR1* amplification classify as integrative subtype 6. It is plausible that these amplifications may be passenger events rather than driver events in the tumors that do not classify as the relevant integrative subtypes.

The current treatment paradigm for these tumors does not include testing for integrative subtype or targeting the subtype-defining gene amplifications. Metastatic $HR^+/HER2^-$ breast cancer is typically treated in the first line with endocrine therapy (most commonly an aromatase inhibitor), often in combination with a CDK4/6 inhibitor [4-6]; in the second line, endocrine therapy is typically used again, either alone, in combination with a CDK4/6 inhibitor if not used in the first-line [7-9], or in combination with an mTOR inhibitor. [10] After progression on two lines of endocrine therapy, the disease is often considered endocrine-resistant and treated with sequential single-agent chemotherapies until progression. [11] There is an urgent need to find more effective therapies for $HR^+/HER2^-$ metastatic breast cancer, and we hypothesize that targeting the FGFR axis in tumors that may be driven by FGFR signaling, as defined either by amplification or integrative subtype, may improve outcomes for patients with these tumor types.

This study evaluates the safety and efficacy of infigratinib, an FGFR 1 to 3 inhibitor, in combination treatment for eligible $HR^+/HER2^-$ breast cancer patients whose tumors classify as the IC2 or IC6 subtypes (see criterion 2 in Section 3.1). As noted above, IC2 and IC6 are associated with alternations in FGF and/or FGFR.

2.2 Study Agent - Infigratinib

2.2.1 Regulatory status: Infigratinib (BGJ398) was approved by FDA as Truseltiq pursuant the Accelerated Approval regulations on 28 May 2021 for the indication of previously-treated, unresectable, locally-advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement, in adults.

2.2.2 Mechanism of action: Infigratinib (BGJ398) is an orally-bioavailable, potent, selective inhibitor of the fibroblast growth factor receptors (FGFR 1-3, but 60-fold less active on FGFR4). The FGFR family of receptor tyrosine kinases consists of four members (FGFR1-4), which serve as the high affinity receptors for 22 FGF ligands. These growth factors control cell proliferation, migration, angiogenesis, apoptosis, and differentiation. A subfamily of FGF ligands including FGF19 additionally act as endocrine hormones. [12]

2.2.3 Pharmacokinetics: The pharmacokinetics of infigratinib was investigated in mouse, rat, and dog after oral and intravenous administration. In all 3 species, the clearance and the

volume of distribution at steady state was high. The terminal elimination half-life in plasma was 9.3 hours in mouse, 4.5 hours in rat, and 3.1 hours in dog. The absolute bioavailability was 2.4% in dog and approximately 30% in mouse and rat. In oncology patients, the mean terminal elimination half-life on Day 1 was 3 to 7 hours; accumulation was observed with daily dosing at doses ≥ 60 mg, with mean accumulation ratio ranging from 3 to 8 on Day 15 and Day 28.

2.2.4 Metabolism: The *in vitro* metabolism of [^{14}C]-infigratinib was studied in hepatocytes from rat, dog, and human. Two main biotransformation pathways were observed in all species investigated: N-oxidation to BQR917 (predominant pathway in dog) and D-deethylation to BHS697 (predominant pathway in human) (in rat, the two pathways were of similar importance). Additional biotransformation pathways included glutathione conjugation, O-demethylation, hydrolysis, C-hydroxylation, and others. The *in vivo* metabolism of [^{14}C]-infigratinib was studied in rats and dogs, and of unlabeled infigratinib in dogs and humans. 13 metabolites were identified and semi-quantified in human plasma with the cleavage product CQM157 the most abundant one; all except 1 minor metabolite were also detected in rat and/or dog plasma after oral dosing.

2.2.5 Major route of elimination: The major route of elimination in rats and dogs dosed orally or intravenously with [^{14}C]-infigratinib was the feces. Urinary excretion amounted to ≤ 6.5% of dose. In rats, 2.6% of the dose was recovered in bile and 0.16% in urine. In dogs, 1.5% of the dose was recovered in urine.

2.2.6 Potential for drug interactions: Infigratinib is likely subject to a major intestinal metabolic first-pass effect via cytochrome P450 3A (CYP3A), and consequently, concomitant use with CYP3A inhibitors or inducers is expected to have clinical implications. Accordingly, strong inhibitors or inducers or CYP3A4, as well as narrow therapeutic index substrates of CYP3A4, are prohibited on this study (Appendix A); moderate inhibitors or inducers of CYP3A4, as well as sensitive CYP3A substrates, are to be used with caution on this study (Appendix B).

2.2.7 Safety in animal studies: Repeated-dose toxicity studies were performed in rat and dog and are summarized below:

- Infigratinib increased serum fibroblast growth factor 23 (FGF23) and serum calcium and/or phosphorus, associated with ectopic mineralization (mostly lungs and kidneys) and bone growth plate thickening and increased trabecular bone. Generally these changes were either reversible or showed a trend toward reversibility. FGF23 is secreted by osteocytes and acts on the kidney to decrease reabsorption and increase excretion of phosphorus; it is hypothesized that inhibition of the FGF23/FGFR pathway leads to the observed phosphorus elevation with infigratinib.
- Vasculopathy was observed in rat studies at higher dose levels; in dog studies, this was observed only in the gallbladder.
- In rats and dogs increases in alanine aminotransferase, aspartate aminotransferase, and/or decreases in glucose were noted. These changes were either without correlative histopathological findings or (in dogs at high doses) with minimal liver cell necrosis as well as bile ducts hypertrophy/hyperplasia.

- There was an accumulation of foam cell aggregates in the lung.
- Decreases in reticulocyte, platelet, total white blood cells, neutrophils, and lymphocytes as well as bone marrow hypocellularity were noted at higher doses.
- Cornea opacity (trend towards reversibility) as well as epithelial thinning for the tongue and nasal cavity (reversible) as well as incisors (not reversible) were observed.
- Longer hair/fur was noted starting at approximately week 8 and continuing through recovery. In dogs, reversible atrophy of the sebaceous gland was seen.

2.2.8 Efficacy in animal studies: *In vivo* studies in mice and rats have shown that significant tumor growth inhibition and tumor regression can be achieved with infigratinib in a variety of FGFR-dependent tumor xenograft models, at well tolerated doses when given orally once per day.

2.2.9 Safety in humans: Infigratinib has been evaluated in cancer patients in two phase 1 studies in patients with advanced solid malignancies (NCT01697605 and NCT01004224) and three phase 2 studies (NCT01975701 in glioblastoma; NCT02150967 in cholangiocarcinoma, and NCT02160041 in solid tumors and/or hematologic malignancies). It has also been evaluated in combination with the PI3K alpha specific inhibitor BYL719 in a phase 1b study (NCT01928459), a combination no longer being pursued. Approximately 650 subjects (healthy adult volunteers and adult patients with malignancies) have received infigratinib.

Dose-limiting toxicities: There were no DLTs reported in NCT01697605. In NCT01004224, where infigratinib was given as a single agent, there was one DLT in the 100 mg cohort (out of 6 subjects) (Grade 3 AST/ALT elevation), one DLT in the 125 mg cohort (out of 8 subjects) (hyperphosphatemia greater than 14 days despite adequate therapy), and 2 DLTs in the 150 mg cohort (out of 6 subjects) (one Grade 3 AST/ALT elevation and one Grade 1 corneal toxicity). The maximum tolerated dose was determined to be 125 mg daily. The 3 weeks on / 1 week off schedule was implemented based on observations of the timing and duration of drug interruptions during Cycle 1 necessitated by episodes of hyperphosphatemia: median time to drug interruption during continuous dosing was 22 days and median duration of the interruption was 7 days.

Treatment-emergent adverse events: Table 1 summarizes adverse events, regardless of relationship, to infigratinib as a single agent at the maximum tolerated dose of 125 mg, 3 weeks on, 1 week off (N = 433 subjects), and Table 2 summarizes Grade 3 to 4 adverse events. The on-target effects on calcium-phosphorus homeostasis result in the observed increases in calcium (13.4% any grade, 3.2% Grade 3-4), phosphorus (61.2% any grade, 6.7% Grade 3 to 4), and creatinine (23.8% any grade). These are not associated with clinical symptoms and in general have been mild to moderate in severity, manageable, and reversible. Guidelines for management of on-target hyperphosphatemia have been implemented.

Ocular adverse events (corneal or retinal) occur in about 50% of subjects, but in general are mild to moderate in severity and reversible: for example, Grade 1 to 2 dry eye was reported in 21.5% and Grade 1 to 2 blurry vision in 9.9%. Grade 3 ocular events occurred in 3% of subjects; no Grade 4 ocular events have been reported. Grade 3 adverse events of cataract (N = 3, 0.7%), visual impairment (N = 2, 0.5%), and keratitis (N = 2, 0.5%) were the events that

occurred in more than one subject; others were reported once. Adverse events of blurred vision, visual impairment, and keratitis led to study drug discontinuation for N = 2, 0.5% subjects each. Since the cornea and retina were identified from preclinical safety studies as a potential target organ of interest, protocol-mandated ophthalmologic examinations have been performed routinely and frequently throughout studies.

Subjects have been monitored for potential QT prolongation: N = 3 (0.7%) of subjects have had a new QTc value > 500 msec, N = 4 (1.0%) have had a QTcF change of > 60 msec, and N = 63 (15.0%) have had a QTcF change > 30 and ≤ 60 msec. None of these events was considered serious nor led to treatment withdrawal or dose reduction/interruption. Subjects have also been monitored for potential decrease in ventricular ejection fraction by echocardiogram or multi-gated acquisition. N = 6 (1.4%) of subjects had a Grade 2 abnormality (no Grade 3-4 events), which did not lead to study drug discontinuation.

Other notable adverse events include stomatitis (34.9%) and alopecia (26.8%).

Table 1: Adverse events occurring in ≥ 10% of adult oncology subjects treated with infigratinib monotherapy

Preferred Term	Cholangiocarcinoma Subjects n (%) (N = 118)	Urothelial Carcinoma Subjects n (%) (N = 82)	All Other Monotherapy Oncology Subjects n (%) (N = 233)	Total n (%) (N = 433)
Total no. of subjects	115 (97.5)	81 (98.8)	231 (99.1)	427 (98.6)
Hyperphosphataemia	87 (73.7)	33 (40.2)	145 (62.2)	256 (61.2)
Fatigue	53 (44.9)	35 (42.7)	87 (37.3)	175 (40.4)
Constipation	48 (40.7)	31 (37.8)	80 (34.3)	159 (36.7)
Stomatitis	59 (50.0)	22 (26.8)	70 (30.0)	151 (34.9)
Decreased appetite	28 (23.7)	31 (37.8)	70 (30.0)	129 (29.8)
Nausea	32 (27.1)	24 (29.3)	69 (29.6)	125 (28.9)
Diarrhoea	30 (25.4)	17 (20.7)	70 (30.0)	117 (27.0)
Alopecia	45 (38.1)	25 (30.5)	46 (19.7)	116 (26.8)
Blood creatinine increased	26 (22.0)	35 (42.7)	42 (18.0)	103 (23.8)
Dry mouth	31 (26.3)	27 (32.9)	43 (18.5)	101 (23.3)
Dry eye	41 (34.7)	16 (19.5)	36 (15.5)	93 (21.5)
Dysgeusia	39 (33.1)	18 (22.0)	34 (14.6)	91 (21.0)
Vomiting	28 (23.7)	17 (20.7)	43 (18.5)	88 (20.3)
Anaemia	17 (14.4)	28 (34.1)	30 (12.9)	75 (17.3)
Arthralgia	34 (28.8)	14 (17.1)	20 (8.6)	68 (15.7)
Dyspepsia	21 (17.8)	6 (7.3)	39 (16.7)	66 (15.2)
Aspartate aminotransferase increased	21 (17.8)	6 (7.3)	36 (15.5)	63 (14.5)
Abdominal pain	14 (11.9)	14 (17.1)	34 (14.6)	62 (14.3)
Dyspnoea	11 (9.3)	14 (17.1)	36 (15.5)	61 (14.1)
Hypercalcaemia	27 (22.9)	12 (14.6)	19 (8.2)	58 (13.4)
Weight decreased	20 (16.9)	9 (11.0)	29 (12.4)	58 (13.4)
Alanine aminotransferase increased	17 (14.4)	5 (6.1)	34 (14.6)	56 (12.9)
Dry skin	25 (21.2)	10 (12.2)	21 (9.0)	56 (12.9)
Hypophosphataemia	22 (18.6)	10 (12.2)	21 (9.0)	53 (12.2)
Palmar-plantar erythrodysaesthesia syndrome	32 (27.1)	9 (11.0)	10 (4.3)	51 (11.8)
Pyrexia	18 (15.3)	7 (8.5)	26 (11.2)	51 (11.8)
Back pain	17 (14.4)	9 (11.0)	24 (10.3)	50 (11.5)
Pain in extremity	20 (16.9)	7 (8.5)	23 (9.9)	50 (11.5)
Cough	15 (12.7)	9 (11.0)	25 (10.7)	49 (11.3)
Lipase increased	14 (11.9)	12 (14.6)	22 (9.4)	48 (11.1)
Nail disorder	10 (8.5)	21 (25.6)	17 (7.3)	48 (11.1)
Headache	20 (16.9)	2 (2.4)	24 (10.3)	46 (10.6)
Hyponatraemia	13 (11.0)	12 (14.6)	21 (9.0)	46 (10.6)
Asthenia	6 (5.1)	7 (8.5)	32 (13.7)	45 (10.4)
Blood phosphorus increased	4 (3.4)	9 (11.0)	32 (13.7)	45 (10.4)
Blood alkaline phosphatase increased	14 (11.9)	7 (8.5)	23 (9.9)	44 (10.2)
Epistaxis	17 (14.4)	8 (9.8)	19 (8.2)	44 (10.2)
Vision blurred	23 (19.5)	10 (12.2)	10 (4.3)	43 (9.9)
Urinary tract infection	13 (11.0)	14 (17.1)	14 (6.0)	41 (9.5)

Includes Studies NCT01697605 (CSR in preparation; data cutoff 18Mar2019), NCT01004224, NCT01975701, NCT02150967 (ongoing; data cutoff 31May2019), NCT02160041.

Table 2: Grade 3 or 4 adverse events occurring in ≥ 1.0% of adult oncology subjects treated with infigratinib monotherapy

Preferred Term	Cholangiocarcinoma Subjects n (%) (N = 118)	Urothelial Carcinoma Subjects n (%) (N = 82)	All Other Monotherapy Oncology Subjects n (%) (N = 233)	Total n (%) (N = 433)
Total no. of subjects	79 (66.9)	55 (67.1)	131 (56.2)	256 (61.2)
Hypophosphataemia	14 (11.9)	7 (8.5)	12 (5.2)	33 (7.6)
Hyponatraemia	12 (10.2)	5 (6.1)	13 (5.6)	30 (6.9)
Hyperphosphataemia	14 (11.9)	1 (1.2)	14 (6.0)	29 (6.7)
Lipase increased	9 (7.6)	8 (9.8)	10 (4.3)	27 (6.2)
Fatigue	6 (5.1)	6 (7.3)	12 (5.2)	24 (5.5)
Stomatitis	13 (11.0)	2 (2.4)	6 (2.6)	21 (4.8)
Alanine aminotransferase increased	4 (3.4)	2 (2.4)	10 (4.3)	16 (3.7)
Palmar-plantar erythrodysaesthesia syndrome	7 (5.9)	5 (6.1)	3 (1.3)	15 (3.5)
Anaemia	5 (4.2)	5 (6.1)	4 (1.7)	14 (3.2)
Hypercalcaemia	7 (5.9)	2 (2.4)	5 (2.1)	14 (3.2)
Dyspnoea	0	2 (2.4)	11 (4.7)	13 (3.0)
Abdominal pain	6 (5.1)	2 (2.4)	4 (1.7)	12 (2.8)
Aspartate aminotransferase increased	4 (3.4)	0	8 (3.4)	12 (2.8)
Decreased appetite	1 (0.8)	5 (6.1)	6 (2.6)	12 (2.8)
Nausea	3 (2.5)	3 (3.7)	6 (2.6)	12 (2.8)
Vomiting	1 (0.8)	3 (3.7)	7 (3.0)	11 (2.5)
Dehydration	2 (1.7)	1 (1.2)	7 (3.0)	10 (2.3)
Diarrhoea	3 (2.5)	3 (3.7)	3 (1.3)	9 (2.1)
Gamma-glutamyltransferase increased	2 (1.7)	1 (1.2)	6 (2.6)	9 (2.1)
Pain in extremity	3 (2.5)	1 (1.2)	5 (2.1)	9 (2.1)
Sepsis	2 (1.7)	1 (1.2)	6 (2.6)	9 (2.1)
Blood alkaline phosphatase increased	5 (4.2)	0	3 (1.3)	8 (1.8)
General physical health deterioration	2 (1.7)	1 (1.2)	5 (2.1)	8 (1.8)
Urinary tract infection	2 (1.7)	3 (3.7)	3 (1.3)	8 (1.8)
Back pain	0	0	6 (2.6)	6 (1.4)
Blood bilirubin increased	3 (2.5)	0	3 (1.3)	6 (1.4)
Pyrexia	2 (1.7)	1 (1.2)	3 (1.3)	6 (1.4)
Arthralgia	2 (1.7)	3 (3.7)	0	5 (1.2)
Asthenia	0	2 (2.4)	3 (1.3)	5 (1.2)
Dysphagia	0	1 (1.2)	4 (1.7)	5 (1.2)
Hypertension	1 (0.8)	0	4 (1.7)	5 (1.2)
Mucosal inflammation	0	1 (1.2)	4 (1.7)	5 (1.2)
Pneumonia	0	0	5 (2.1)	5 (1.2)

Includes Studies NCT01697605 (CSR in preparation; data cutoff 18Mar2019), NCT01004224, NCT01975701, NCT02150967 (ongoing; data cutoff 31May2019), NCT02160041.

Serious adverse events: Serious adverse events (SAEs) to single-agent infigratinib are summarized in Table 3. The most common SAEs reported (approximately 2%) were pyrexia, dyspnea, general physical health deterioration, sepsis, vomiting, abdominal pain, anemia, hypercalcemia, and pneumonia. Most of the SAEs would be expected for oncology subjects and for the indications under study.

Table 3: SAEs occurring in 0.5% of adult oncology subjects treated with infigratinib monotherapy

Preferred Term	Cholangiocarcinoma Subjects n (%) (N = 118)	Urothelial Carcinoma Subjects n (%) (N = 82)	All Other Monotherapy Oncology Subjects n (%) (N = 233)	Total n (%) (N = 433)
Total no. of subjects	44 (37.3)	29 (35.4)	91 (39.1)	164 (37.9)
Pyrexia	6 (5.1)	3 (3.7)	3 (1.3)	12 (2.8)
Dyspnoea	0	1 (1.2)	9 (3.9)	10 (2.3)
General physical health deterioration	2 (1.7)	1 (1.2)	6 (2.6)	9 (2.1)
Sepsis	2 (1.7)	1 (1.2)	6 (2.6)	9 (2.1)
Vomiting	1 (0.8)	2 (2.4)	6 (2.6)	9 (2.1)
Abdominal pain	5 (4.2)	2 (2.4)	1 (0.4)	8 (1.8)
Anaemia	3 (2.5)	2 (2.4)	3 (1.3)	8 (1.8)
Hypercalcaemia	4 (3.4)	2 (2.4)	2 (0.9)	8 (1.8)
Pneumonia	0	0	8 (3.4)	8 (1.8)
Acute kidney injury	2 (1.7)	2 (2.4)	2 (0.9)	6 (1.4)
Constipation	3 (2.5)	0	3 (1.3)	6 (1.4)
Dehydration	0	1 (1.2)	5 (2.1)	6 (1.4)
Nausea	0	2 (2.4)	4 (1.7)	6 (1.4)
Urinary tract infection	2 (1.7)	2 (2.4)	2 (0.9)	6 (1.4)
Dysphagia	0	1 (1.2)	3 (1.3)	4 (0.9)
Hyponatraemia	2 (1.7)	1 (1.2)	1 (0.4)	4 (0.9)
Pleural effusion	2 (1.7)	0	2 (0.9)	4 (0.9)
Arthralgia	2 (1.7)	1 (1.2)	0	3 (0.7)
Asthenia	0	1 (1.2)	2 (0.9)	3 (0.7)
Back pain	0	0	3 (1.3)	3 (0.7)
Bile duct obstruction	1 (0.8)	0	2 (0.9)	3 (0.7)
Bone pain	1 (0.8)	1 (1.2)	1 (0.4)	3 (0.7)
Cellulitis	2 (1.7)	1 (1.2)	0	3 (0.7)
Chest pain	1 (0.8)	1 (1.2)	1 (0.4)	3 (0.7)
Cholangitis	2 (1.7)	0	1 (0.4)	3 (0.7)
Decreased appetite	0	1 (1.2)	2 (0.9)	3 (0.7)
Diarrhoea	1 (0.8)	1 (1.2)	1 (0.4)	3 (0.7)
Fatigue	0	0	3 (1.3)	3 (0.7)
Hypophosphataemia	2 (1.7)	1 (1.2)	0	3 (0.7)
Infection	1 (0.8)	0	2 (0.9)	3 (0.7)
Muscular weakness	1 (0.8)	1 (1.2)	1 (0.4)	3 (0.7)
Pain in extremity	1 (0.8)	0	2 (0.9)	3 (0.7)
Pulmonary embolism	0	0	3 (1.3)	3 (0.7)
Respiratory failure	0	1 (1.2)	2 (0.9)	3 (0.7)
Septic shock	0	1 (1.2)	2 (0.9)	3 (0.7)
Small intestinal obstruction	1 (0.8)	2 (2.4)	0	3 (0.7)
Stomatitis	1 (0.8)	1 (1.2)	1 (0.4)	3 (0.7)

Includes Studies NCT01697605 (CSR in preparation; data cutoff 18Mar2019), NCT01004224, NCT01975701, NCT02150967 (ongoing; data cutoff 31May2019), NCT02160041.

Deaths: Of the 433 subjects treated with infigratinib monotherapy, N = 45 (10.4%) have died on-treatment. Most deaths were deemed related to study indication / disease progression. One death due to cardiac arrest and 1 death due to intestinal ischemia were considered to be related to study drug.

2.2.10 Efficacy in humans: In NCT01004224, a phase 1 dose-escalation study, 4 of 36 subjects with non-small cell lung cancer and 3 of 8 subjects with urothelial carcinoma achieved partial response (Figure 1). [13] Of the 26 subjects with metastatic breast cancer (21 with *FGFR1* amplification), 4 had reduced tumor burden but did not achieve partial response (3 with *FGFR1* amplification). [13] In addition, of the 37 additional subjects with urothelial carcinoma, 12 achieved partial response and 1 achieved complete response (CR). [14] In NCT02150967, 15 of 59 subjects achieved partial response.

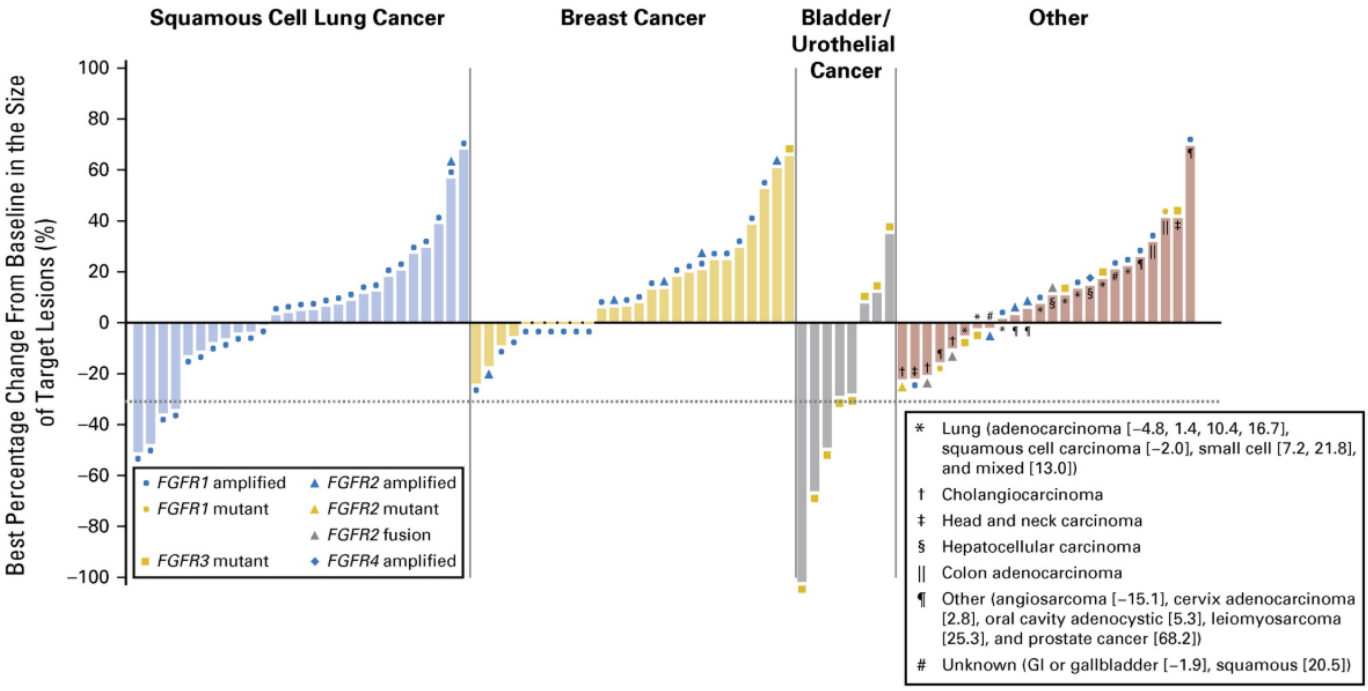


Figure 1. Waterfall plots of best change from baseline in the size of target lesions for patients treated at least 100 mg infigratinib. From Nogova *et al* (2016) *JCO.*

Subsequently, in a phase 2 study of infigratinib 125 mg orally daily 3 weeks on / 1 week off in N = 67 subjects with metastatic urothelial carcinoma with *FGFR3* alterations, an overall response rate of 25.4% and a disease control rate of 64.2% was observed. [14] In another phase 2 study of infigratinib 125 mg orally daily 3 weeks on / 1 week off in N = 61 subjects with advanced or metastatic cholangiocarcinoma containing FGFR2 fusions or other FGFR alterations, an overall response rate of 14.8% and a disease control rate of 75.4% was observed. [15]

2.2.11 Additional information: Further details are available in the Investigator's Brochure, which is included with the IRB submission. This study will be conducted under IND 147595 (pre-assigned). Infigratinib was approved by FDA as Truseltiq pursuant the Accelerated Approval regulations on 28 May 2021 for the indication of previously-treated, unresectable, locally-advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement, in adults.

2.3 Rationale

2.3.1 Rationale for combination of infigratinib with endocrine therapy: An analysis of 1,980 subjects with molecular data and 20 years of follow-up was recently performed. In this work, it was found that tumors classifying as integrative subtype 2 (characterized by the 11q13/14 amplification including *FGF3/4/19* and accounting for approximately 5% of all $HR^+/HER2^-$ breast tumors) or integrative subtype 6 (characterized by the 8p12 amplification including *FGFR1* and account for approximately 5% of all $HR^+/HER2^-$ tumors) exhibit an exceedingly high risk of distant relapse up to 20 years post-diagnosis (median 42 to 55%). [2] Substantial improvement in progression-free survival has been seen in $HR^+/HER2^-$ metastatic breast cancer with the addition of CDK4/6 inhibition to endocrine therapy, [4-9] but virtually all tumors will eventually progress, leading to breast cancer-related death. The current treatment paradigm of metastatic $HR^+/HER2^-$ FGF(R)-altered breast cancer does not include inhibition of the FGFR pathway. As a single agent in humans, infigratinib has shown some antitumor activity in pre-treated metastatic breast cancers with *FGFR1* amplification, but not achieving the level of a partial response (Figure 1). [13] Breast tumors with FGF(R) pathway alterations are in urgent need of more effective therapies, and we propose that combining infigratinib with endocrine therapy could achieve this goal.

Accumulating preclinical and clinical data suggests that *FGFR1* amplification may drive endocrine therapy resistance in breast cancer. [16,17] For example, *FGFR1*-amplified cell lines showed resistance to 4-hydroxytamoxifen, which was reversed by RNA silencing of FGFR1. [18] ER^+/*FGFR1*-amplified tumors treated with letrozole prior to surgery did not show decreases in proliferation as measured by Ki67 as is typically seen in sensitive tumors, and this primary resistance to aromatase inhibition appeared to be mediated by an upregulation of FGFR1 and FGF ligand expression allowing persistent activation of estrogen response. [17] Similarly, another study found that time to progression on first-line endocrine therapy was shorter in *FGFR1*-amplified ER^+ metastatic breast cancers than in ER^+ metastatic breast cancers that were not *FGFR1*-amplified, a difference not seen for first-line chemotherapy. [19] Combining lucitanib (a non-selective FGFR inhibitor) with fulvestrant improved growth inhibition of ER^+/*FGFR1*-amplified cell lines and patient-derived xenografts. [17] Another study validated the finding of intrinsic endocrine therapy resistance in ER^+/*FGFR1*-amplified primary tumors, and also reported a similar phenomenon for tumors with *CCND1/FGF3/4/19* amplification. [20]

In sum, these data provide a rationale for combining infigratinib with endocrine therapy may overcome the intrinsic endocrine therapy resistance of ER^+/*FGFR1*-amplified or ER^+/*CCND1/FGF3/4/19*-amplified tumors. For those subjects whose tumors have demonstrated primary or secondary resistance to endocrine therapy (ie, by progression on an aromatase inhibitor or fulvestrant), adding FGFR inhibition may allow these tumors to sensitize to endocrine therapy.

Notably, FGFR inhibition in combination with fulvestrant has been attempted previously in breast cancer, in a phase 2, randomized, placebo-controlled study of dovitinib in combination with fulvestrant in postmenopausal subjects with hormone receptor-positive, HER2-negative

breast cancer that progressed during or after prior endocrine therapy. [21] This study of N = 97 subjects showed median progression-free survival of 5.5 months in the dovitinib arm and 5.5 months in the placebo arm (HR 0.68) in the overall cohort. Findings were not significantly different in the *FGF* pathway-amplified subgroup (N = 31): median PFS 10.9 months in the dovitinib arm and 5.5 months in the placebo arm (HR 0.64). However, dovitinib is one of several non-selective multi-kinase inhibitors with greater impact on VEGFR than FGFR (another example is lucitinib), and subsequent studies have strongly suggested that these multi-kinase inhibitors may not effectively inhibit the FGFR pathway in subjects. [22,23] The efficacy of FGFR inhibition is most established thus far in *FGFR*-altered (most commonly *FGFR3*-mutated) advanced urothelial carcinoma, the setting for which the selective FGFR inhibitor erdafitinib received FDA approval as Balversa on 12 April 2019 (Accelerated Approval). Dovitinib was studied in this setting as well in a phase 2 study that treated N = 12 *FGFR3*-mutated and N = 31 *FGFR3*-wild-type advanced urothelial cancer subjects. [24] In this study, the ORR in the *FGFR3*-mutated subgroup was 0% (3.2% in the wild-type subgroup). Also, and importantly, no hyperphosphatemia was observed in these subjects, nor in other subjects who have been treated with dovitinib. Hyperphosphatemia is a key on-target effect of FGFR inhibition and its absence with dovitinib and other multi-kinase inhibitors suggests poor FGFR inhibition. [22,23] Conversely, in the phase 2 study of FGFR-altered advanced urothelial cancer that led to erdafitinib's approval, the ORR was 32% (28 of 87 subjects) with 69% experiencing hyperphosphatemia, [25] and in a similar phase 2 study of infigratinib, the ORR was 25% (16 of 67 subjects) with 50% experiencing hyperphosphatemia. [14] Dovitinib is no longer widely considered an effective FGFR inhibitor, [22,23] while the new generation of selective FGFR inhibitors are rapidly gaining ground in establishing their efficacy in FGFR-altered cancers. [14,15,25] We therefore believe it is time to assess the hypothesis that selective FGFR inhibition in combination with endocrine therapy may have a benefit for FGFR-altered hormone receptor-positive advanced breast cancer patients.

2.3.2 Comparison to other active trials: To our knowledge, there are 2 active clinical trials examining FGFR inhibition in combination with endocrine therapy in metastatic breast cancer, one of which also adds CDK4/6 inhibition. NCT04024436 opened October 2019 and is a nonrandomized phase 2 study will administer TAS-120 (Taiho) in combination with fulvestrant to 4 cohorts, 3 of which will have an *FGFR2* amplification and 1 of which will have a high-level (ratio to centromere ≥ 5) *FGFR1* amplification. Neither of these studies will examine the efficacy of FGFR inhibition in combination with endocrine therapy in tumors harboring amplification of the ligand (*FGF3*; integrative subtype 2). The hypothesis driving the present trial is that the unique drivers identified via integrative subtyping (a subset of tumors with *FGFR1* amplification classifying as integrative subtype 6; and a subset of tumors with *FGF3* amplification classifying as integrative subtype 2) will be uniquely sensitive to FGFR inhibition.

2.3.3 Rationale for dose of tamoxifen: The dose and schedule selected for tamoxifen (20 mg/day by mouth continuously) is FDA-approved for the treatment of ER^+ metastatic breast cancer.

2.4 Screening Tumor Sequencing Assays

Potential subjects will be eligible if their tumor classifies as integrative cluster 2 (IC2) or 6 (IC6) based on the results of the FoundationOne (F1CDx) FDA-approved assay. There are 11 validated integrative subtypes or clusters of breast cancer, defined initially from the METABRIC cohort based on the integration of genomic copy number alterations and transcriptional profiles. [3] Our recent study examining 20 years of clinical follow-up from 1,980 subjects in the initial METABRIC cohort revealed substantial variability in the risk of relapse amongst $HR^+/HER2^-$ subjects. [2] In particular, integrative subtypes 1, 2, 6, and 9 exhibited exceedingly high (median 42 to 55%) risk of distant relapse up to 20 years post-diagnosis. Each of these integrative subtypes is characterized by distinct copy number amplification events and concomitant over-expression of candidate driver genes: integrative subtype 2 has the *FGF3/FGF4/FGF19*, *CCND1* (11q13/14) amplification and integrative subtype 6 has the *FGFR1* (8p12) amplification. While these characteristic amplifications are almost universally present within tumors classifying as the relevant integrative subtype, the converse is not true: only approximately one-quarter of $ER^+/HER2^-$ tumors that carry the *CCND1/FGF3/4/19* amplification classify as integrative subtype 2, and approximately one-half of $ER^+/HER2^-$ tumors that carry the *FGFR1* amplification classify as integrative subtype 6. It is plausible that these amplifications may be passenger events rather than driver events in the tumors that do not classify as the relevant integrative subtypes. Using additional information from targeted sequencing panels can improve the accuracy of integrative cluster classification, and we hypothesize better delineate in which tumors the FGFR pathway is the oncogenic driver than the simple presence of the amplification. [2,3] Thus, subjects will be eligible if their tumor's F1CDx results are consistent with integrative cluster 2 or 6, per the classifier. The classifier was developed to predict integrative cluster classification from the copy number values and mutational status of the genes on the F1CDx panel in two large cohorts of breast tumors, METABRIC [3] and The Cancer Genome Atlas [28]. This classifier will be applied to the integer copy number values and gene mutation calls generated by the F1CDx assay and analysis.

2.5 Study Design

- The primary purpose for this study is treatment. The protocol is designed to evaluate one or more interventions for treating a disease, syndrome, or condition.
- The interventional model is Sequential.
- The number of intervention arms is up to 3.
- The study will be not be masked (not blinded).
- The study will be not be randomized.

This is a phase 1b study evaluating the safety and tolerability of infigratinib. Cohort 1 will utilize the combination of tamoxifen and infigratinib. We anticipate that this combination may play a role in the future development of infigratinib for hormone receptor-positive breast cancer, necessitating the establishment of their safety. For example, tamoxifen and infigratinib might be used in the early-stage, (neo)adjuvant setting as well as the late-stage, metastatic setting.

In Cohort 1, up to 3 dose levels of infigratinib may be evaluated (125 mg; 100 mg; and 75 mg) in combination with tamoxifen. This pilot study is a necessary step for the future development of infigratinib in combination with tamoxifen and will serve as a safety run-in evaluation for a follow-up study. For this cohort, a 3 + 3 design will be employed starting at 100 mg, and allowing subjects who start at 100 mg to escalate to 125 mg (see Section 12.4).

2.6 Correlative Studies Background

2.6.1 Organoid cultures: Three-dimensional organoid cultures established from viable tumor cells have the potential to re-capitulate *in vitro* subject- and tumor-specific phenotypes, enabling the study of drug response and tumor evolution in the lab. [32-34] Tumor organoid cultures can be established as a renewable source of tissue for *in vitro* and i*n vivo* experimentation; they are amenable to high-throughput drug screens and complementing xenograft-based approaches. Organoid culture can be used to evaluate the efficacy of novel therapeutic agents in specific genetic contexts. It is planned to establish organoids from tumors in this study, classifying as integrative subtypes 2 and 6, allowing testing of novel drug combinations to improve response and overcome resistance to FGFR inhibition in these high-risk subgroups. Furthermore, as these organoids will be treated *in vitro* with the same agents that the study subjects from whose tumors they were derived will be, we will be able to compare response between the *in vitro* and subjects. We will also be able to compare the genomic alterations that arise with treatment in subjects (Section 2.6.2) with those that arise with treatment in the organoids. These experiments may inform our understanding of genomic determinants of sensitivity and resistance to FGFR inhibition, as well as the optimal combinations of therapies to produce response in FGFR-altered breast tumors.

2.6.2 Cell-free DNA analyses: Cell-free DNA is believed to be representative of the heterogeneity present even in micro-metastatic lesions. [35] Thus, it may better capture the spectrum of subclonal populations with the potential to grow in response to therapy than serial tumor biopsies. Furthermore, it has been shown that cell-free DNA sequencing can detect and characterize clonal dynamics in metastatic breast cancer. [36-38] It is planned to collect blood from subjects prior to initiation of study drug, after the first 2 weeks of therapy, and at time of confirmed progression. The blood samples will be separated into plasma and buffy coat and banked. Sequencing (eg, whole-exome or whole-genome) of the cell-free DNA extracted from these banked plasma samples will allow us to identify novel mutations or copy number changes that appear at time of progression in subjects who initially responded, as well as to compare baseline genomic changes between responders and non-responders. The banked buffy coat samples will allow us to identify somatic variants that act as driver mutations and compare them to a matched normal sample through tumor-normal whole-genome sequencing. Furthermore, we can cross-reference these findings with genomic findings in the organoid models (Section 2.6.1). These analyses may allow us to identify genetic mechanisms of resistance to the study drug and/or endocrine therapy.

2.6.3 Proteomic profiling: Proteomic changes may be examined in tumor cells and the surrounding microenvironment *in situ* to delineate compensatory signaling pathways and mechanisms of response/resistance to the evaluated targeted agents. Paired pre- and

post-treatment tissue samples from the trial may be profiled on the Nanostring GEOMx Digital Spatial Profiling (DSP) platform (Research Use Only) [39,40] or with mutiplexed ion beam imaging (MIBI). [41-43] There is growing evidence that functional heterogeneity in the tumor and microenvironment contribute to treatment response, highlighting the importance of spatially resolved approaches such as DSP. DSP enables geographic and phenotypic selection of tissue regions – for example, those that are enriched for pancytokeratin-positive tumor cells. Molecular changes observed with treatment may inform intelligent combinations of therapy in the future to overcome primary resistance or enhance treatment response.

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Inclusion and Exclusion Criteria are provided on Participant Eligibility Checklist following. This document may be extracted from this document for use in screening potential subjects.

The Participant Eligibility Checklist in the following subsection must be completed in its entirety for each subject prior to registration. The Participant Eligibility Checklist may be extracted from this document for use in screening potential subjects. The completed, signed, and dated checklist must be retained in the subject's study file, and the study's Regulatory Binder. Screening results will be collectively documented on the Study Participant Log.

Pursuant to Stanford Medicine SOP "Confirmation of Participant Eligibility in Clinical Trials," the treating Physician (investigator); the Study Coordinator; and a third reviewer from the study team (eg, investigator or back-up study coordinator) will verify that the subject's eligibility is accurate; complete; and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note.

Participant Eligibility Checklist

I. Protocol Information

Protocol Title:	A Phase 1B Study of Infigratinib in Combination with Tamoxifen in Hormone Receptor-Positive, HER2-Negative, FGFR-Altered Advanced Breast Cancer
eProtocol number: OnCore number:	IRB-53650 BRS0113
Principal Investigator [per 21CFR§312.3(b)]:	Jennifer L Caswell-Jin, MD

II. Subject Information

Subject name / Unique ID:	/	
Gender	☐ Male	☐ Female

3.1 Inclusion Criteria

Prospective Participant Must MATCH ALL these Inclusion Criteria to be Eligible	Yes	No	Supporting Documentation *
1. History of biopsy-proven ER-positive and/or PR-positive, HER2-negative breast cancer and radiographic evidence of metastatic disease, or locally recurrent unresectable disease. ER-positivity and PR-positivity are defined as ≥ 1% cells staining positive by immunohistochemistry. HER2-negativity is defined by IHC or FISH, per ASCO-CAP 2018 guidelines	☐	☐	
2. Cancer subtype indicative of alterations to the fibroblast growth factor ligand or receptor (FGF/FGFR alteration): Predicted integrative (IntClust) subtype classification of IC2 or IC6 according classifier on targeted sequencing data from FoundationOne.	☐	☐	

Prospective Participant Must MATCH ALL these Inclusion Criteria to be Eligible	Yes	No	Supporting Documentation *
3. Evaluable or measurable disease. **Cohort 1 only**: Evaluable or measurable disease, as defined by RECIST v1.1. Bone-only disease is acceptable.	☐	☐	
4. ≥ 18 years old	☐	☐	
5. Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2	☐	☐	
6. Prior cancer therapy (except for endocrine therapy, denosumab, or bisphosphonates) must be discontinued for 2 weeks prior to initiation of study drugs. Recovery from adverse events of previous cancer therapies to baseline or Grade 1 except for alopecia or stable Grade 2 neuropathy. Radiotherapy must also be completed at least 2 weeks prior to initiation of study drugs	☐	☐	
7. Absolute neutrophil count (ANC) ≥ 1,000/mm^3	☐	☐	
8. Platelets ≥ 75,000/mm^3	☐	☐	
9. Hemoglobin ≥ 9.0 g/dL	☐	☐	
10. Total bilirubin ≤ 1.8 mg/dL (unless documented Gilbert's disease)	☐	☐	
11. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 90 U/L	☐	☐	
12. Estimated glomerular filtration rate (GFR) ≥ 45 mL/min	☐	☐	
13. Phosphorus between 2.5 and 4.5 mg/dL, inclusive	☐	☐	
14. Total corrected (for albumin) serum calcium between 8.5 and 10.5 mg/dL, inclusive	☐	☐	
15. Amylase < 200 U/L	☐	☐	
16. Lipase < 120 U/L	☐	☐	
17. Ability to understand and the willingness to sign a written informed consent document	☐	☐	

Prospective Participant Must MATCH ALL these Inclusion Criteria to be Eligible	Yes	No	Supporting Documentation *
18. Agrees to take sevelamer, if indicated, and has no contraindications to use of this medication (that is: known hypersensitivity to sevelamer or component of the formulation; bowel obstruction; active bowel mucosal injury such as ulcerative colitis or gastrointestinal bleeding).	☐	☐	
19. Agrees to follow low-phosphate diet, if indicated	☐	☐	
20. Able to swallow and retain oral medication	☐	☐	
21. Women must be postmenopausal, defined as (at least one of): • ≥ 60 years of age; • amenorrhea for at least 24 months; • amenorrhea for at least 12 months with serum estradiol < 20 pg/mL; • prior bilateral oophorectomy; **OR** • treatment with a luteinizing hormone (LH)-releasing hormone agonist (such as goserelin acetate or leuprolide acetate) initiated at least 28 days prior to study enrollment.	☐	☐	
22. Women being treated with a LH-releasing agonist but who are otherwise of childbearing potential (did not undergo total hysterectomy or bilateral tubal ligation at least 6 weeks before first dose of study drug) must have a negative pregnancy test within 7 days of the first dose of study drug.	☐	☐	
23. Women who are being treated with an LH-releasing agonist but are otherwise of childbearing potential must agree to use barrier contraception or an intrauterine device while taking study drug and for 3 months following their last dose of study drug. Alternatively, total abstinence is acceptable if preferred by the subject.	☐	☐	

Prospective Participant Must MATCH ALL these Inclusion Criteria to be Eligible	Yes	No	Supporting Documentation *
24. Sexually-active men must agree to 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 during this period. A condom is required to be used also by vasectomized men as well as during intercourse with a male partner to prevent delivery of the drug via seminal fluid.	☐	☐	

3.2 Exclusion Criteria

Prospective Participants Must NOT Match ANY of These Exclusion Criteria	Yes	No	Supporting Documentation *
1. History of another primary malignancy within 3 years 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.	☐	☐	
2. Neurologic symptoms related to central nervous system metastases requiring increasing doses of corticosteroids. Note that subjects with central nervous system metastases ARE eligible if they are on a stable corticosteroid dose for at least 2 weeks preceding study entry.	☐	☐	
3. Current evidence of corneal or retinal disorder/keratopathy including, but not limited to, bullous/band keratopathy, corneal abrasion, inflammation/ulceration, keratoconjunctivitis, confirmed by ophthalmologic examination. Subjects with asymptomatic ophthalmologic conditions assessed by the investigator to pose minimal risk for study participation may be enrolled in the study.	☐	☐	

Prospective Participants Must NOT Match ANY of These Exclusion Criteria	Yes	No	Supporting Documentation *
4. 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.	☐	☐	
5. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral infigratinib (eg, ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).	☐	☐	
6. Current evidence of endocrine alterations of calcium/phosphate homeostasis, eg, parathyroid disorders, history of parathyroidectomy, tumor lysis, or tumoral calcinosis.	☐	☐	
7. Currently receiving or planning during study participation to receive treatment with agents that are known strong inducers or inhibitors of CYP3A4 and medications which increase serum phosphorus and/or calcium concentration. Subjects are not permitted to receive enzyme-inducing anti-epileptic drugs, including carbamazepine, phenytoin, phenobarbital, and primidone. See Appendix A for a list of prohibited concomitant medications and supplements.	☐	☐	
8. Has consumed grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges, or products containing juice of these fruits within 7 days prior to first dose of study drug.	☐	☐	
9. Have used amiodarone within 90 days prior to first dose of study drug.	☐	☐	
10. Has used medications known to prolong the QT interval and/or are associated with a risk of Torsades de Pointes (TdP) 7 days prior to first dose of study drug. See Appendix A for a list of prohibited concomitant medications and supplements.	☐	☐	

Prospective Participants Must NOT Match ANY of These Exclusion Criteria	**Yes**	**No**	**Supporting Documentation ***
11. Has used calcium or vitamin D within 3 days prior to first dose of study drug. Calcium supplementation may subsequently be used as clinically indicated (for hypocalcemia) on study.	☐	☐	
12. Have clinically significant cardiac disease including any of the following: a. Congestive heart failure requiring treatment (New York Heart Association Grade ≥ 2), left ventricular ejection fraction (LVEF) < 50% or local lower limit of normal as determined by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO), or uncontrolled hypertension (refer to the European Society of Cardiology and European Society of Hypertension guidelines [Williams *et al*., 2018]) b. Presence of Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Grade ≥ 2 ventricular arrhythmias, atrial fibrillation, bradycardia, or conduction abnormality c. Unstable angina pectoris or acute myocardial infarction ≤ 3 months prior to first dose of study drug d. Corrected QT interval-Fredericia (QTcF) > 470 msec (males and females). Note: If the QTcF is > 470 msec in the first electrocardiogram (ECG), a total of 3 ECGs separated by at least 5 minutes should be performed. If the average of these 3 consecutive results for QTcF is ≤ 470 msec, the subject meets eligibility in this regard. e. Known history of congenital long QT syndrome	☐	☐	
13. Have had a recent (≤ 3 months) transient ischemic attack or stroke.	☐	☐	
14. Pregnant or nursing	☐	☐	

* All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

V. Statement of Eligibility

By signing this form of this trial I verify that this subject is: ☐ eligible / ☐ ineligible for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the IRB of record, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Study Coordinator printed name:	Date:
Signature:	

Investigator printed name:	Date:
Signature:	

Triple-check reviewer printed name:	Date:
Signature:	

3.3 Informed Consent Process

All subjects must be provided a consent form describing the study with sufficient information for subjects to make an informed decision regarding their participation. Subjects must sign the IRB approved informed consent prior to participation in any study specific procedure. The subject must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Study Timeline

Primary Completion:

It is anticipated that the study will reach primary completion (30 days after final subject completes treatment with study agents) 24 months from the time the study opens to accrual.

Study Completion:

It is anticipated that the study will reach study completion (final date on which data are collected) 36 months from the time the study opens to accrual.

4. TREATMENT PLAN

Potential subjects who preliminarily meet inclusion criteria and exclusion criteria as determined by study staff (for example, the investigator or clinical research coordinator) will meet with study staff to review the study and informed consent in detail. At this time, inclusion and exclusion criteria will be confirmed with the subjects and treating clinicians as necessary.

All eligible subjects (meeting criteria described in Section 3) will receive the drug combination of infigratinib with tamoxifen. Once a dose level for infigratinib is determined, Cohort 1 will close.

All subjects in whom a research biopsy of a disease site is deemed feasible and safe by the investigator will be required to undergo a biopsy to donate 4 to 8 cores of tumor tissue before and on-treatment to be used for research purposes, including genomic/transcriptomic/proteomic analysis and organoid culture derivation as described in Section 2.6. The on-treatment biopsy is recommended to occur on Day 15 of treatment, but any time on treatment is acceptable. Tissue will be transported to the Curtis lab for processing and analysis. Subjects who require a tumor biopsy for eligibility assessment will undergo the collection of tissue cores for research simultaneously, whenever possible. Archival tumor tissue, including stored at Stanford University and at other institutions, may be obtained for use for tissue correlative studies as well. Only tissue not needed for diagnostic purposes will be used for research.

Subjects in Cohort 1 will receive tamoxifen 20 mg orally continuously starting on Day 1 and will additionally receive infigratinib orally daily 3 weeks on, 1 week off (28-day cycle) at the dose level dictated by study protocol (125 mg, 100 mg, or 75 mg).

Subjects will continue receiving cycles as above until 18 months on treatment, progression, or unacceptable toxicity (or other reasons outlined in Section 4.3). If toxicity is deemed per the investigator to be related to endocrine therapy (tamoxifen) and not infigratinib, subjects will be given the option of continuing infigratinib only (without endocrine therapy) until progression.

Details on study procedures during Screening, Treatment, and Post-Treatment are provided in the Study Calendar and footnotes (Section 9).

4.1 General Concomitant Medication and Supportive Care Guidelines

4.1.1 Concomitant Medication

Administration of other anticancer therapies within 2 weeks of enrollment, except ongoing administration of a bisphosphonate drug or denosumab as treatment for bone metastasis or ongoing administration of a luteinizing hormone-releasing hormone agonist (such as goserelin acetate or leuprolide acetate) or other endocrine therapy, is prohibited.

Palliative radiotherapy on study is permitted for the treatment of painful bony lesions providing the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of infigratinib with radiotherapy, infigratinib treatment should be interrupted during palliative radiotherapy, resuming infigratinib treatment after recovery to ≤ Grade 1 radiotherapy-related toxicity.

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

Strong inhibitors of CYP3A4 such as the ones listed in Appendix A are prohibited because infigratinib is a likely substrate of this isoenzyme.

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

Subjects must also avoid the consumption of grapefruits; grapefruit juice; grapefruit hybrids; pomegranates; star fruits; pomelos; Seville oranges; or juice within 7 days prior to the first dose of infigratinib and throughout the treatment period due to a potential CYP3A4 interaction with study drug.

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

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

Medications that are allowed but should be administered with caution are provided in Appendix B. The rationale for these medications is provided below.

Infigratinib is characterized by pH-dependent solubility, and therefore, medicinal products that alter the pH of the upper GI tract may alter the solubility of infigratinib, and limit bioavailability. These agents include, but are not limited to, proton pump inhibitors (eg, omeprazole), H2-antagonists (eg, ranitidine) and antacids. If possible, proton pump inhibitors should be avoided due to their long PD effect and replaced with H_2-antagonists or antacids. Study drug should be taken ≥ 2 hours before or 10 hours after dosing with a gastric protection agent.

Infigratinib is a substrate of CYP3A4. Therefore, moderate inhibitors and inducers should be used with caution if an alternative is not available. If anticoagulation is required, heparin and/or low-molecular-weight heparins or direct thrombin inhibitors and/or Factor Xa inhibitors that are not metabolized by CYP3A4 (eg, dabigatran, edoxaban) are preferred. If unavoidable, anticoagulants that are CYP3A4 substrates and have a narrow therapeutic index [eg, warfarin sodium or any other coumadin-derivative anticoagulants or certain direct thrombin inhibitors (eg, argatroban or Factor Xa inhibitors, eg, rivaroxaban)] should be used with caution.

Infigratinib was shown in vitro to inhibit the drug transporter breast cancer resistance protein (BCRP), with an IC_{50} of 210 nM. While the clinical relevance of this inhibition is unknown, drugs transported by BCRP should be used with caution.

Anti-emetics are recommended as clinically appropriate at the first sign of nausea and vomiting or as prophylaxis to prevent emesis, along with supportive care according to clinical practice guidelines.

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 B for list of drugs that need to be used with caution. Aprepitant (brand name: Emend) is both a sensitive substrate and a moderate CYP3A4 inhibitor and should be used with caution if an alternative is not available.

Preliminary clinical data have shown that infigratinib has no effect on cardiac conduction or ECG intervals (see current version of the infigratinib Investigator's 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 subjects should be carefully monitored. See Appendix B for list of drugs that need to be used with caution. Please note that the list might not be comprehensive.

Otherwise, concomitant treatment considered necessary for the subject's well-being may be given at discretion of the treating physician. All concomitant medications (including herbal supplements and vitamins), blood products, as well as interventions (eg, paracentesis, etc.) received by subjects from screening until the end of study visit will be recorded in the CRF.

4.1.2 Supportive Care Guidelines

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

Hematopoietic Growth Factors

Hematopoietic growth factors [eg, erythropoietin (EPO), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF)] and blood transfusions 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), the National Comprehensive Cancer Network (NCCN), or other appropriate regional societies.

Management of Hyperphosphatemia

Hyperphosphatemia is a recognized on-target effect of potent and selective inhibitors of the FGFR pathway.

The goal of a low-phosphate diet, when one is recommended per management strategy below, is to restrict dietary phosphate to 600 to 800 mg/day by avoiding high-phosphate foods. High-phosphate foods include dairy products; meats, nuts, and other high-protein foods; processed foods; and dark colas. In general, subjects will be instructed to liberalize their diet on days they are not taking infigratinib (including Days 22 to 28, and during interruption of infigratinib for indications other than hyperphosphatemia), unless their serum phosphorus is currently > 5.5 mg/dL. Similarly, subjects who are taking sevelamer (phosphate-lowering medication) will be instructed to hold it on days they are not taking infigratinib (including Days 22 to 28, and during interruption of infigratinib for indications other than hyperphosphatemia), unless their serum phosphorus is currently > 5.5 mg/dL.

Below is the recommended management strategy for hyperphosphatemia. Section 6 also outlines instructions for when to interrupt and/or dose-reduce infigratinib in addition to these recommendations for management. Notably, these instructions for increased monitoring of serum phosphorus, interruption, and dose reduction begin if serum phosphorus > 7.0 mg/dL.

All subjects will have a serum phosphorus checked on C1D4:

- If serum phosphorus > 5.5 and ≤ 7.0 mg/dL, subjects will be instructed to follow a low-phosphate diet and to take sevelamer 800 mg orally 3 times daily with meals.
- If serum phosphorus > 7.0 mg/dL, subjects will be instructed to follow a low-phosphate diet and to take sevelamer 1200 mg orally 3 times daily with meals.

All subjects will have a serum phosphorus checked on Cycle 1 Day 15:

- For subjects who are not currently following a low-phosphate diet or taking sevelamer:
  - If serum phosphorus > 5.5 and ≤ 7.0 mg/dL, subjects will be instructed to follow a low-phosphate diet and to take sevelamer 800 mg orally 3 times daily with meals.
  - If serum phosphorus > 7.0 mg/dL, subjects will be instructed to follow a low-phosphate diet and to take sevelamer 1200 mg orally 3 times daily with meals.
- For subjects who are currently following a low-phosphate diet and taking sevelamer:
  - If serum phosphorus < 5.0 mg/dL, subjects will be given the option of liberalizing their diet or stopping the sevelamer (not both).
  - If serum phosphorus > 5.5 and ≤ 7.0 mg/dL, subjects will be instructed to increase the dose of sevelamer to 1200 mg orally 3 times daily with meals.
  - If serum phosphorus > 7.0 mg/dL, subjects will be instructed to increase the dose of sevelamer to 1600 mg orally 3 times daily with meals.

Subsequent (after Cycle 1) management of hyperphosphatemia is as follows:

- For subjects who are not currently following a low-phosphate diet or taking sevelamer:
  - If serum phosphorus > 5.5 and ≤ 7.0 mg/dL, subjects will be instructed to follow a low-phosphate diet and to take sevelamer 800 mg orally 3 times daily with meals.

  - If serum phosphorus > 7.0 mg/dL, subjects will be instructed to follow a low-phosphate diet and to take sevelamer 1200 mg orally 3 times daily with meals.

- For subjects who are currently either following a low-phosphate diet or taking sevelamer, but not both:
  - If serum phosphorus > 5.5 and ≤ 7.0 mg/dL, subjects will be instructed to follow a low-phosphate diet and to take sevelamer 800 mg orally 3 times daily with meals.
  - If serum phosphorus > 7.0 mg/dL, subjects will be instructed to follow a low-phosphate diet and to take sevelamer 1200 mg orally 3 times daily with meals.
- For subjects who are currently following a low-phosphate diet and taking sevelamer 800 mg orally 3 times daily:
  - If serum phosphorus > 5.5 and ≤ 7.0 mg/dL, subjects will be instructed to increase sevelamer to 1200 mg orally 3 times daily with meals.
  - If serum phosphorus > 7.0 mg/dL, subjects will be instructed to increase sevelamer to 1600 mg orally 3 times daily with meals.
- For subjects who are currently following a low-phosphate diet and taking sevelamer 1200 mg orally 3 times daily:
  - If serum phosphorus > 5.5 mg/dL, subjects will be instructed to increase sevelamer to 1600 mg orally 3 times daily with meals.

Management of Diarrhea

Subjects should be instructed to notify their physician immediately at the first signs of poorly formed or loose stool or an increased frequency of bowel movements. Administration of antidiarrheal/anti-motility agents is recommended at the first sign of diarrhea as initial management. Some subjects may require concomitant treatment with more than one antidiarrheal agent. When therapy with antidiarrheal agents does not control the diarrhea to tolerable levels, study drug should be temporarily interrupted or dose reduced (see Section 6).

Management of Skin Toxicity

Alopecia:

Grade 1	Consider minoxidil 5% (OTC) solution or foam once daily to scalp.
Grade 2	Consider minoxidil 5% (OTC) solution or foam twice daily to scalp. Consider fluocinonide 0.05% solution daily to scalp.

Palmar-plantar erythrodysesthesia syndrome: See also Section 6 for when to interrupt or dose-reduce infigratinib (Grade 3).

Grade 1	Consider urea 20% or ammonium lactate 12% lotions twice daily to hands and feet.
Grade 2 or 3	Consider urea 20% or ammonium lactate 12% lotions twice daily to hands and feet. Consider fluocinonide 0.05% solution twice daily to hands and feet.

Paronychia: Also see Section 6 for when to interrupt or dose-reduce infigratinib (Grade 3).

Grade 1 to 3	Consider cefadroxil 500 mg orally twice daily or TMP/SMX orally twice daily for 14 days. Soak for 15 minutes daily in white vinegar in tap water 1:1. Obtain bacterial cultures to confirm sensitivity to antimicrobial. Consult dermatology.

Stomatitis: Subjects should be instructed to follow good oral hygiene during therapy. Prophylactic dexamethasone 10 mg/5 mL swish/spit 4 times a day for the first 8 weeks can be considered for prevention of stomatitis, [44] for example, for subjects who have had significant stomatitis from previous cancer therapies. Also see Section 6 for when to interrupt or dose-reduce infigratinib (Grade 3).

Grade 1	Consider dexamethasone elixir 0.5 mg/mL swish and spit 1 teaspoon (5 mL) 3 times daily.
Grade 2	Consider dexamethasone elixir 0.5 mg/mL swish and spit 1 teaspoon (5 mL) 3 times daily AND doxepin 10 mg/mL swish and spit 1 teaspoon 5 mL every 6 hours as needed for pain.
Grade 3	Consider dexamethasone elixir 0.5 mg/mL swish and spit 1 teaspoon (5 mL) 3 times daily AND doxepin 10 mg/mL solution swish and spit 1 teaspoon 5 mL every 6 hours as needed for pain. Consider clotrimazole 10 mg lozenges four times daily.

4.2 Criteria for Removal from Study

Subjects may withdraw from treatment at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral, or administrative reasons.

Reasons for subject discontinuation of study treatment may include:

- Objective disease progression according to RECIST criteria v1.1;
- 18 months of study drug therapy has been completed;
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity deemed per investigator to be related to study drug, which may also be an adverse event;
- Significant protocol violation;
- Lost to follow-up;
- Subject refused further treatment;
- Study terminated by the investigator or sponsor;
- Death;
- Pregnancy.

Reasons for subject withdrawal from study follow-up may include:

- Completed study follow-up;
- Study terminated by the PI or infigratinib distributor QED Therapeutics;
- Lost to follow-up;
- Refusal for further follow-up for survival;
- Start of an alternative treatment regimen;
- Death.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return for a final visit, and follow-up with the subject regarding any unresolved adverse events. The early termination final visit should include all assessments listed for the End of Treatment visit. If the subject withdraws consent for disclosure of future information, no further study specific evaluations should be performed, and no additional data should be collected. The investigators may retain and continue to use any data collected before such refusal for further follow-up.

4.3 Alternatives

Standard treatment options for $HR^+/HER2^-$ metastatic breast cancer after progression on endocrine therapy in combination with a CDK4/6 inhibitor include alternative endocrine therapy, sometimes in combination with an mTOR inhibitor (everolimus), or one of numerous chemotherapy options (eg, taxanes, anthracyclines, capecitabine, gemcitabine, and vinorelbine). For the potential subset of subjects who not yet received a CDK4/6 inhibitor, standard treatment for $HR^+/HER2^-$ metastatic breast cancer that has not progressed on endocrine therapy in combination with a CDK4/6 inhibitor is endocrine therapy in combination with a CDK4/6 inhibitor or, in select subjects with lower-risk disease, endocrine therapy alone.

5. INVESTIGATIONAL AGENT INFORMATION

5.1 Investigational Agent

For a summary, see Section 2.2. For complete details, see Investigator's Brochure, provided as a separate document.

5.1.1 Infigratinib Dosage Form

Hard gelatin capsules in dosage strengths from 25 mg and 100 mg (expressed as mg of infigratinib free-base). Excipients will include microcrystalline cellulose, lactose monohydrate, HPMC2910, crospovidone, colloidal silicon dioxide, magnesium stearate, and hard gelatin capsule. Infigratinib will be manufactured under Good Manufacturing Practice for investigational use.

5.1.2 Subject Instructions for Infigratinib Dosing

Subjects should be instructed to take the daily dose of infigratinib in the morning as much as their schedule and appointment allow, at approximately the same time each day (24 ± 4 hour interval).

Infigratinib should be taken in the fasted state at least 1 hour before or 2 hours after a meal. It should be taken with a large glass of water (~250 mL) and consumed over as short a time as possible. Subjects should be instructed to swallow the capsules whole and not chew them.

Subjects in Cohort 1 should take their daily dose of tamoxifen 4 to 8 hours after their dose of infigratinib.

If the subject forgets to take the scheduled dose of infigratinib in the morning, he/she should not take the dose more than 4 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 dosing with infigratinib, re-dosing is not permitted the same day. Dosing should resume the next day.

Infigratinib is characterized by pH-dependent solubility; therefore, medicinal products that alter the pH of the upper GI tract may alter the solubility of infigratinib and limit bioavailability. These agents include, but are not limited to, proton pump inhibitors (eg, omeprazole), H_2-antagonists (eg, ranitidine) and antacids. If possible, proton pump inhibitors should be avoided due to their long pharmacodynamic effect and replaced with H_2-antagonists or antacids. Infigratinib should be taken at least 2 hours before or 10 hours after dosing with a gastric protection agent.

Subjects must avoid the consumption of grapefruits, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or juice within 7 days prior to the first dose of infigratinib and throughout the treatment period. This is due to a potential CYP3A4 interaction with study drug. Normal oranges and orange juice are allowed.

5.1.3 Packaging and Labeling

Infigratinib capsules will be packaged in high-density polyethylene bottles with child-resistant closures. Labels will include storage conditions for the drug.

5.2 Availability

QED Therapeutics will supply infigratinib drug product.

5.3 Agent Ordering

Infigratinib will be shipped by QED Therapeutics to the Investigational Drug Service at Stanford University Medical Center, shipping address:

Stanford Health Care
Stanford University
Investigational Drug Service
300 Pasteur Dr, Room H0302
Stanford, CA, USA 94305

5.4 Agent Accountability

Infigratinib capsules will 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, infigratinib should be stored according to the instructions specified on the drug label and in the Investigator's Brochure. Refer to the Pharmacy Manual for further details.

The investigator or designee must maintain an accurate record of the shipment and dispensing of infigratinib in a drug accountability log. Subjects in the infigratinib group will be asked to return all used and unused bottles of infigratinib and packaging on a regular basis, at the end of the study, or at the time of study drug discontinuation. Drug accountability will be assessed by the investigator and/or study personnel, and captured in a subject drug accountability log. This information must be captured in the source document at each subject visit.

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

6. DOSE MODIFICATIONS

Individually, each subject will be allowed up to dose-reduce to 75 mg infigratinib, as follows (see also Table 5).

- If a subject's infigratinib dose is 125 mg, 2 dose reductions of infigratinib are permitted.
- If a subject's infigratinib dose is 100 mg, 1 dose reduction of infigratinib is permitted.
- If a subject's infigratinib dose is 75 mg, no dose reduction of infigratinib is permitted, with infigratinib treatment discontinuation the only option.

Subjects should discontinue infigratinib if toxicities persist following dose reductions to the lowest level allowed, unless it has been discussed and approved by the QED Therapeutics' Medical Monitor.

Following resolution of toxicity to baseline or ≤ Grade 1, or ≤ Grade 2 for hematologic toxicities, treatment is resumed at either the same or lower dose of study drug as per the criteria in Table 6. Adverse event lab abnormalities outlined in Table 6 should be followed at least weekly until the specified resolution. 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 subject should have a second dose reduction.

Subjects who are withdrawn from the study for a study related AE or an abnormal laboratory value must be followed as described in Section 7.3.

Table 5. Dose Modification Scheme for Infigratinib

Dose Reduction			
	Dose level 3	(Starting) Dose level 2	Dose level 1
Infigratinib	125 mg	100 mg	75 mg

In exceptional situations, study drug may continue even if the subject experienced one of the treatment stopping rules. The decision to allow for continuation of treatment will be made on a case-by-case basis following discussion between QED Therapeutics and the investigator.

Table 6. Criteria for Interruption and Re-initiation of Infigratinib for AEs Considered to be Possibly Related to Infigratinib

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
CARDIAC DISORDERS	
Cardiac - Prolonged QTcF Interval	
Grade 1 and 2: QTcF ≥ 481msec and ≤ 500 msec (asymptomatic)	Maintain dose level of infigratinib. Two additional ECGs separated by at least 5 minutes should be performed to confirm the finding. If the finding is confirmed, single ECG assessments should be performed every 2 weeks for 2 additional cycles, or as clinically indicated. If abnormality is detected, 2 additional ECGs separated by at least 5 minutes should be performed to confirm the finding. • If ECG assessments show no QTcF ≥ 481 msec, for subsequent cycles ECG monitoring will be performed at each subsequent visit, per visit schedule. • If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤ 500 msec), then ECG monitoring must continue every 2 weeks for all subsequent cycles.
Grade 3: QTcF > 500msec or > 60 ms change from baseline as identified on the ECG by the investigator	Hold infigratinib. Two additional ECGs separated by at least 5 minutes should be performed to confirm the finding. If the finding is confirmed, the subject should be admitted to the hospital for at least 24 hours of continuous telemetry; once confirmed no further prolongation of QTc and no arrhythmias over 24 hour period, subject can be discharged. After discharge, subject should return to clinic weekly for ECG until normalization. • Exclude other causes of QTcF prolongation such as hypokalemia, hypomagnesaemia, and decreased blood oxygenation. • Subjects 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, subjects may be re-treated at one lower dose level at the investigator's discretion.

Table 6. Criteria for Interruption and Re-initiation of Infigratinib for AEs Considered to be Possibly Related to Infigratinib

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
Grade 3: QTcF > 500msec or > 60 ms change from baseline as identified on the ECG by the investigator (continued)	Single ECG assessments should be performed for 2 additional cycles every 2 weeks or as clinically indicated. If abnormality is detected, 2 additional ECGs separated by at least 5 minutes should be performed to confirm the finding. • If ECG assessments show no QTcF ≥ 481 msec, ECG monitoring will be performed at each subsequent visit, per visit schedule for subsequent cycles. • If ECG assessments are still abnormal (QTcF ≥ 481 msec and ≤ 500 msec), then ECG monitoring must continue every 2 weeks or as clinically indicated, for all subsequent cycles. • Subjects who experience recurrent QTcF ≥ 500msec after one dose reduction will be withdrawn from study. If QTcF > 500 msec or > 60 msec change from the baseline is observed, a plasma sample for determination of infigratinib concentration should be obtained with the time of sample collection noted.
Grade 4: Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Discontinue infigratinib. A plasma sample for determination of infigratinib concentration should be obtained with the time of sample collection noted.
Cardiac Disorders – Others	
Grade ≥ 3 OR Congestive heart failure Grade ≥ 2	Discontinue infigratinib.
INVESTIGATIONS-HEMATOLOGY *	
ANC Decreased (Neutropenia)*	
Grade 3 (ANC < 1.0 to 0.5 × 10^9/L)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 2 or baseline, then • If resolved within ≤ 7 days, maintain dose level of infigratinib • If resolved between > 7 days and 14 days, decrease by 1 dose level of infigratinib • If not resolved within ≤ 14 days, discontinue infigratinib
Grade 4 (ANC < 0.5 × 10^9/L)	Hold dose of infigratinib until resolved to CTCAE ≤ Grade 2, decrease by 1 dose level of infigratinib • If not resolved within ≤ 14 days, discontinue infigratinib

Table 6. Criteria for Interruption and Re-initiation of Infigratinib for AEs Considered to be Possibly Related to Infigratinib

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
Febrile Neutropenia * General Comment: Consider administering G-CSF per NCCN guidelines (Version 2.2019) "Management of Neutropenia": that is, if any of the following risk factors for an infection-associated complication are present – sepsis syndrome, age > 65 years, ANC < 100/mcL, clinically documented infection, invasive fungal infection, hospitalization at the time of fever, or prior episode of febrile neutropenia.	
Grade 3 (ANC < 1.0 × 10^9/L, single temperature of > 38.3°C or a sustained temperature of ≥ 38.0°C)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 2, then • If resolved within ≤ 7 days, decrease by 1 dose level of infigratinib. • If not resolved within 7 days, discontinue subject from study drug
Grade 4	Discontinue infigratinib.
Anemia * General Comment: Consider packed RBC transfusion for hemoglobin < 7 g/dL, or < 8 g/dL for subjects with preexisting cardiovascular disease, per AABB guidelines, or if the investigator suspects the subject is symptomatic from anemia.	
Grade 3 (hemoglobin < 8.0 g/dL)	Hold dose of infigratinib until resolved or corrected to CTCAE Grade ≤ 2 or baseline, then maintain dose level
Grade 4	Hold dose of infigratinib until resolved or corrected to CTCAE Grade ≤ 2 or baseline, then decrease by 1 dose level
Platelet Count Decreased (Thrombocytopenia) *	
Grade 3 (platelet < 50 to 25 × 10^9/L) without ≥ Grade 2 bleeding	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 2 or baseline • If resolved within ≤ 7 days, maintain dose level of infigratinib • If resolved between > 7 days and 14 days, decrease by 1 dose level of infigratinib • If not resolved within ≤ 14 days, discontinue infigratinib
Grade 3 (platelet < 50 to 25 × 10^9/L) with bleeding or Grade 4 (platelet < 25 × 10^9/L)	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 2 or baseline, then decrease by 1 dose level • If not resolved within ≤ 14 days, discontinue infigratinib

Table 6. Criteria for Interruption and Re-initiation of Infigratinib for AEs Considered to be Possibly Related to Infigratinib

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
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 (≥ 2.00 to 3.0 × ULN or 2.0 to 3.0 × baseline)	Hold dose of infigratinib until resolved to Grade ≤ 1 or baseline • If resolved within ≤ 7 days, maintain dose level of infigratinib • If resolved between > 7 days and 14 days, decrease by 1 dose level of infigratinib • If not resolved within ≤ 14 days, discontinue infigratinib
Grade ≥ 3 (> 3.0 × ULN or > 3 × baseline)	Discontinue infigratinib
INVESTIGATIONS – HEPATIC	
AST or ALT	
Grade 3 (> 5.0 to 20.0 × ULN) without bilirubin elevation > 2.0 × ULN	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 or baseline • If resolved within ≤ 7 days, decrease by 1 dose level of infigratinib • If not resolved within ≤ 7 days, discontinue infigratinib
Grade 4 (> 20.0 × ULN) without bilirubin elevation > 2.0 × ULN	Discontinue infigratinib
AST or ALT and Bilirubin	
AST or ALT > 3.0 to 5.0 × ULN and total bilirubin > 2.0 × ULN without liver metastasis or evidence of disease progression in the liver	Hold dose of infigratinib until both transaminases and bilirubin resolved to CTCAE Grade ≤ 1 or baseline. • If resolved within ≤ 7 days, decrease by 1 dose level of infigratinib. • If not resolved within ≤ 7 days, discontinue infigratinib
AST or ALT > 5.0 × ULN and total bilirubin > 2.0 × ULN	Discontinue infigratinib

Table 6. Criteria for Interruption and Re-initiation of Infigratinib for AEs Considered to be Possibly Related to Infigratinib

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 General Comment: Assess for symptoms of acute pancreatitis (abdominal pain or tenderness), and, if present, consider a CT scan or other imaging study to assess the pancreas, liver, and gallbladder to confirm the diagnosis of acute pancreatitis and assess for complications.	
Grade 3 (> 2.0 to 5.0 × ULN)	• Hold dose of infigratinib until resolved to CTCAE Grade ≤ 2 • decrease by 1 dose level of infigratinib • If not resolved within ≤ 14 days, discontinue infigratinib For recurrent Grade 3 asymptomatic lipase or amylase elevation despite dose reduction, infigratinib should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤ Grade 2.
Grade 4 (> 5.0 × ULN)	For any Grade 4 asymptomatic lipase or amylase elevation, infigratinib should be held and continuation of therapy should be discussed with the medical monitor following resolution to ≤ Grade 2.
Hyperphosphatemia	
Serum phosphorus > 5.5 to 7.0 mg/dL	Maintain dose level of infigratinib and optimize phosphate lowering therapy (see “Management of Hyperphosphatemia” in Section 4.2).
Serum phosphorus > 7.0 mg/dL	If serum phosphorus is > 7.0 mg/dL, serum phosphorus should be monitored every 2 to 3 days until ≤ 7.0 mg/dL. For serum phosphorus that is > 7.0 mg/dL for more than 7 days, or for a single serum phosphorus > 9.0 mg/dL: • Hold infigratinib dose until resolved to serum phosphorus ≤ 5.5 mg/dL. For serum phosphorus that is > 7.0 mg/dL for more than 7 days: • Restart infigratinib at the same dose level with increased phosphate binder dosing if the subject did not receive maximal phosphate binder dosing (sevelamer 1600 mg 3 times daily). • Reduce one dose level of infigratinib if the subject had received maximal phosphate lowering therapy (sevelamer 1600 mg three times daily). Continue maximal phosphate binder dosing. For serum phosphorus that is > 9.0 mg/dL: • Reduce one dose level of infigratinib. Restart infigratinib with maximal phosphate binder dosing. It is recommended that phosphate binder dosing continues during infigratinib dose interruptions for hyperphosphatemia.

Table 6. Criteria for Interruption and Re-initiation of Infigratinib for AEs Considered to be Possibly Related to Infigratinib

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
Hypercalcemia	
Serum calcium Grade 2	Hold infigratinib dose until resolved to Grade 1 or baseline: • If resolved within ≤ 7 days after suspending infigratinib, maintain dose level • If resolved between > 7 days and 14 days after suspending infigratinib, decrease by 1 dose level • If not resolved within ≤ 14 days, discontinue infigratinib
Serum calcium ≥ Grade 3	Discontinue subject from study drug
NERVOUS SYSTEM DISORDERS	
Any Grade 2 neurotoxicity	Omit dose of infigratinib until resolved to CTCAE Grade ≤ 1, then decrease by 1 dose level of infigratinib • If not resolved within ≤ 14 days, discontinue infigratinib
Any Grade ≥ 3 neurotoxicity	Discontinue infigratinib
GASTROINTESTINAL SYSTEM DISORDERS	
Pancreatitis	
Grade ≥ 2	Discontinue infigratinib
Diarrhea	
General Comment:	Antidiarrheal medication is recommended at the first sign of abdominal cramping, loose stools or overt 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 • For reoccurrence of diarrhea CTCAE Grade 2, hold dose of infigratinib until resolved to CTCAE Grade ≤ 1, decrease infigratinib by 1 dose level
Grade 3	• Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 • Optimize anti-diarrheal treatment • Decrease infigratinib by 1 dose level • For reoccurrence of diarrhea CTCAE Grade 3, despite optimal antidiarrheal treatment, discontinue infigratinib
Grade 4	Discontinue infigratinib

Table 6. Criteria for Interruption and Re-initiation of Infigratinib for AEs Considered to be Possibly Related to Infigratinib

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
Vomiting	
Grade 2 not controlled by optimal anti-emetic therapy	Hold infigratinib doses until ≤ Grade 1, decrease by 1 dose level • If not resolved within ≤ 14 days, discontinue infigratinib
Grade 3 not controlled by optimal anti-emetic therapy, or Grade 4	Discontinue infigratinib
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, decrease infigratinib by 1 dose level • If resolved after > 14 days, discontinue infigratinib
Grade ≥ 1 retinal vein occlusion, Grade 3 or 4 central serous retinopathy and central serous retinopathy-like events, and Grade 3 or 4 other eye disorders	Discontinue infigratinib
Other Ocular/Visual Toxicity	
Grade ≥ 3	Discontinue infigratinib •
SKIN DISORDERS	
Palmar-plantar erythrodysesthesia syndrome	
Grade 3	Hold dose of infigratinib until resolved to Grade ≤ 1, and then resume infigratinib at decrease by 1 dose level
Paronychia	
Grade 3	Hold dose of infigratinib until resolved to Grade ≤ 1, and then resume infigratinib at decrease by 1 dose level.
Stomatitis	
Grade 3	Hold dose of infigratinib until resolved to Grade ≤ 1, and then resume infigratinib at decrease by 1 dose level.
Grade 4	Discontinue infigratinib

Table 6. Criteria for Interruption and Re-initiation of Infigratinib for AEs Considered to be Possibly Related to Infigratinib

Worst Toxicity CTCAE (v5.0) Grade (Unless Otherwise Specified)	**Recommended Dose Modifications any Time During a Cycle of Therapy**
GENERAL DISORDERS	
Fatigue	
Grade ≥ 3	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1 • If resolved within ≤ 7 days, maintain dose level of infigratinib. • If resolved after > 7 days, discontinue infigratinib
OTHER CLINICALLY SIGNIFICANT AEs	
Grade 3	Hold dose of infigratinib until resolved to CTCAE Grade ≤ 1, then decrease by 1 dose level of infigratinib • If not resolved within ≤ 14 days, discontinue infigratinib
Grade 4	Discontinue infigratinib

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram; QTcF, QTc corrected by Fridericia's formula; ULN, upper limit of normal.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

7.1.1 Related to Study Drug (Infigratinib)

- Adverse events related to calcium/phosphorous homeostasis are expected and on-target effects of infigratinib. Hyperphosphatemia in particular is a reliable biomarker of pathway inhibition and rapidly normalizes upon drug discontinuation without sequelae. Among 433 subjects treated with infigratinib monotherapy, hyperphosphatemia was seen in 62% and in 7% it was Grade 3 or 4. Adverse events associated with calcium/phosphate imbalance (including soft tissue mineralization or ectopic calcifications) have been rare. There have been 3 suspected unexpected SAEs reported related to calcium/phosphorus homeostasis: (1) hepatic failure due to lesion calcification occurring over 6 months after study drug discontinuation, (2) one episode of hypercalcemia, and (3) one episode of hypophosphatemia/hypocalcemia.
- Ophthalmologic adverse events may occur with infigratinib, and mandated ophthalmologic examinations have been performed routinely and frequently. Most of these events are Grade 1 or 2: for example, dry eye in 22% and blurry vision in 10%. Grade 3 ocular events have occurred in 3%, and no Grade 4 ocular events have occurred. Grade 3 ocular events included cataract (0.7%), visual impairment (0.5%), and keratitis (0.5%).
- Gastrointestinal adverse events are frequently reported. For subjects treated with monotherapy, the most frequent GI AEs (regardless of relationship to study drug) were constipation (37%), decreased appetite (30%), nausea (29%), diarrhea (27%), vomiting (20%), and dyspepsia (15%). Stomatitis was reported in 35%, and in 5% was Grade 3 or 4.

- Skin, hair, and nail changes are frequently reported. For subjects treated with monotherapy, 27% experienced alopecia, 13% experienced dry skin, and 12% experienced palmar-plantar erythrodysaesthesia syndrome.
- For others, please see Section 2.2 (especially Tables 2 to 4) and the Investigator's Brochure.

7.1.2 Related to Tamoxifen (Cohort 1) (reported percentages are from N = 3,094 subjects in the ATAC trial)

- Hot flashes (64%) (placebo 48%)
- Vaginal discharge (30%) (placebo 15%)
- Nausea (26%) (placebo 24%)
- Fluid retention (32%) (placebo 30%)
- Mood disturbances
- Thrombotic events (0.8% deep vein thrombosis, 0.5% pulmonary embolism, 0.4% superficial phlebitis)
- For others, please see tamoxifen package insert from the FDA.

7.2 Adverse Event Definitions

An AE is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s).

An SAE is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, ie, defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires in-patient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - Treatment on an emergency out-patient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - Social reasons and respite care in the absence of any deterioration in the subject's general condition

Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (eg, hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study drug(s).

Progression of underlying malignancy is not considered as an AE if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria v1.1, or other

criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE.

Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some subjects. In this situation, progression is evident in the subject's clinical symptoms, but is not supported by the tumor measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.

If there is any uncertainty about an AE being due to progression of the disease under study, it should be reported as an AE or SAE.

7.3 Adverse Events Reporting

Adverse events (AEs) will be documented and recorded at each scheduled or unscheduled visit, including end-of-treatment and during follow-up, using NCI CTCAE v5.0. Subjects will be followed for AEs for 30 days after the last treatment administration or until all drug-related toxicities have resolved (or the Investigator determines in his/her clinical judgment that no further improvement is expected), whichever is later. For serious adverse events (SAEs), the active reporting period will be from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 30 calendar days after the last administration of the investigational product. SAEs experienced by a subject after the active reporting period has ended should be reported if the Investigator becomes aware of them.

Conditions already present at the time of informed consent should be recorded in the Medical History CRF.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE.

The following information is to be captured in the CRF for each AE: severity grade (CTCAE v5.0, Grade 1 to 5); duration (start and end dates); relationship to study drug (infigratinib or tamoxifen) (reasonable possibility that AE is related: No, Yes); action taken with respect to study drug (none, dose reduction, temporarily interrupted, permanently discontinued, unknown, not applicable); whether medication or therapy was given (no concomitant medication/non-drug therapy given, concomitant medication/non-drug therapy given); outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown); and whether the event is serious and seriousness criteria.

7.4 Reporting Serious Adverse Events

Every SAE, regardless of suspected causality, occurring after the subject has signed informed consent through 30 days after the subject has taken his/her last dose of study drug, will be

reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study-specific CRF, and to Helsinn Healthcare SA by email (drug-safety@helsinn.com) using their provided CRFs, within 24 hours of learning of its occurrence. Following review by the Stanford DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences. Any SAEs experienced after this 30-day period should only be reported to the DSMC if the investigator suspects a causal relationship to the study drug.

Any additional information for the SAE including recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow-up information is submitted in the same way as the original SAE Report. Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

If the SAE is not an expected event as per the current Investigator's Brochure or Package Insert (new occurrence or increased frequency) and is thought to be related to the study drug (a Suspected Unexpected Serious Adverse Reaction, "SUSAR"), it must also be reported to Helsinn Healthcare SA via email (drug-safety@helsinn.com) using their provided CRFs within 24 hours of learning of the event and to the FDA via an IND Safety Report within 15 days (7 days if life-threatening or death). QED Therapeutics and partner, the Helsinn Group, will be responsible to send investigator notifications to investigators involved with infigratinib studies.

7.5 Pregnancy

Female subjects must be discontinued from study drug in the event of pregnancy.

To ensure subject safety, each pregnancy of a subject or partner of a male subject occurring while the subject is on study drug must be reported to the Stanford DSMC and Helsinn Healthcare SA (via email at drug-safety@helsinn.com) using their provided CRFs within 24 hours of learning of its occurrence.

For Stanford DSMC reporting, the pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Consent to report information regarding pregnancy and pregnancy outcomes should be obtained from the partner of the male subject. Pregnancy of a subject or partner of a male subject should be recorded on a Pregnancy Notification Form and entered on the Pregnancy eCRF. Pregnancy follow-up should be recorded and include an assessment of the possible relationship to the study drug of any pregnancy outcome. Pregnancy and pregnancy follow-up should be reported to the Stanford DSMC and Helsinn Healthcare SA (via email at drug-safety@helsinn.com) using their provided CRFs.

8. CORRELATIVE/SPECIAL STUDIES

Two types of specimens, tumor tissues and plasma, will be collected for correlative studies.

8.1 Laboratory Correlative Studies

8.1.1 Tumor Tissue Collection and Processing

8.1.1.1 Collection of Specimen(s)

Fresh tumor tissue will be collected on subjects participating in the study during the pre-treatment and on-treatment research biopsies, which are mandatory if deemed safe and feasible by the investigator. Procedures will be done according to best clinical practice guidelines as are all procedures at Stanford Hospital. Four to eight research-specific core biopsies will be taken, depending on the biopsy site and investigator assessment of safety and feasibility. Research biopsies will not be taken if there is felt to be more than minimal additional risk. Details on processing of specimens are provided in the lab manual.

8.1.1.2 Coding of specimens for privacy protection

Study staff (eg, the protocol director or clinical research coordinator) will create a unique anonymous identifier for each specimen at time of subject data collection and entry into the secure REDCap database. The unique anonymized identifier will be assigned sequentially within each cohort (eg, INF1001, INF1002, etc; INF2001, INF2002, etc). All tissue specimens will be labeled with this anonymous identifier and no subject-identifiable information. The link between anonymous identifier and subject information will be stored in the secure REDCap database.

8.1.2 Plasma Collection and Processing

8.1.2.1 Collection of Plasma Specimen(s)

20 cc of blood will be collected in black and tan top Streck Cell-Free DNA BCT tubes at screening or on Cycle 1 Day 1, on Cycle 1 Day 15 (± 3 days), and then again at End of Treatment. Details on processing of specimens are provided in the lab manual.

8.1.2.2 Coding of specimens for privacy protection

As with the tissue specimens (Section 8.1.1), plasma specimens will be labeled with the same anonymous identifier and no subject-identifiable information. The link between anonymous identifier and subject information will be stored in the secure REDCap database.

9. STUDY CALENDAR

Protocol Activity	Screening	On Treatment (1 Cycle = 28 days)						Post-Treatment		
	(Within 21 days of Cycle 1, Day 0)	Cycle 1			Cycle 2		Cycles ≥ 3	End of Treatment / withdrawal (0 to 14 days from decision to discontinue) [23]	30-day Follow-up Safety Visit (+ 7 days) [24]	Other Follow-up[25]
		Day 1 (± 3 days)	Day 4 (± 1 day)	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)			
Informed Consent [1]	X									
Medical/Tumor History [2]	X									
Physical Examination (within 24 hours prior to start of each cycle)[3]	X	X		X	X		X	X	X	(X)
ECOG Performance Status [4]	X	X		X	X		X	X	X	(X)
Safety Labs/Measurements										
Vital Signs (within 24 hours prior to start of each cycle) [5]	X	X		X	X		X	X	X	(X)
Hematology (CBC, differential, platelets) [6]	X	X		X	X	X	X	X		(X)
Complete metabolic panel [7]	X	X	X	X	X	X	X	X		(X)
Amylase, lipase [8]	X	X		X	X	X	X	X		(X)
Calcium, magnesium, phosphorus [9]	X	X	X	X	X	X	X	X		(X)
Urinalysis [10]	X									
Pregnancy Test [11]	X	X						X		
Electrocardiogram [12]	X				X		C4D1, C6D1 (± 7 days) then every 6 cycles (all ± 14 days)	X		
Transthoracic echocardiogram [13]	X				X			X		
Ophthalmology evaluation [14]	X				X ± 7 days		C3D1, C4D1, C6D1 (± 7 days), then every 3 cycles (± 14 days)	X		

Protocol Activity	Screening	On Treatment (1 Cycle = 28 days)						Post-Treatment		
	(Within 21 days of Cycle 1, Day 0)	Cycle 1			Cycle 2		Cycles ≥ 3	End of Treatment / withdrawal (0 to 14 days from decision to discontinue) [23]	30-day Follow-up Safety Visit (+ 7 days) [24]	Other Follow-up[25]
		Day 1 (± 3 days)	Day 4 (± 1 day)	Day 15 (± 3 days)	Day 1 (± 3 days)	Day 15 (± 3 days)	Day 1 (± 3 days)			
Registration [1]	≤ 7 days bef Cycle 1, Day 1									
Treatment										
Infigratinib administration [15]		Daily as 3 weeks on / 1 week off for entire cycle			3 weeks on / 1 week off		3 weeks on / 1 week off			
Cohort 1: Tamoxifen administration [16]			Continuous		Continuous		Continuous			
Tumor Assessment										
CT (chest, abdomen, pelvis) [17]	**X**						C3D1 (+7 days), then every 2 cycle (**±** 7 days)	(**X**)		
Plasma collection [18]		**X**		**X**				**X**		
Research tumor biopsy [19]	**X**			**X**						
Tumor sequencing [20]	**X**									
Other Clinical Assessment										
Adverse event assessment [21]	**X**	Monitor and record at every study visit						**X**	**X**	**X**
Concomitant medications [22]	**X**	Monitor and record at every study visit						**X**	**X**	

1. Informed Consent: Must be obtained prior to undergoing any study specific procedure and may occur prior to the 21-day screening period. Registration will considered to be signed informed consent with triple-signed eligibility checklist, with the final signature being the Stanford Principal Investigator or his/her designee.

2. Medical History / Tumor History: To be collected within 21 days prior to C1D1. Includes history of other diseases (active or resolved) and concomitant illnesses. Oncology history includes information on prior regimens (including dosing and duration of administration, description of best response observed, recurrence date), surgery and radiation therapy. It also includes review of the predicted integrative subtype from FoundationOne. These assays may also be done during screening, as indicated (see footnote 22, "Tumor sequencing").

3. Physical Examination: Includes an examination of major body systems. Weight for the purposes of dose calculation will be recorded at screening and within 7 days pre-dose Day 1 of each cycle. Weight will also be collected at End of Treatment. Height will be measured at baseline.

4. ECOG Performance Status:

Score	Definition
0	Fully active, able to carry on all pre-disease activities without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work or office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

5. Vital signs: Blood pressure, pulse rate, and body temperature to be recorded in the same position, either supine or sitting.

6. Hematology: No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. On treatment, to be performed prior to dosing with study medications unless otherwise indicated. Lab abnormalities that are adverse events specified in Table 6 must be followed at least weekly until resolution to the grade specified in Table 6.

7. Complete metabolic panel: No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. Lab abnormalities that are adverse events specified in Table 6 must be followed at least weekly until resolution to the grade specified in Table 6.

8. Amylase, lipase: No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. Lab abnormalities that are adverse events specified in Table 6 must be followed at least weekly until resolution to the grade specified in Table 6.

9. Calcium, magnesium, phosphorus (serum): No need to repeat on C1D1 if baseline assessment performed within 72 hours prior to that date. Lab abnormalities that are adverse events specified in Table 6 must be followed at least weekly until resolution to the grade specified in Table 6.

10. Urinalysis: Macroscopic or microscopic.

11. Pregnancy Test: For female subjects of childbearing potential, a serum or urine pregnancy test must be performed within 7 days of first day of study drug and at end-of-treatment. Additional pregnancy test to be repeated when potential pregnancy is suspected.

12. Electrocardiogram: 12-lead ECG to be performed during Screening, at Cycle 2 Day 1 (± 3 days), Cycle 4 Day 1 (± 7 days), Cycle 6 Day 1 (± 7 days), and then every 6 cycles (± 14 days), and at End-of-Treatment. Additional assessments should be conducted as clinically indicated.

13. Echocardiogram: Transthoracic echocardiogram to be performed during Screening, at Cycle 2 Day 1 (± 3 days), and at End-of-Treatment. Additional assessments should be conducted as clinically indicated.

14. Ophthalmology evaluation: Ophthalmologic examination will be performed by an ophthalmologist during Screening, on Day 1 (± 7 days) of Cycles 2, 3, 4 and 6; then every 3 cycles (± 14 days); and at End-of-Treatment, as well as urgently with any new onset of visual symptoms. These assessments will include visual acuity testing, slit lamp examination of the anterior eye segment, intraocular pressure, dilated fundoscopy, and retinal optical coherence tomography (OCT). Additional examinations such as specular microscopy (that enables a magnified, direct view of the corneal epithelium) and corneal pachymetry will be performed as clinically indicated.

15. Infigratinib Administration: One cycle of infigratinib will be provided to subjects at the beginning of each cycle. Starting dose level of infigratinib for individual subjects will be as defined by study protocol, and may be either 125 mg; 100 mg; or 75 mg infigratinib, each dose level administered as 3 weeks on, 1 week off for every 28-day cycle.

16. Tamoxifen Administration: In Cohort 1, tamoxifen will be prescribed to subjects and will be started at 4 to 8 hours after the administration of infigratinib, starting on Cycle 1 Day 1. Dose is tamoxifen 20 mg/day by mouth continuously.

17. Tumor assessment by imaging: Baseline CT imaging can be done within 28 days prior to C1D1 (versus 21 days for all other baseline/screening assessments). Assessment of response will be made using RECIST v1.1. Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, on treatment every 8 weeks and whenever disease progression is suspected (eg, symptomatic deterioration). After 12 months of therapy, imaging can be spaced out to every 12 weeks at the Investigator's discretion. To be repeated at End of Treatment/Withdrawal only if not done in the previous 4 weeks. Confirmation of response (CR/PR) should be done at least 4 weeks after the initial response. The allowable time window for disease assessments is ± 7 days, on treatment, starting from C1D1, except for the first post baseline assessment (+ 7-day window allowed). Timing should follow calendar days and should not be adjusted for delays in cycle starts.

18. Plasma collection: Two Streck tubes will be collected on Cycle 1 Day 1 prior to study drug initiation, on Cycle 1 Day 15 (± 3 days), and at End of Treatment. Buffy coat separated from the same blood collection will be used for tumor-normal sequencing.

19. Tumor biopsy: A pre-treatment and on-treatment tumor biopsy is mandatory if deemed safe (not posing more than minimal additional risk) and feasible by the investigator. The on-treatment tumor biopsy is recommended to be performed on or around Day 15 of therapy, but can be performed at any time on therapy per protocol.

20. Tumor sequencing: If a potential subject has not had FoundationOne tumor sequencing performed, allowing assessment of predicted integrative subtype, this assay may be sent to determine eligibility.

21. Adverse event assessments: Adverse events (AEs) will be documented and recorded at each scheduled or unscheduled visit, including end-of-treatment and during follow-up, using NCI CTCAE v5.0. Subjects will be followed for AEs for 30 days after the last treatment administration or until all drug-related toxicities have resolved (or the Investigator determines in his/her clinical judgment that no further improvement is expected), whichever is later. For serious adverse events (SAEs), the active reporting period will be from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 30 calendar days after the last administration of the investigational product. SAEs experienced by a subject after the active reporting period has ended should be reported if the Investigator becomes aware of them. The reporting period for non-serious AEs will be from the time the subject has taken at least one dose of study treatment through Day 30 after last dose. If a subject begins a new anticancer therapy, the AE reporting period for non-serious AEs will end at the time the new treatment is started.

22. Concomitant medications: Concomitant medications will be recorded from 30 days prior to the start of study treatment through 30 days after the last dose of study treatment. Concomitant medications will be collected at each scheduled or unscheduled visit, including at end-of-treatment. All concomitant medications should be recorded in the CRF including supportive care drugs (eg, anti-emetic treatment and prophylaxis), herbal supplements or vitamins, the drugs used to treat adverse events or chronic diseases, and non-drug supportive interventions (eg, transfusions).

23. End of Treatment: To be performed 0 to 14 days after the decision made to discontinue study drug. Obtain these assessments if not completed during the previous week on study. CT scan should be performed at End of Treatment unless CT scan was performed within the previous 4 weeks.

24. 30-Day Follow-Up Safety Visit: Performed 30 to 37 days after last dose of study drug. Information related to concomitant medications and adverse events will be collected for 30 days after the last dose of the study drug.

25. Follow-Up: Subjects continuing to experience toxicity following discontinuation of study treatment will continue to be followed including for adverse events, at least every week (± 3 days) for 4 weeks, and subsequently every 4 weeks (± 7 days), until resolution or determination, in the clinical judgment of the Investigator, that no further improvement is expected. If a follow-up is required beyond 30 to 37 days after last dose of study drug, not all assessments need to be performed. Only assessments that are clinically indicated are necessary for this timepoint.

10. MEASUREMENTS

10.1 Primary endpoint:

The primary endpoint is the incidence of dose-limiting toxicities (DLTs) in the first 2 cycles of therapy at a specific dose. In Cohort 1, in a subset of subjects who start at infigratinib 100 mg and complete 2 cycles with no DLTs and who remain on study for Cycles 3 and 4, the dose of infigratinib will be increased to 125 mg starting with Cycle 3 and the number of DLTs in Cycles 3 and 4 will be counted toward the primary endpoint (for the 125 mg dose), in addition to the number of DLTs in Cycles 1 and 2 (for the 100 mg dose). For all other subjects, the primary endpoint will be the number of DLTs in Cycles 1 and 2.

DLTs will be graded using NCI CTCAE (Common Terminology Criteria for Adverse Events), v5.0. DLTs will be defined as an adverse event (AE) or abnormal laboratory value at least possibly related to therapy with infigratinib including those AEs and abnormal laboratory values that result in a failure to meet the criteria for re-treatment. The criteria for defining a DLT, which are pre-specified based on the pre-clinical toxicity of infigratinib, are listed in Table 7.

Individual subjects who had a DLT may be retreated, after recovery, at the next lowest dose level.

Investigators will notify QED Therapeutics within 7 days of any DLTs observed.

Table 7. Criteria for defining dose-limiting toxicities

TOXICITY	DLT CRITERION
Skipped/ delayed dose	The inability to administer infigratinib on ≥ 75% of scheduled treatment days during cycle 1 at that dose (ie, ≥ 16 days of the 21 days of planned treatment) due to unresolved adverse event of any grade and considered at least possibly, probably, or definitely related to the study drug. Delay in 2nd cycle administration at that dose due to failure of recovery from a possibly, probably, or definitely related adverse event to Grade ≤ 1 or baseline by Day 43 (Day 28 of Cycle 1 + 15 days), except for alopecia.
Blood/ bone marrow	Neutropenia • Febrile, CTCAE Grade ≥ 3. • CTCAE Grade ≥ 3 for > 7 consecutive days Thrombocytopenia • CTCAE Grade 3 for > 7 consecutive days and/or with signs of clinically significant bleeding. • CTCAE Grade 4 Anemia CTCAE Grade 4
Renal/ genitourinary	Creatinine: • CTCAE Grade 1 for > 7 consecutive days and serum inorganic phosphorus > 5.5 mg/dL and/or serum total calcium x serum inorganic phosphorus > 55 mg^2/dL^2 and despite phosphorus lowering therapy for ≥ 14 days • CTCAE Grade 2 for > 7 consecutive days • CTCAE Grade ≥ 3

Table 7. Criteria for defining dose-limiting toxicities

TOXICITY	DLT CRITERION
Hepatic	Bilirubin: • CTCAE Grade 2 for > 7 consecutive days • CTCAE Grade ≥ 3 AST or ALT: • Grade 3 for > 7 consecutive days • CTCAE Grade 4 Hy's Law • ALT or AST ≥ 3 x upper limit of normal (ULN) **AND** • Serum total bilirubin > 2 x ULN For patients with known hepatic metastases: • AST or ALT > 8 x ULN **OR** • AST or ALT > 5 x ULN for ≥ 14 days
Pancreas	Pancreatitis CTCAE Grade ≥ 2 Amylase/lipase (serum-high): CTCAE Grade ≥ 3 asymptomatic amylase and/or asymptomatic lipase not reversible to CTCAE Grade ≤ 2 within 7 days
Cardiac	QTcF interval > 500ms Other cardiac CTCAE Grade ≥ 3
Constitutional	Fatigue CTCAE Grade 3 for > 7 consecutive days Fatigue CTCAE Grade 4
Ocular/visual	Any ocular/visual toxicity CTCAE Grade ≥ 3.
Gastrointestinal	CTCAE Grade 3 or 4 nausea/vomiting and/or diarrhea despite the use anti-emetic and anti-diarrhea therapy, respectively
Metabolic/ laboratory	Hyperphosphatemia (serum-high): • Serum inorganic phosphorus > 7.0 mg/dL for > 7 consecutive days despite phosphorus-lowering therapy for at least 14 days. • Serum inorganic phosphorus > 9.0 mg/dL, despite phosphorus-lowering therapy for at least 14 days. • Serum inorganic phosphorus > 10.0 mg/dL Hypercalcemia (serum-high) • Serum calcium CTCAE Grade 2 for > 7 consecutive days. • Serum calcium CTCAE Grade ≥ 3.
Other	Any death not clearly due to the underlying disease or known, extraneous causes. Clinical evidence for any grade (CTCAE Grade ≥ 1) of ectopic, *de-novo*-calcification within the soft tissue including the peri-articular spaces and vascular as well as visceral tissues (eg, kidney, lung, stomach, myocardium, etc.) Any other CTCAE Grade 3 or 4 non-hematological toxicity except with following exclusions: • Alkaline phosphatase CTCAE Grade ≥ 3. • Lymphocytopenia CTCAE Grade ≥ 3 unless considered clinically significant.

10.2 Secondary endpoints:

1. Incidence of treatment-emergent adverse events (TEAE). A TEAE is defined as an adverse event with initial onset or increasing in severity after the first dose of study treatment until 30 days after last dose of study drug. TEAEs will be assessed and documented at each scheduled or unscheduled visit during the reporting period. Each TEAE will be assessed according to whether it is serious or non-serious, whether it is expected or unexpected according to the Investigator's Brochure, and whether it is related or unrelated to the study treatment. Each TEAE will be assigned a grade according to CTCAE v5.0. A serious adverse event is one that results in death, is life-threatening, requires in-patient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, may have caused a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage. Pregnancy during the reporting period will be classified as a serious adverse event.
2. Objective tumor response, per RECIST v1.1 (see Appendix C), in subjects with measurable disease. An objective tumor response can be observed at any time on study between 8 weeks after starting therapy (C3D1) through 18 months after starting therapy.
3. Progression-free survival (PFS), defined as the number of days to either progressive disease as defined per RECIST v1.1 or death.
4. Clinical benefit, defined as an objective tumor response or stable disease at 6 months, defined per RECIST v1.1 (see Appendix C).

10.2.1 Measurement Methods

For those subjects with bone-only disease, RECIST v1.1 criteria will not be used to assess response. Subjects will stop study drug at when disease is deemed by the investigator to have progressed.

10.2.2 Measurement Time Points

Antitumor activity will be assessed through radiological tumor assessments conducted at baseline, on treatment every 8 weeks (± 7 days), and whenever disease progression is suspected (eg, symptomatic deterioration). After 12 months of therapy, imaging can be spaced out to every 12 weeks (± 7 days) at the Investigator's discretion. Studies will be repeated at End of Treatment/Withdrawal only if not done in the previous 4 weeks. Confirmation of response (CR/PR) should be done at least 4 weeks after the initial response. Timing should follow calendar days (starting from C1D1) and should not be adjusted for delays in cycle starts.

10.3 Outcomes for ClinicalTrials.gov

The outcomes for ClinicalTrials.gov represent the study objectives.

10.3.1 Primary Outcome

Primary Outcome Title: Dose-limiting Toxicity (DLT)

Primary Outcome Measure Description: The primary outcome for this study is dose-limiting toxicities (DLTs) during the first 2 cycles of therapy at a specific dose. All grades per the Common Terminology Criteria for Adverse Events (CTCAE). DLT is defined as a related and clinically-significant adverse event (AE), including missed doses due to a related AE. Due to limited number of characters that can present in this field, it is not possible to consistently provide additional details across all sub-elements of this outcome. See protocol. The outcome is expressed as the number of DLT events by the assigned infigratinib dose level, a number without dispersion.

Time Frame: 8 weeks.

10.3.2 Secondary Outcomes

1. **Outcome Title**: Treatment-emergent Adverse Events (TEAE)

   Outcome Measure Description: Treatment-emergent adverse events (TEAEs) are defined as adverse events of any grade with initial onset or increasing in severity after the first dose of study treatment until 30 days after last dose of study drug. Pregnancy during the reporting period will be classified as a serious adverse event. The outcome will be expressed as the number of events by the infigratinib dose level at the time of the event, stratified by relatedness and Common Terminology Criteria for Adverse Events (CTCAE) grade. The result is a number without dispersion.

   Time Frame: 2 years

2. **Outcome Title**: Objective Tumor Response

   Outcome Measure Description: Objective tumor response will be assessed as achieving a Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 Complete Response (CR) or a Partial Response (PR). The outcome will be reported as the number of subjects by each participant's final infigratinib dose level that achieve an overall response (OR) to treatment, ie, CR or PR, within 18 months of starting treatment. The outcome will be reported as a number without dispersion. RECIST criteria are:

   • CR = Disappearance of all target lesions

   • PR = ≥ 30% decrease in the sum of the longest diameter of target lesions

   • Overall Response (OR) = CR + PR

   • Progressive disease (PD) = 20% increase in the sum of the longest diameter of target lesions, and/or the appearance of one or more new lesion(s)

   • Stable disease (SD) = Small changes that do not meet any of the above criteria

   Time Frame: up to 18 months

3. **Outcome Title**: Progression-free Survival (PFS)

   Outcome Measure Description: Progression-free survival (PFS) means the subject is alive without return or relapse of the tumor. The outcome is defined as the number of

days to either progressive disease as defined per RECIST v1.1 or death, by each participant's final infigratinib dose level, and reported as the median PFS with full range. RECIST criteria are:

• CR = Disappearance of all target lesions

• PR = ≥ 30% decrease in the sum of the longest diameter of target lesions

• Overall Response (OR) = CR + PR

• Progressive disease (PD) = 20% increase in the sum of the longest diameter of target lesions, and/or the appearance of one or more new lesion(s)

• Stable disease (SD) = Small changes that do not meet any of the above criteria

Time Frame: Up to 2 years.

4. **Outcome Title**: Clinical Benefit

Outcome Measure Description: Clinical benefit will be assessed as achieving a Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 Complete Response (CR) ; Partial Response (PR); or Stable Disease (SD). The outcome will be reported as the number of subjects by each participant's final infigratinib dose level that achieve a CR; PR; or SD, within 6 months of starting treatment. The outcome will be reported by treatment and dose level as a number without dispersion. RECIST criteria are:

• CR = Disappearance of all target lesions

• PR = ≥ 30% decrease in the sum of the longest diameter of target lesions

• SD = Small changes that do not meet any of the above criteria

• Progressive disease (PD) = 20% increase in the sum of the longest diameter of target lesions, and/or the appearance of one or more new lesion(s)

• SD = Small changes that do not meet any of the above criteria

Time Frame: up to 6 months

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

This study will be conducted under IND 147595 for infigratinib (pre-assigned). Infigratinib was approved by FDA as Truseltiq pursuant the Accelerated Approval regulations on 28 May 2021 for the indication of previously-treated, unresectable, locally-advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement, in adults

The protocol, the proposed informed consent and all forms of subject information related to the study (eg, advertisements used to recruit subjects) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data Sharing with Collaborators

Distributor QED Therapeutics expects to share data from this study with the Helsinn Group (collaborator/partner).

11.3 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.4 Data Management Plan

The Protocol Director, or designee, will prepare and maintain adequate and accurate subject case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be created in the Stanford Research Electronic Data Capture (REDCap) and will be maintained by the Protocol Director, co-Protocol Director, and clinical research coordinator team. All subjects will be registered in the OnCore database, allowing the Stanford SRC to judge the aggregate accrual and stopping rules for the study.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design and Sample Size Determination

Statistical analyses of this non-randomized, phase 1B study will be primarily descriptive in nature. Formal statistical methods will not be used to determine the number of subjects per cohort/dose level in this phase 1B study. Summary statistics for discrete variables will be provided as frequencies and for continuous variables as the mean, standard deviation, median, and ranges.

Cohort 1 will utilize the combination of tamoxifen and infigratinib at 3 infigratinib dose levels (125 mg; 100 mg; and 75 mg). This combination may play a role in the future development of infigratinib for hormone receptor-positive breast cancer, necessitating the establishment of their safety. For example, tamoxifen and infigratinib might be used in the early-stage, (neo)adjuvant setting as well as the late-stage, metastatic setting. Therefore, the design is based on patient resources and current drug development.

12.2 Interim analyses

There will be no additional statistical stopping rules other than the 3+3 design rule for Cohort 1 as described in Section 2.5, and there will be no planned interim analysis.

12.3 Descriptive Statistics and Exploratory Data Analysis

The exploratory elements described in Section 1.3 will be included in the descriptive statistics and exploratory data analyses.

12.4 Primary Safety Analysis

Cohort 1 (infigratinib plus tamoxifen) will follow the 3+3 design evaluating 3 infigratinib doses levels, starting at 100 mg infigratinib 3 weeks on/1 week off) and moving to, if needed, 75 mg or 125 mg infigratinib 3 weeks on/1 week off. Given the nature of this cohort to be a safety run-in and the limited number of available subjects for this population, intra-subject dose-escalation will be allowed. The risk with intra-subject dose-escalation is that a dose may be declared overly toxic when the toxicities should be attributed to the number of cycles rather than the dose, but it is believed this is a conservative approach focused on subject safety.

Initially, 3 subjects will be treated at 100 mg for 2 cycles. If there are no DLTs observed in a subject at 100 mg after 2 cycles, the subject will escalate to 125 mg for 2 additional cycles. If 1 DLT is observed at 100 mg, an additional 3 subjects will be treated at 100 mg. If 2 or more DLTs are observed at 100 mg, an additional 3 subjects will be treated at 75 mg. If 1 DLT is observed at 75 mg, an additional 3 subjects will be treated at 75 mg. If no DLTs are observed in the first 3 subjects at 100 mg, but 1 DLT is observed at 125 mg, an additional 3 subjects will be treated at 125 mg. If 2 or more DLTs are observed at 125 mg, Cohort 1 will close. If a dose achieves no DLTs in 3 subjects after 2 cycles or 1 DLT in 6 subjects after 2 cycles, that dose will be declared safe for use in the main phase 2 trial.

If a subject withdraws prior to the completion of the first 2 cycles of therapy without having experienced a DLT, an additional subject will be enrolled at that dose level.

12.5 Secondary Safety Analysis

The secondary safety analysis relates to the incidence of treatment-emergent adverse events (TEAEs). TEAEs are those with initial onset or increasing in severity after the first dose of study treatment. TEAEs will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects who experienced any AE, serious AE (SAE), treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1) in Cohort 1.

Laboratory Test Abnormalities

The number and percentage of subjects who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

12.6 Efficacy Analysis

Tumor response will be presented in the form of subject data listings that include, but are not limited to:

- The classified integrative subtype (IC2 or IC6)
- Received (maximum) dose
- Overall tumor response at each imaging assessment point
- Best overall response

In addition, disease progression date, death date, date of first response, and last tumor assessment date will be listed, together with progression-free survival. A Kaplan-Meier plot will be created for progression-free survival overall, for IC2-classified tumors separately, and for IC6-classified tumors separately.

12.7 Analysis Population

All subjects who received at least one dose of the study drug (infigratinib) will be analyzed for the safety and efficacy outcomes outlined in sections 12.4; 12.5; and 12.6.

12.8 Accrual Considerations

There are approximately 600 new breast cancer patients seen annually at the Stanford Cancer Institute, an estimated 50 percent metastatic and 60% HR-positive, HER2-negative. Based on METABRIC, we estimate that approximately 5% of HR-positive, HER2-negative tumors are integrative subtype 2 and 5% are integrative subtype 6. [2,3] We thus anticipate approximately 20 eligible subjects per year, adequate for the accrual goals. If accrual unexpectedly falls short, additional clinical sites may be added to the study.

12.9 Criteria for future studies

If an MTD for infigratinib in combination with tamoxifen is identified with an acceptable number of DLTs (see Section 12.4), the combination will be deemed acceptable for future studies in this biomarker-selected population of advanced breast cancer. Should this combination prove safe, the study team is planning additional studies to assess efficacy in multiple populations of breast cancer subjects whose tumors harbor FGFR pathway alterations.

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APPENDICES

APPENDIX A: List of prohibited medications and substances

Category	Drug Names
Strong inhibitors of CYP3A4	clarithromycin, conivaptan, fluconazole, fluvoxamine, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, norfloxacin, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole grapefruit, grapefruit juice, grapefruit hybrids, pomegranates, star fruits, pomelos, Seville oranges or products containing juice of these fruits
Strong inducers of CYP3A4	avasimibe, carbamazepine, nevirapine, phenobarbital, phenytoin, pioglitazone, primidone, rifabutin, rifampin, St. John's wort, troglitazone
Medications which increase serum phosphorus and/or calcium	calcium, parathyroid hormone, phosphate, vitamin D (including multivitamins containing vitamin D)
Medications with established potential for QT prolongation or TdP	amiodarone, anagrelide, arsenic trioxide, astemizole (off US market), azithromycin, bepridil (off US market), chloroquine, chlorpromazine, cisapride (off US market), citalopram, clarithromycin, cocaine, disopyramide, dofetilide, domperidone (not on US market), dronedarone, droperidol, erythromycin, escitalopram, flecainide, halofantrine, haloperidol, ibutilide, levofloxacin, levomethadyl (off US market), mesoridazine (off US market), methadone, moxifloxacin, pentamidine, pimozide, probucol (off US market), procainamide (oral off US market), quinidine, sevoflurane, sotalol, sparfloxacin (off US market), sulpiride (not on US market), terfenadine (off US market), thioridazine, vandetanib

Abbreviations: CYP – cytochrome P; TdP – Torsades de Pointes; US – United States.

APPENDIX B: List of drugs to be used with caution while on study

Category	Drug Names
CYP3A substrates with narrow therapeutic index	alfentanil, cyclosporine, diergotamine, dihydroergotamine, ergotamine, fentanyl, sirolimus, tacrolimus, terfenadine, warfarin sodium or any other coumadin-derivative anticoagulants, direct thrombin inhibitors (eg, argatroban), and Factor Xa inhibitors (eg, rivaroxaban)
Moderate inhibitors of CYP3A4	amprenavir, aprepitant, atazanavir, cannabinoids, casopitant, cimetidine, ciprofloxacin, darunavir, diltiazem, fosamprenavir, imatinib, metronidazole, Schisandra sphenanthera, sertraline, suboxone, tofisopam, verapamil, zafirlukast
Moderate inducers of CYP3A4	bosentan, cotrimoxazole, efavirenz, etravirine, ethosuximide, genistein, metyrapone, mexiletine, modafinil, nafcillin, talviraline, tipranavir
Medications which alter the pH of the GI tract [a,b]	antacids, H_2antagonists (eg, ranitidine), proton-pump inhibitors (eg, omeprazole)
Medications that have possible risk of TdP/QT prolongation	alfuzosin, amantadine, atazanavir, chloral hydrate, clozapine, dolasetron, eribulin, famotidine, felbamate, fingolimod, foscarnet, fosphenytoin, gatifloxacin, gemifloxacin, granisertron, iloperidone, indapamide, isradipine, lapatinib, lithium, moexipril, nicardipine, nilotinib, octreotide, ofloxacin, ondansetron, oxytocin, paliperidone, pasireotide, quetiapine, ranolazine, risperidone, roxithromycin, sertindole, sunitinib, tamoxifen, tizanidine, vardenafil, venlafaxine, ziprasidone
Medications that have conditional risk of TdP/QT prolongation	amitriptyline, amisulpride, ciprofloxacin, clomipramine, desipramine, diphenhydramine, doxepin, fluoxetine, galantamine, imipramine, nortriptyline, paroxetine, protriptyline, sertraline, solifenacin, trazodone, trimethoprim-sulfa, trimipramine
BCRP substrates	atorvastatin, irinotecan, methotrexate, rosuvastatin, simvastatin, sulfasalazine, topotecan

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome p; F DA, Food and Drug Administration; GI, gastrointestinal; TdP, Torsades de Pointes

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

[b] If possible, proton pump inhibitors should be avoided due to their long pharmacodynamic effect and replaced with H_2 antagonists or antacids.

APPENDIX C: RECIST v1.1

Measurable Lesions

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5 to 8 mm).
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

Non-measurable disease

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease**:** Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

Normal sites

- Cystic lesions**:** Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes**:** Nodes with short axis < 10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

RECORDING TUMOR ASSESSMENTS

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Target lesions

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

be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce, the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise, a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to < 10 mm (normal), the actual measurement should still be recorded.

Non-target disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

OBJECTIVE RESPONSE STATUS AT EACH EVALUATION.

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

Target disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate: Progression has not been documented; and
    - One or more target measurable lesions have not been assessed; or

- Assessment methods used were inconsistent with those used at baseline; or
- One or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure); or
- One or more target lesions were excised or irradiated and have not reappeared or increased.

Non-target disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (< 10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally, the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example, due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

Supplemental Investigations

If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.

If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

Objective Response Status at each Evaluation			
Target Lesions	**Non-target Lesions**	**New Lesions**	**Objective status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD