Official Title: A Phase 2 Study of Futibatinib in Patients with Specific FGFR Aberrations

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Clinical Study Protocol

A PHASE 2 STUDY OF FUTIBATINIB IN PATIENTS WITH SPECIFIC *FGFR* ABERRATIONS

Futibatinib (TAS-120)

Protocol TAS-120-202

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Amendment 1: 07 February 2020

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Sponsor

Taiho Oncology, Inc.
101 Carnegie Center, Suite 101
Princeton, NJ 08540, USA

This clinical study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) Guidelines and applicable regulatory requirements.

SUMMARY OF CHANGES

The primary purpose of this amendment is to increase the sample size for patients in Cohort A. In addition, the benefit/risk sections and procedures in response to the COVID-19 pandemic have been modified and feedback from regulatory agencies has been incorporated. Substantive changes are described in the table below. All changes have been incorporated into the study synopsis as appropriate; the Table of Contents and list of abbreviations and terms have also been updated when necessary.

In addition to these substantive changes, minor administrative alterations were made as necessary throughout the protocol, including formatting adjustments and correction of typographical errors. These editorial changes do not affect the rationale or planned conduct of the study or analyses.

Section # **Section Name**	**Description of Change**	**Rationale**
Throughout	Changed “trial” to “study” (except when referred to as a clinical trial) Changed “subjects” and “participants” to “patients” (except when referring to healthy subjects) Changed “study therapy/treatment/medication” to “study drug” (except when referring to overall study treatment period) “Tumor response assessment” and “tumor assessment” changed to “response assessment”	Consistency throughout protocol
Throughout	In: Synopsis (Study Objectives and Endpoints – Cohorts A & B), Section 2 (Table 4), Section 11.5.3.1.2 (Secondary Efficacy Analyses) Specified DOR as “Key Secondary” endpoint and other secondary endpoints as “Additional Secondary” for Cohorts A & B	Clarify key secondary endpoint
Throughout	Changed “the signing of the ICF” to “receiving documented informed consent”, “the ICF is signed” / “from the day of ICF signature” / “from when the patient signs the ICF” to “informed consent has been documented”, and “completion of the ICF” to “documented consent”	To align with COVID-19 updates in this amendment
Synopsis Objectives and Endpoints and Table 5	“PopPK and exposure response will be analyzed from blood samples collected during treatment.” in Exploratory Endpoint section changed to “PK data will be pooled with data from other cohorts or other studies for a popPK analysis. The relationship between popPK model derived exposure and response will be explored.”	Align with protocol amendment updates
Synopsis Number of Patients	Updated number of patients in Cohort A from 60 to 100.	Obtain additional safety and efficacy data
Synopsis and 4.1. Inclusion Criteria	Changed “gastric or GEJ cancer” to “gastric or GEJ adenocarcinoma” for Inclusion #5.b.i Added “for Cohorts A and B and bone marrow tissue for Cohort C” to Inclusion #6	Clarified sample collection
Synopsis Evaluation Criteria	Deleted “on-site” from “on-site response assessments” for Cohorts A and B Updated PK description for Cohort C	Clarified evaluation criteria

Section # Section Name	Description of Change	Rationale
Synopsis Statistical Methods	The sample size in Cohort A was increased from 60 to 100 patients. Updated total number of patients from 115 to 155. Added "Additional interim analyses may be performed if required for regulatory purposes." to interim analysis section. Added "per RECIST 1.1" to objective response rate definition in primary efficacy analysis for Cohorts A and B. Updated overall response rate and disease control rate definition in secondary efficacy analyses section. Added "Population PK and Exposure-Response Analyses" section.	Obtain additional safety and efficacy data and clarify timepoints for analysis
Synopsis Population PK and Exposure-Response Analyses	Added section.	Clarified PK analyses
Study Schema (Synopsis and Section 3.1)	Updated Cohort A with new sample size and revised GEJ cancer to GEJ adenocarcinoma in Cohort B.	Align with protocol amendment updates
Schedule of Events	Added "The first study drug administration will occur on C1D1."	Clarified start date
Schedule of Events Table 2 (Cohort C)	"Tumor tissue sample" deleted. PET scan notes updated and added "(+/- 7 days)". Added "visit" to lymph node biopsy "Bone marrow biopsy" changed to "Bone marrow tissue submission" and assessment notes updated and added that archival sample can be used for baseline submission.	Clarified schedule of events
Schedule of Events Table 3 (Study Extension)	Deleted ECOG performance status assessment Added pregnancy testing during treatment period and removed from safety follow-up visit.	Align with protocol amendment updates
List of Abbreviations	Updated with additional terms	Align with protocol amendment updates
3.4 Study Completion and Study Extension	Added "in either Cohort A, B, or C, whichever comes last" to first bullet. Added "The Sponsor will inform study sites when a Study Extension phase is initiated."	Clarified study extension criteria
3.6. End of Trial	Added "The end of the trial will occur when all patients (including patients in the Study Extension phase, if any) have discontinued treatment and undergone all protocol-mandated assessments (including the 30-day Safety Follow-Up Visit)."	Clarified end of study definition
4.2. Exclusion Criteria and Synopsis	Change "and" to "or" in Exclusion #5	Added to exclusion criteria

Section # Section Name	Description of Change	Rationale
Table 7	Changed “permanently discontinue futibatinib” to “consider permanent discontinuation of futibatinib” in Grade 3 toxicity Deleted “however” in Grade 3 toxicity	Clarify discontinuation
Table 8	Removed “Grade” column. Added lab values in rows 3 and 4. Changed “it’s” to “serum phosphate has” in row 4. Footnote removed “c” and updated footnotes accordingly. Removed “regardless of the grade (including Grade 1 and 2)” from Footnote d (currently Footnote c).	Removed grading categories for hyper-phosphatemia
5.4.3 Drug Interactions	Updated drug interaction information	Clarified drug interactions
5.6.4 Accountability	Added “The patient will be provided a diary to record when they have taken the study drug each day.”	Clarified study drug accountability
6.0 Study Assessments Serum Chemistry	Removed “bicarbonate” from Assessment list.	Corrected laboratory tests
6.0 Study Assessment AE monitoring	Removed “through 30 days” and added “until Safety Follow-Up Visit” from Assessment list.	Clarified safety follow-up
6.3 Considerations during the COVID-19 Pandemic	Added section to include text related to implementation of alternate procedures for study conduct during COVID-19.	Added in compliance with FDA and EMA guidelines
7. Pharmaco-kinetics	Updated PK description	Clarified PK analysis
8.1.1 Efficacy Criteria	Added “Planned time points for all efficacy assessments are provided in the Schedule of Events”. Deleted “Primary objective and additional secondary objectives will be assessed by an IRC.”	Added clarification
8.1.3 Tumor Definitions	Added “The following definitions are outlined according to RECIST 1.1 criteria:”	Added clarification
8.3 Efficacy Endpoints	Deleted Table 15 and explanatory text. Referred to Table 4, Section 11.5.3.1.2, and SAP.	Added clarification
9.1 Adverse Events	Added “unless the Investigator deems it related to study drug.” Deleted “For all AEs that occur between signing ICF, there is no need to record those that are unrelated unless it is mandatory by local regulations.”	Added clarification

Section # Section Name	Description of Change	Rationale
9.4.1 Definitions of Serious Adverse Events	Deleted “possibly” statement of SAEs resulting in death.	Added clarification
9.4.2 Reporting of Serious Adverse Events (within 24 hours)	Deleted “of the Safety Follow-up Period”. Added “immediately and no later than” and deleted “within”. Added paragraph on SAE reporting outside of follow-up period.	Added clarification
9.4.3 Reporting of Deaths (within 24 hours)	Added “immediately and no later than” and deleted “within”. Added “Death due to disease progression is not a reportable event, unless the Investigator deems it related to study drug. In the latter case, the event must be reported within 24 hours from the times the Investigator first becomes aware of the death.”	Added clarification regarding reportable deaths
11.1 Estimation of Sample Size	Added subheading for each cohort. The sample size in Cohort A was increased from 60 to 100 patients. Updated total number of patients from 115 to 155. Included additional justification for increase in sample size. Updated Table 15 to reflect n=100.	Obtain additional safety and efficacy data
11.2 Timing of Analysis	Changed heading from “Planned Interim Analysis” to “Timing of Analysis”. Added detailed information about final analyses for each cohort.	Clarify final analyses
11.5 Statistical Analysis	Added “This section outlines the statistical methodology to be used to summarize the study results. A more detailed methodology for summary and stastical analyses of the data collected in this study are documented in the SAP. The SAP will be prepared as a separate document by the Sponsor.”	Added clarification
11.5.3 Efficacy Analyses	Updated table references to Table 4 and Table 5.	Align with amendment
11.5.5 Pharmacokinetic Analysis	Changed “concentration vs time data” to “PK data”	Added clarification
14.2 Documented Informed Consent	Changed Section title. Replaced “written” with “documented” throughout section. Deleted “sign”.	To align with COVID-19 updates in this amendment
16 References	Updated reference list.	Revised for ongoing study
Appendix C.	Replaced reference to FDA Draft Guidance for Industry, Clinical Drug Interaction Studies – Study Design, Data Analysis, and Clinical Implications, October 2017 with FDA Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers. Content current as of: 03/10/2020	Revised reference to current FDA guidance
Appendix C	Added CYP3A Substrates table.	Added to appendix

STUDY SUMMARY

Protocol Synopsis

Protocol Title:

A Phase 2 Study of Futibatinib in Patients with Specific *FGFR* Aberrations

Rationale:

Fibroblast growth factor receptor (*FGFR*) signaling plays a crucial role in cancer cell proliferation, migration, angiogenesis, and survival. Recent studies have uncovered increasing evidence that deregulated FGFRs can function as driving oncogenes in certain tumor types, maintaining the malignant properties of cancer cells. When FGFRs are amplified, rearranged, or undergo fusion, aberrant activation of downstream pathways results in mitogenic, mesenchymal, and antiapoptotic responses in cells. Therefore, FGFRs are attractive targets for therapeutic intervention in cancer treatment.

The Phase 2 study described in this protocol will evaluate the efficacy and safety of futibatinib in patients with *FGFR* aberrations in 3 distinct cohorts. Patients will be enrolled into 1 of 3 cohorts: patients with advanced, metastatic, or locally-advanced solid tumors harboring *FGFR* rearrangements (excluding primary brain tumors and intrahepatic cholangiocarcinoma [iCCA]); patients with gastric or gastro-esophageal junction (GEJ) cancer harboring *FGFR2* amplification; and patients with myeloid or lymphoid neoplasms (MLN) harboring *FGFR1* rearrangements.

Study Objectives and Endpoints:

Cohorts A and B

Primary	
To evaluate the objective response rate (ORR) in patients with solid tumors harboring *FGFR* rearrangements or gastric cancer (including GEJ cancer) harboring *FGFR2* amplifications based on independent central review of radiologic images (IRC)	ORR, defined as the proportion of patients experiencing a best overall response of partial response (PR) or complete response (CR) (per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST 1.1]), based on IRC
Secondary	
Key secondary: • To evaluate duration of response (DOR) based on IRC Additional secondary: • To evaluate ORR based on Investigator assessment • To evaluate progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) • To assess safety and tolerability	• DOR defined as the time from the first documentation of response (CR or PR per RECIST 1.1 based on IRC) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first, based on IRC • ORR, defined as the proportion of patients experiencing a best overall response of partial response of PR or CR (per RECIST 1.1), based on Investigator assessment • DCR, defined as the proportion of patients experiencing a best overall response of stable disease (SD), PR, or CR (per RECIST 1.1), based on IRC • PFS, defined as the time from first dose of study drug to the date of death (any cause) or disease progression (based on IRC), whichever occurs first • OS, defined as the time from the date of first dose to the death date • Safety based on reported AEs and on-study laboratory parameters, graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events, Version 5.0 (NCI-CTCAE V5.0).
Exploratory	
• To assess the possible impact of genetic alterations or other laboratory abnormalities on the efficacy of futibatinib • To assess the population pharmacokinetics (PopPK) and exposure response	• Assessment of genetic alterations in circulating tumor DNA (ctDNA), tumor biopsy, and/or plasma samples, and their possible correlation with clinical outcome. • PK data will be pooled with data from other cohorts or other studies for a popPK analysis. • The relationship between popPK model derived exposure and response will be explored.

Cohort C

Overall Objective The overall objective of Cohort C is to assess the clinical activity of futibatinib as monotherapy in the treatment of patients with myeloid/ lymphoid neoplasms (MLN) harboring *FGFR1* rearrangements.	
Primary	
To evaluate complete response rate	CR rate, defined as the proportion of patients who achieved a CR
Secondary	

• To evaluate:
  ○ ORR
  ○ CR + complete response with incomplete hematological recovery (CRi) rate
  ○ Complete or partial cytogenetic responses (CCyR or PCyR) rate
  ○ Duration of CR
  ○ Duration of CR+CRi
  ○ DOR
  ○ Time-to-events
• To assess the safety and tolerability
	• ORR, defined as the proportion of patients who achieved a CR, CRi, or PR
	• CR+CRi rate, defined as the proportion of patients who achieved a CR or CRi
	• CCyR rate, defined as the proportion of patients who achieved CCyR
	• PCyR rate, defined as the proportion of patients who achieved PCyR
	• Duration of CR defined as the time from the first documentation of CR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• Duration of CR+CRi defined as the time from the first documentation of CR/CRi to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• DOR defined as the time from the first documentation of CR, CRi, or PR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• PFS, defined as the time from first dose of study drug to the date of death (any cause) or disease progression, whichever occurs first
	• Relapse-free survival (RFS), defined as the time from the first documentation of CR to the first documentation of disease relapse or death due to any cause, whichever occurs first.
	• Event-free survival (EFS) (leukemia presentation only), defined as the time from first dose of study drug to treatment failure, disease relapse after CR, or patient death from any cause.
	• OS, defined as the time from the date of first dose to the death date.
	• Safety based on reported AEs and on-study laboratory parameters, graded according to the NCI-CTCAE V5.0

Exploratory	
• To assess the pharmacodynamic effects of treatment with futibatinib • To assess the association of response and mechanisms of resistance in tumor tissue biopsies and/or blood • To assess the popPK and exposure response	• Changes in pharmacodynamic markers assessed in bone marrow tissue biopsies. • Exploratory association of tissue and/or blood markers with tumor efficacy endpoints and/or tumor resistance to futibatinib. • PK data will be pooled with data from other cohorts or other studies for a popPK analysis. • The relationship between popPK model derived exposure and response will be explored.

Overall Design:

Study TAS-120-202 is an open-label, multinational, 3-arm, Phase 2 study evaluating the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of futibatinib in patients with *FGFR* aberrations. Eligible patients will be assigned to 1 of 3 treatment cohorts based on diagnosis and *FGFR* gene aberration status.

Patients will receive futibatinib at an oral dose of 20 mg once a day on a continuous 28-day cycle. Treatment will continue until disease progression, unacceptable toxicity, or any other of the criteria for treatment discontinuation is met (Section 4.4). For patients who discontinue treatment for reasons other than disease progression, response assessments should be continued until radiologic disease progression is documented or until initiation of subsequent new anticancer therapy (whichever occurs first).

Patients will be followed for survival every 12 weeks (±2 weeks) until survival events (deaths) have been reported for 75% of enrolled patients, the patient withdraws consent, or the study is terminated early by the Sponsor.

Additional cohorts may be added in the future in case of new emerging efficacy data. This change will be implemented through a protocol amendment which will describe the rationale for the addition(s).

Number of Patients:

The study will enroll approximately 100 patients with advanced, metastatic, or locally advanced solid tumor harboring *FGFR* rearrangements, except for primary brain tumor or iCCA); 35 patients with advanced, metastatic, or locally advanced gastric or GEJ cancer harboring *FGFR2* amplification; and 20 patients with MLN harboring *FGFR1* rearrangements.

Entry Criteria:

Inclusion Criteria

1. Provide documented informed consent (refer to Section 6.3)
2. ≥18 years of age (or meets the country's regulatory definition for legal adult age, whichever is greater)
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1

4. Has recovered from the acute toxic effects of prior anticancer therapy to baseline or Grade 1 (except toxicities which are not clinically significant such as alopecia)
5. Known *FGFR* aberration status and tumor type that meet all of the criteria for 1 of the following cohorts:
   a. Cohort A
      i. Histologically confirmed, locally advanced, advanced, or metastatic solid tumors harboring a *FGFR1-4* rearrangement determined in tumor tissue using next-generation sequencing (NGS), fluorescence in situ hybridization (FISH), or other assays that can determine gene rearrangements in tumor tissues. Patients with primary brain tumor or iCCA are not eligible.
      ii. Measurable disease per RECIST 1.1
      iii. Had disease progression/recurrence after standard treatment for their advanced or metastatic cancer
   b. Cohort B
      i. Histologically confirmed, locally advanced, advanced, or metastatic gastric or GEJ adenocarcinoma harboring a *FGFR2* amplification. The tumor must have an *FGFR2*/CEN10 ratio of ≥5 or an *FGFR2* copy number ≥10 signals per cell determined in tumor tissue using NGS, FISH, or other assays that can determine gene amplification in tumor tissues.
      ii. Measurable disease per RECIST 1.1
      iii. Received at least 2 prior systemic regimens for advanced/metastatic disease
      iv. Experienced disease progression/recurrence during or after the most recent prior systemic treatment for advanced/metastatic gastric or GEJ cancer
   c. Cohort C
      i. Confirmed MLN with a *FGFR1* rearrangement as defined by WHO criteria
      ii. Not a candidate for hematological stem cell transplant (HSCT) or relapsed after HSCT and donor lymphocyte infusion, and progressed and not a candidate for other therapies
6. Has archival or fresh tumor tissue (preferably in block format) for Cohorts A and B and bone marrow tissue for Cohort C available to send to central laboratory.
7. Adequate organ function as defined by the following criteria:
   a. Cohorts A and B:
      i. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L
      ii. Platelet count ≥75,000/mm^3 (≥75 × 109/L)
      iii. Hemoglobin ≥9.0 g/dL
      iv. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 × upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤5.0 × ULN.
      v. Total bilirubin ≤1.5 × ULN, or ≤3.0 × ULN for patients with Gilbert's syndrome.
      vi. Creatinine clearance (CrCl) (calculated or measured value): ≥40 mL/min. For calculated CrCl, use the Cockcroft-Gault formula (Section 6).
      vii. Phosphorus <1.5 ULN
   b. Cohort C
      i. ALT and AST ≤3.0 × ULN; if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤5.0 × ULN.

ii. Total bilirubin ≤1.5 × ULN, or ≤3.0 × ULN for patients with Gilbert's syndrome.
iii. CrCl (calculated or measured value): ≥40 mL/min. For calculated CrCl, use the Cockcroft-Gault formula (Section 6).
iv. Phosphorus <1.5 ULN

8. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test prior to administration of the first dose of futibatinib. Female patients are not considered to be of child-bearing potential if they are post-menopausal, defined as no menses for 12 months without an alternative medical cause or permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
9. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 90 days after the last dose or longer based on local requirements.
10. Ability to take medications orally (feeding tube is not permitted).
11. Willing and able to comply with scheduled visits and study procedures.

Exclusion Criteria

1. Currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the Investigator and the Sponsor's Medical monitor is required to establish eligibility.
2. History and/or current evidence of any of the following disorders:
   a. Non-tumor related alteration of the calcium-phosphorus homeostasis that is considered clinically significant in the opinion of the Investigator
   b. Ectopic mineralization/calcification including (but not limited to) soft tissue, kidneys, intestine, or myocardia and lung, considered clinically significant in the opinion of the Investigator
   c. Retinal or corneal disorder confirmed by retinal/corneal examination and considered clinically significant in the opinion of the Investigator.
3. Corrected QT interval using Fridericia's formula (QTcF) >470 msec. Patients with an atrioventricular pacemaker or other condition (for example, right bundle branch block) that renders the QT measurement invalid are an exception and the criterion does not apply.
4. Treatment with any of the following within the specified time frame prior to the first dose of futibatinib:
   a. Major surgery within 4 weeks (surgical incision should be fully healed)
   b. Radiotherapy for extended field within 4 weeks or limited field radiotherapy within 2 weeks
   c. A drug that has not received regulatory approval for any indication within 14 or 21 days of treatment for a nonmyelosuppressive or myelosuppressive agent, respectively.
5. Received strong inhibitors or inducers of CYP3A4 within 2 weeks of first dose
6. Prior treatment with an FGFR inhibitor
7. A serious illness or medical condition(s) including, but not limited to, the following:
   a. Known acute systemic infection
   b. Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months
   c. History or current evidence of uncontrolled ventricular arrhythmia
   d. Chronic diarrhea diseases considered to be clinically significant in the opinion of the Investigator
   e. Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death

f. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or futibatinib administration, or may interfere with the interpretation of study results, and in the judgment of the Investigator would make the patient inappropriate for entry into this study

8. Active central nervous system (CNS) metastasis and/or carcinomatous meningitis. Patients with previously treated brain metastases that are clinically and radiologically stable (for at least 4 weeks prior to enrollment) are eligible.
9. Known additional malignancy that is progressing or has required active treatment within the past 2 years. Patients with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
10. Pregnant or breastfeeding.

Evaluation Criteria:

Efficacy

Cohorts A and B

For patients in Cohorts A and B, response assessments (including computed tomography [CT]/magnetic resonance imaging [MRI]) will be performed by the Investigator/local radiologist according to RECIST 1.1 guidelines) (Eisenhauer et al. 2009). Primary objective and additional secondary objectives will be assessed by an IRC.

Results of the local assessments, including response for target and non-target lesions and appearance of new lesions, will be the basis for the continuation or discontinuation of study drug decisions.

Cohort C

Efficacy will be assessed based on Investigators' assessment of imaging, bone marrow, peripheral blood, and extramedullary disease. Depending on the presentation response will be determined based on Treatment Response Criteria for MDS/MPN (Savona et al. 2015), Response Evaluation Criteria in Lymphoma (RECIL 2017) (Younes et al. 2017), and International Working Group (IWG) response criteria for AML (Cheson et al. 2003).

A review of the response assessments will be conducted by an adjudication committee.

Safety

The assessment of safety will be based on the incidence of treatment-emergent adverse events (TEAEs) and on-study laboratory parameters. Grading of TEAEs will be performed using NCI-CTCAE V5.0.

Pharmacokinetics (PK)

The PK population will consist of all patients who received at least one dose of futibatinib and have evaluable PK data.

Pharmacodynamics

Genetic aberrations will be tested using analytically validated assay on NGS or similar technology at a central laboratory.

A blood sample will be collected to assess *FGF/FGFR* aberrations in ctDNA. In addition to assessing ctDNA as a pharmacodynamic biomarker, samples or a set of samples will be used to verify its utility as an alternative to tumor tissues for the potential companion diagnostic. Samples will be collected and stored, as per the laboratory manual, and analyzed in batches.

Archival or fresh tumor/bone marrow samples will be collected during screening to retrospectively confirm *FGFR* gene status at the Sponsor's designated central laboratories. The remaining samples may be stored at the Sponsor's designated central laboratories for up to 10 years after study completion for future testing.

Statistical Methods:

Determination of Sample Size

Approximately 100 patients with solid tumors harboring *FGFR* rearrangements will be enrolled in Cohort A. Sample size considerations are based on differentiating a null ORR of 10% with a target ORR of 25%. Assuming the true ORR is 25%, the study has over 90% power to reject the null hypothesis that the true ORR is ≤10%, considering a 2-sided alpha of 5%.

A 2-stage Simon design (Simon 1989) will be used for futility assessment, comparing a poor response of ≤10% vs a promising response of ≥25%, at a 5% 1-sided significance level and approximate 90% power.

- In Stage 1 (futility assessment), enrollment will include 35 patients and accrual will continue to Stage 2, if at least 4 (11.4%) of 35 patients respond (CR or PR).
- If the Stage 1 futility boundary is exceeded, Stage 2 will be open and require at least 25 additional patients. To further provide a more precise estimate of objective response rate and a better evaluation of safety profile, a total of 100 patients will be enrolled.

Approximately 35 patients with gastric or GEJ cancer harboring *FGFR2* amplification will be enrolled in Cohort B. Sample size considerations are based on differentiating a historical control ORR of 10% or less, with a target ORR of 35%. Assuming the true ORR is 35%, the cohort has approximately 96% power to reject the null hypothesis that the true ORR is ≤10%, considering a 2-sided alpha of 5%. With a sample size of 35, observing at least 8 responders will have a 95% CI lower bound excluding 10% (ORR of 23% with 95% CI [10.4%-40.1%]).

Approximately 20 patients with MLN harboring *FGFR1* rearrangements will be enrolled in Cohort C. Sample size considerations are based on differentiating a historical control CR rate of 10% or less with a target CR rate of 50%. Assuming the true CR rate is 50%, the cohort has over 95% power to reject the null hypothesis that the true CR rate is ≤10%, considering a 2-sided alpha of 5%. Observing at least 6 responders out of 20 treated patients will have a 95% CI lower bound excluding 10% (CR rate of 30% with 95% CI (11.9%-54.3%).

Interim Analysis

The Sponsor will review the data at the time Cohort A has the required number of patients to determine if the cohort should continue. Additional interim analyses may be performed if required for regulatory purposes.

Efficacy Analyses

Cohorts A and B

Primary Efficacy Analysis

Objective response rate is defined as the proportion of patients with objective evidence of CR or PR (per RECIST 1.1). The primary evaluation of ORR will be based on an independent central review of radiologic images. At the analysis stage, the best objective response will be assigned for each patient as the best response recorded after initiation of study drug and confirmed at least 4 weeks later. If applicable, responses recorded after disease progression or initiation of new anticancer treatment will be excluded. The exact 2-sided CI based on Clopper-Pearson methodology will be derived for ORR.

Secondary Efficacy Analyses

Overall response rate and disease control rate (DCR) based on Investigator assessment will be determined (per RECIST 1.1) as described for the primary analysis of ORR based on independent central review of radiologic images (Section 11.5.3.1.1).

Duration of response will only be evaluated in patients with an objective response of CR or PR. Patients who are alive and progression-free as of the analysis cut-off date will be censored at their last evaluable response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last response assessments prior to initiation of the subsequent anticancer therapy.

Progression-free survival will be estimated using the Kaplan-Meier method. Patients who die without a reported disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last response assessment. Patients who did not have any on-study assessments and did not die will be censored on the first dosing date. Patients who started any subsequent anticancer therapy without a prior reported progression will be censored at the last response assessment prior to initiation of the subsequent anticancer therapy.

Overall survival will be analyzed in a similar manner to PFS. In the absence of confirmation of death or for patients who are alive as of the OS cut-off date, survival time will be censored at the last known date that the patient was alive.

Cohort C

Primary Analysis

Complete response rate defined as the proportion of patients who achieved a CR will be calculated and the exact 2-sided CI will also be derived using the Clopper Pearson methodology.

Secondary Analyses

The overall response, CR+CRi (leukemia presentation only), CCyR, and PCyR rates will be calculated and the exact 2-sided CIs will also be derived using the Clopper-Pearson methodology.

Duration of CR (only in patients who achieved a CR), duration of CR+CRi (only in patients who achieved a CR/CRi [leukemia presentation only]), and duration of response (only in patients with an objective response of CR, CRi [leukemia presentation only], or PR) will be estimated using the Kaplan-Meier method. Patients who are alive and progression-free as of the analysis cut-off date will be

censored at their last evaluable response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last response assessments prior to initiation of the subsequent anticancer therapy.

Progression-free survival will be estimated using the Kaplan-Meier method. Patients who die without a reported disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last response assessment. Patients who did not have any on-study assessments and did not die will be censored on the first dosing date. Patients who started any subsequent anticancer therapy without a prior reported progression will be censored at the last response assessment prior to initiation of the subsequent anticancer therapy.

Relapse-free survival will only be evaluated in patients with an objective response of CR and measured from the first date of achieving CR until the first date of relapsed disease or death from any cause, whichever occurs first. Patients who die without a reported disease relapse will be considered to have relapsed on the date of their death. Patients who did not relapse or die will be censored on the date of their last response assessment. Patients who started any subsequent anticancer therapy without a prior reported relapse will be censored at the last response assessment prior to initiation of the subsequent anticancer therapy.

Event-free survival (EFS) will be estimated only for patients with leukemia presentation using the Kaplan-Meier method. EFS is defined as the time from first dose of study drug to treatment failure, relapse after CR (if applicable), or death from any cause, whichever occurs first. For a patient with none of these events before the end of study follow-up, observation of EFS is censored at the date of last contact prior to the analysis cut-off date. If the patient does not achieve a CR, EFS is defined as the point of treatment failure or death, whichever comes first. Treatment failure for EFS is defined as PD in this study.

Overall survival will be analyzed in a similar manner to PFS. In the absence of confirmation of death or for patients who are alive as of the OS cut-off date, survival time will be censored at the last known date that the patient was alive.

Safety Analyses

The safety analysis will be performed using the All Treated Population.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities terminology and the severity of the toxicities will be graded according to the NCI-CTCAE V5.0, where applicable.

Concomitant medications will be coded according to the World Health Organization Drug Dictionary for Concomitant Medication.

All AEs will be summarized (by incidence) and listed by the System Organ Class, Preferred Term, toxicity/severity grade, and causal relationship to futibatinib. In addition, separate summaries of SAEs and Grade 3 and 4 AEs will be presented.

For all AEs that occurred between receiving documented informed consent and the last day of the Safety Follow-up Period, lists of preferred AE terms, grade, onset date, actions, outcome of AE, date of outcome confirmed, causalities with the study drug, and comments on AEs will be listed by patient.

Hematological and chemistry laboratory parameters will be graded according to the NCI-CTCAE V5.0 where applicable. The worst severity grade, time to maximum Grade 3 or 4 value, and time to resolution (return to baseline grade or below) will be summarized.

Safety data (AEs and clinical laboratory results) will be summarized descriptively. A list of 12-lead electrocardiogram findings will be presented by patient.

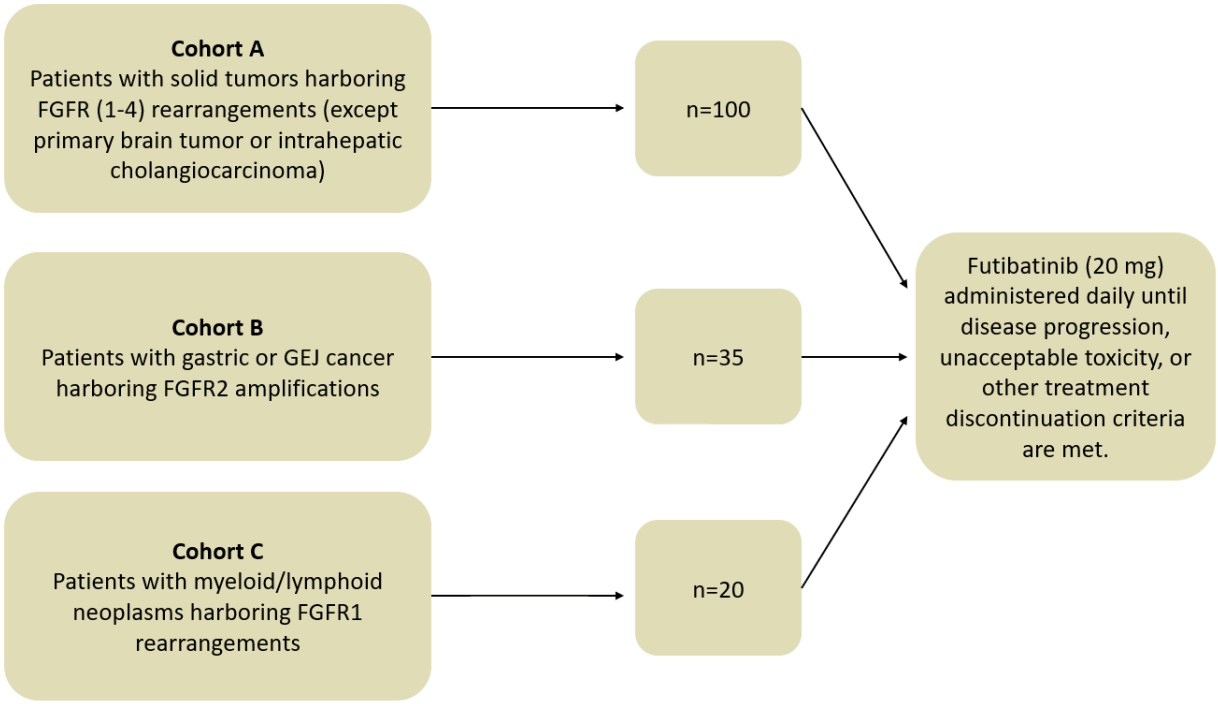
Population PK and Exposure-Response Analyses

PK data will be pooled with data from other studies for a popPK analysis. The relationship between popPK model derived exposure and response will be explored for each cohort. The popPK and Exposure-Response (E-R) analyses will be described in a separate popPK/E-R Analysis Plan.

Pharmacodynamic Analyses

Pharmacodynamic and biomarker data will be summarized descriptively using all patients in the Pharmacodynamic/Biomarker Evaluable Set who have evaluable data available.

Study Schema



Schedule of Events

Evaluations on Day 1 (D1) of a cycle should be performed within 24 hours prior to dosing, unless otherwise noted. Procedures already performed during the screening period within 72 hours prior to dosing do not need to be repeated on Cycle 1 Day 1 (C1D1). The first study drug administration will occur on C1D1. The End of Treatment (EOT) visit must be performed within 7 days after a decision is made to discontinue study drug (for patients who discontinue at a planned study visit, that visit may be considered the EOT visit if all assessments required at EOT are performed). Required assessments for patients in Cohorts A and B are presented in Table 1 and for Cohort C in Table 2. Required assessments during the Study Extension phase are presented in Table 3 for all cohorts.

Table 1: Schedule of Events (Cohorts A and B)

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Documented informed consent	X										Documented informed consent will be obtained prior to any study-related assessments or procedures.
Review eligibility criteria	X										
Demographics/medical history	X										
Review of baseline signs and symptoms	X										
Prior & concomitant medications, AE assessments	→										
Physical examination	X	X				X		X	X		Within 24 hours prior to dosing.
Vital signs	X	X				X		X	X		Heart rate, blood pressure, body temperature, and respiration rate.
Height and weight	X	X				X		X	X		Height at screening only.
ECOG performance status	X	X				X		X	X		Within 24 hours prior to dosing.
12-Lead electrocardiogram	X	X				X		X	X		
Hematology	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing. More frequent assessments may be performed if clinically indicated
Coagulation	X	X				X		X	X		Within 24 hours prior to dosing.
Chemistry (serum or plasma)	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing.

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Pregnancy test	X Within 7 days							X			Serum pregnancy test required for WOCBP. Additional testing may be required by local regulations.
Ophthalmological examination	X			See Note							Examination to be performed by an ophthalmologist or qualified delegate at screening, 4-6 weeks after first dose, and as indicated if symptoms or signs of mineral deposits.
PK blood sampling				See Note							Pre-dose (from -30 min to just before dose), 1 h±30 min post-dose, and 3 h±30 min post-dose
ctDNA blood samples	X							X			
Tumor tissue sample	X										Archival or fresh tumor biopsy
Response assessments (CT/MRI)	X						X	X	X	X	At baseline and the end of every 2 cycles ±7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever comes first). For patients who discontinue treatment for reasons other than radiographic disease progression, imaging will be performed at EOT, (if the prior scan was performed ≥9 weeks) and during Survival Follow-up until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first) unless patient withdraws consent.
Survival status										X	For all patients, unless patient withdraws consent or the study is terminated early by the Sponsor.

Table 2: Schedule of Events (Cohort C)

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Documented informed consent	X										Documented informed consent will be obtained prior to any study-related assessments or procedures.
Review eligibility criteria	X										
Demographics/medical history	X										
Review of baseline signs and symptoms	X										
Prior & concomitant medications, AE assessments	→										
Physical examination	X	X				X		X	X		Within 24 hours prior to dosing.
Vital signs	X	X				X		X	X		Heart rate, blood pressure, body temperature, and respiration rate.
Height and weight	X	X				X		X	X		Height at screening only.
ECOG performance status	X	X				X		X	X		Within 24 hours prior to dosing.
12-Lead electrocardiogram	X	X				X		X	X		
Hematology	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing. More frequent assessments may be performed if clinically indicated
Coagulation	X	X				X		X	X		Within 24 hours prior to dosing.

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Chemistry (serum or plasma)	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing.
Pregnancy test	X Within 7 days							X			Serum pregnancy test required for WOCBP. Additional testing may be required by local regulations.
Ophthalmological examination	X			See Note							Examination to be performed by an ophthalmologist or qualified delegate. At screening, 4-6 weeks after first dose, and as indicated if symptoms or signs of mineral deposits.
PK blood sampling				See Note							Pre-dose (from -30 min to just before dose), 1 h±30 min post-dose, and 3 h±30 min post-dose
ctDNA blood samples	X							X			
CT/MRI	X						X	X	X	X	At baseline and the end of every 2 cycles (±7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever comes first). For patients who discontinue treatment for reasons other than radiographic disease progression, imaging will be performed at EOT, (if the prior scan was performed ≥9 weeks) and during Survival Follow-up until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first) unless patient withdraws consent.

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
PET scan	X				See Note						PET scan to be performed at baseline visit, end of Cycle 1 (± 7 days) if baseline is abnormal, and as clinically indicated for response assessment.
Lymph node biopsy	X	See Note									Recommended at baseline visit if lymph node present at baseline and progression
Bone marrow tissue submission	X	See Note									Archival or fresh bone marrow biopsy tissue sample needs to be submitted at baseline visit. In addition, bone marrow biopsy should be performed in case of normalization of peripheral blood count during the futibatinib treatment. In absence of peripheral blood count normalization, biopsy to be performed every 6 months. Additional biopsies to be performed as clinically indicated.
Survival status										X	For all patients, unless patient withdraws consent or the study is terminated early by the Sponsor.

Table 3: Schedule of Events – Study Extension Phase: All Cohorts

	Treatment Period **At Least Every 3 Cycles**	**Safety Follow-up** **30 (+7) Days After last Dose**	**Notes**
Physical examination	X	X	Within 24 hours prior to dosing on D1
Vital signs	X	X	Heart rate, blood pressure, body temperature, and respiration rate.
Weight	X	X	
Ophthalmological examination	(X)	X	As needed due to local requirements, physician judgment, and/or symptoms or signs of mineral deposits.
12-Lead electrocardiogram	X	X	
Hematology and coagulation	X	X	Within 24 hours prior to dosing on D1
Chemistry (serum or plasma)	X	X	Within 24 hours prior to dosing on D1
Pregnancy test	X		More frequently if required by local regulations.
Prior & concomitant medications, AE assessments	(X)	X	Collect from the time main informed consent is signed through 30 days after administration of the last dose of study drug or until the start of new anticancer therapy, whichever is earlier.
Response assessments/imaging	(X)		All Cohorts: CT/MRI scans at baseline and the end of every 2 cycles (±7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever comes first). Cohort C only: bone marrow, PET, and other response assessments as clinically indicated.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BCR	Breakpoint cluster region (gene)
BCRP	Breast cancer resistance protein
CCA	Cholangiocarcinoma
CI	Confidence interval
CR	Complete response
CCyR	Complete cytogenetic response
COVID-19	Coronavirus Disease of 2019
CrCl	Creatinine clearance
CRc	Cytologic complete response per IWG response criteria for AML (Cheson et al. 2003)
CRi	Complete response with incomplete hematological recovery
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450

Abbreviation	Definition
DCR	Disease control rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event-free survival
EMA	European Medicines Agency
EOT	End of treatment/end of therapy
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor receptor
FISH	Fluorescence in situ hybridization
GEJ	Gastro-esophageal junction
GCP	Good Clinical Practice
HSCT	Hematological stem cell transplant
IB	Investigator's Brochure
iCCA	Intrahepatic cholangiocarcinoma
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Central Review Committee

Abbreviation	Definition
MLN	myeloid/lymphoid neoplasms
MPN	Myeloproliferative neoplasms
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NGS	Next generation sequencing
ORR	Objective response rate
OS	Overall survival
PCyR	Partial cytogenetic response
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetics
PR	Partial response
RECIL	Response Evaluation Criteria in Lymphoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RFS	Relapse-free survival
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease

Abbreviation	Definition
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TOI	Taiho Oncology, Inc.
ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. INTRODUCTION

Futibatinib is a novel and selective small molecule irreversible, covalent inhibitor of fibroblast growth factor receptor (*FGFR*) 1–4 that is currently being tested in patient with different cancers.

Evolving knowledge of the molecular and genetic basis of cancer has led to refinements in the categorization of malignancies based on molecular markers. This, in turn, has led to changes in study design, specifically tumor agnostic studies that enroll patients with the same genetic alterations but not the same histologic or anatomic tumor type. These studies are important because they provide insight into the importance of a genomic alteration across various histologic tumor types and allow for the development of more targeted therapies (Lacombe et al. 2014).

1.1. Disease Background

FGFR signaling plays a crucial role in cancer cell proliferation, migration, angiogenesis, and survival. Recent studies have uncovered increasing evidence that deregulated *FGFRs* can function as driving oncogenes in certain tumor types, maintaining the malignant properties of cancer cells (Turner & Grose 2010). When *FGFRs* are amplified, rearranged, or undergo fusion, aberrant activation of downstream pathways results in mitogenic, mesenchymal, and antiapoptotic responses in cells. Therefore, FGFRs are attractive targets for therapeutic intervention in cancer (Turner & Grose 2010).

FGFR aberrations were found in 7.1% of cancers, with the majority being gene amplifications (66%), followed by mutations (26%) and rearrangements (8%) (Helsten et al. 2016).

Although they are rare, *FGFR2* fusions with multiple partners have been uncovered in many types of cancer, including cholangiocarcinoma (CCA), lung cancer, thyroid cancer, breast cancer, and prostate cancer (Wu et al. 2013; Gallo et al. 2015; Yoshihara et al. 2015). Of all the *FGFRs*, *FGFR2* shows the broadest range of fusion partners. Fusion genes have also been reported in bladder cancer and urothelial carcinoma (Williams et al. 2013; Loriot et al. 2019). It is clear that *FGFR* fusions are emerging as a new class of targetable fusions in solid tumors.

Amplification of *FGFR2* has been described in 4-10% of gastric cancer, particularly of the aggressive diffuse subtype (Deng et al. 2012; Kunii et al. 2008; Jung et al. 2012; Liu et al. 2014). Each year, approximately 990,000 people are diagnosed with gastric cancer worldwide, and about 738,000 people die from this disease (Ferlay et al. 2010), making gastric cancer the fourth most common cancer and the second most common cause of cancer death (Jemal et al. 2010). While the incidence of gastric cancer has been decreasing, the incidence of gastro-esophageal junction (GEJ) cancer doubled in Western countries from the 1970s to the 1990s, with rates stabilizing today (Buas & Vaughan, 2013).

In vitro, *FGFR2*-amplified gastric cancer cell lines have been shown to be selectively sensitive to the inhibitory effects of *FGFR* tyrosine kinase inhibitors (Kunii et al. 2008).

Myeloid and lymphoid neoplasms with abnormalities of the *FGFR1* gene have been recognized as a distinct disease group in the 2008 World Health Organization (WHO) classification of hematopoietic neoplasms (Bain et al. 2008). These myeloproliferative neoplasms are characterized by eosinophilia, lymphadenopathy, and a high incidence of T-cell non-Hodgkin

lymphoma with progression to acute myeloid leukemia (MacDonald et al. 1995). They occur over a wide age range of 3 to 84 years, with a median of 44 years, and with a very slight male predominance (male to female ratio of 1.2:1) (Jackson et al. 2010). This is a very rare disease, with fewer than 100 patients reported around the world (MacDonald et al. 2002; Jackson et al. 2010). There is a marked absence of curative treatments for these patients. Of the 4 FGFRs, FGFR2 and FGFR3 have been identified as having comparatively more frequent gene rearrangements (Courjal et al. 1997). However, although hematopoietic neoplasms with *FGFR1* rearrangements are uncommon entities, they are extremely aggressive and resistant to standard treatments. One of the most frequently observed cytogenetic abnormalities is t(8;22) (p11.2;q11.2). The t(8;22) abnormality results in an in-frame fusion of FGFR1 on 8p11 and the breakpoint cluster region (BCR) gene on 22q11. The resultant fusion proteins activate tyrosine kinases, which may result in the development of hematologic malignancies (Villafuerte-Gutiérrez et al. 2018).

This Phase 2 clinical trial will investigate the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of futibatinib in patients with tumors harboring specific *FGFR* aberrations. Patients will be enrolled into one of 3 cohorts: patients with solid tumors harboring *FGFR* rearrangements (excluding primary brain tumors and intrahepatic CCA [iCCA]); patients with gastric or GEJ cancer harboring *FGFR2* amplification; and patients with myeloid or lymphoid neoplasms (MLN) harboring *FGFR1* rearrangement.

1.2. Futibatinib (TAS-120)

1.2.1. Clinical Overview

As of 5 September 2019, a total of 460 subjects (41 healthy volunteers and 419 patients) have been treated with futibatinib across 4 clinical trials.

- Study 10059010 is an ongoing, Phase 1 study being conducted in Japan to evaluate the PK, safety, and preliminary efficacy of futibatinib in patients with advanced solid tumors administered futibatinib three times a week (doses 8 to 240 mg) or daily (QD, doses 8 to 120 mg). The most frequently reported treatment-emergent AEs (TEAEs) (>20% of all patients at all dose levels) were hyperphosphatemia, decreased appetite, diarrhea, constipation, nausea, stomatitis, and vomiting. Adverse events were mainly Grade 1 or 2.
- Study TAS-120-101 is an ongoing, 3-part global study to evaluate the PK, safety, and efficacy of futibatinib administered 3 times a week (doses 8 to 200 mg) or QD (doses 4 to 24 mg):
  - Phase 1 Dose Escalation (completed with a total of 86 patients receiving either daily or 3-times-per-week dosing)
  - Phase 1 Dose Expansion, which includes additional cohorts in CCA, gliomas, urothelial carcinoma, and basket cohorts with *FGF/FGFR* aberrations
  - Phase 2 study initiated in April 2018, evaluating futibatinib at a QD dose of 20 mg, in patients with iCCA harboring *FGFR2* gene rearrangements

  - The most frequently reported TEAEs (>20%) in patients administered futibatinib 20 mg QD (recommended Phase 2 dose) were hyperphosphatemia, diarrhea, constipation, nausea, dry mouth, increased ALT, increased AST, and fatigue.

- Study 10059020, a Phase 1, PK, and bioequivalence study in healthy adult males. This completed study compared two futibatinib formulations and found them to be biologically equivalent.
- Study TAS-120-102, a food effect study in healthy adult subjects. This completed study evaluated the effect of food on the PK of futibatinib under fasting or fed conditions and demonstrated that PK was affected by the consumption of a high-fat, high-calorie meal.

Efficacy has been observed in different tumor types:

- Solid tumors harboring *FGFR* rearrangements, including iCCA, head and neck, unknown primary, and gastric cancer
- Gastric cancer with *FGFR2* amplification
- MPN with *FGFR1* rearrangement
- Other solid tumors with different FGFR aberrations

Refer to the current Investigator's Brochure (IB) for more detailed background information on futibatinib.

1.3. Summary of Study Rationale

Based on available preclinical and clinical data to date, the Sponsor concludes that the benefit-risk assessment results of futibatinib support the continued enrollment and treatment of patients in clinical trials and supports further investigation of futibatinib in tumors with *FGFR* aberrations.

The Phase 2 study described in this protocol will evaluate the efficacy and safety of futibatinib in patients with *FGFR* aberrations in 3 distinct cohorts.

Based on prior safety and efficacy experience in the broad Phase 1 dose escalation and expansion study, a dose of 20 mg QD of futibatinib has been selected for use in this Phase 2 study. The study drug is administered continuously without interruption. Treatment cycles of 28 days will be used to define the protocol specified interval for tumor measurement and other interventions.

2. OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study are shown in Table 4 and Table 5.

Table 4: Objectives and Endpoints (Cohorts A and B)

Primary	
To evaluate the objective response rate (ORR) in patients with solid tumors harboring *FGFR* rearrangements or gastric cancer (including GEJ cancer) harboring *FGFR2* amplifications based on independent central review of radiologic images (IRC)	ORR, defined as the proportion of patients experiencing a best overall response of partial response (PR) or complete response (CR) (per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST 1.1]), based on IRC
Secondary	
Key secondary: • To evaluate duration of response (DOR) based on IRC Additional secondary: • To evaluate ORR based on Investigator assessment • To evaluate progression-free survival (PFS), disease control rate (DCR), and overall survival (OS) • To assess safety and tolerability	• DOR defined as the time from the first documentation of response (CR or PR per RECIST 1.1 based on IRC) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first, based on IRC • ORR, defined as the proportion of patients experiencing a best overall response of partial response of PR or CR (per RECIST 1.1), based on Investigator assessment • DCR, defined as the proportion of patients experiencing a best overall response of stable disease (SD), PR, or CR (per RECIST 1.1), based on IRC • PFS, defined as the time from first dose of study drug to the date of death (any cause) or disease progression (based on IRC), whichever occurs first • OS, defined as the time from the date of first dose to the death date • Safety based on reported AEs and on-study laboratory parameters, graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events, Version 5.0 (NCI-CTCAE V5.0),
Exploratory	
• To assess the possible impact of genetic alterations or other laboratory abnormalities on the efficacy of futibatinib • To assess the population pharmacokinetics (popPK) and exposure response	• Assessment of genetic alterations in circulating tumor DNA (ctDNA), tumor biopsy, and/or plasma samples, and their possible correlation with clinical outcome. • PK data will be pooled with data from other cohorts or other studies for a popPK analysis. • The relationship between popPK model derived exposure and response will be explored

Table 5: Objectives and Endpoints: Cohort C

Overall Objective The overall objective of Cohort C is to assess the clinical activity of futibatinib as monotherapy in the treatment of patients with MLN harboring *FGFR1* rearrangements.	
Primary	
To evaluate complete response (CR) rate	CR rate, defined as the proportion of patients who achieved a CR.
Secondary	

• To evaluate:
  o ORR
  o CR + complete response with incomplete hematological recovery (CRi) rate
  o Complete or partial cytogenetic responses (CCyR or PCyR) rate
  o Duration of CR
  o Duration of CR+CRi
  o DOR
  o Time-to-events
• To assess the safety and tolerability
	• ORR, defined as the proportion of patients who achieved a CR, CRi, or PR
	• CR+CRi rate, defined as the proportion of patients who achieved a CR or CRi
	• CCyR rate, defined as the proportion of patients who achieved CCyR
	• PCyR rate, defined as the proportion of patients who achieved PCyR
	• Duration of CR defined as the time from the first documentation of CR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• Duration of CR+CRi defined as the time from the first documentation of CR/CRi to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• DOR defined as the time from the first documentation of CR, CRi, or PR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• PFS, defined as the time from first dose of study drug to the date of death (any cause) or disease progression, whichever occurs first
	• Relapse-free survival (RFS), defined as the time from the first documentation of CR to the first documentation of disease relapse or death due to any cause, whichever occurs first.
	• Event-free survival (EFS) (**leukemia presentation only**), defined as the time from first dose of study drug to treatment failure, disease relapse after CR, or patient death from any cause.
	• OS, defined as the time from the date of first dose to the death date.
	• Safety based on reported AEs and on-study laboratory parameters, graded according to the NCI-CTCAE V5.0.

Exploratory	
• To assess the pharmacodynamic effects of treatment with futibatinib • To assess the association of response and mechanisms of resistance in tumor tissue biopsies and/or blood • To assess the popPK and exposure response	• Changes in pharmacodynamic markers assessed in bone marrow tissue biopsies. • Exploratory association of tissue and/or blood markers with tumor efficacy endpoints and/or tumor resistance to futibatinib. • PK data will be pooled with data from other cohorts or other studies for a popPK analysis. • The relationship between popPK model derived exposure and response will be explored.

3. INVESTIGATIONAL PLAN

3.1. Overview of Study Design

Study TAS-120-202 is an open-label, multinational, 3-arm, Phase 2 study evaluating the efficacy, safety, tolerability, PK, and pharmacodynamics of futibatinib in patients with *FGFR* aberrations. Eligible patients will be assigned to 1 of 3 treatment cohorts based on diagnosis and *FGFR* gene aberration status (Figure 1):

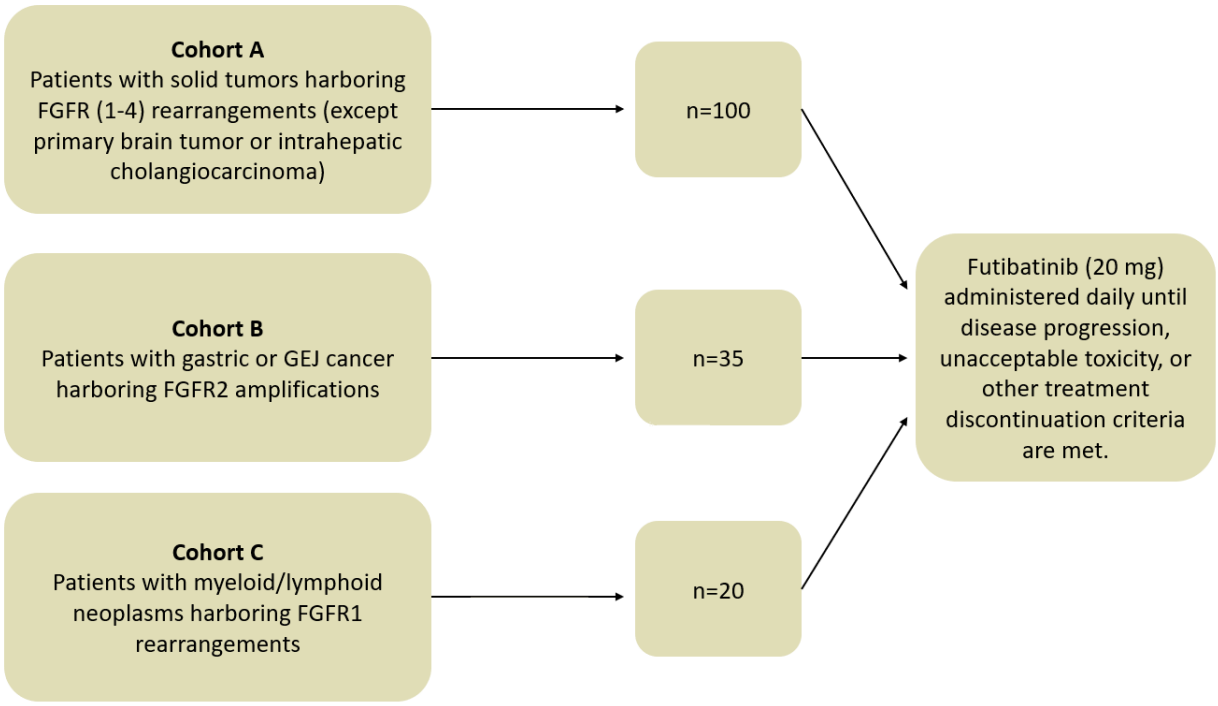

Figure 1: Study Schema

Patients will receive futibatinib at an oral dose of 20 mg once a day on a continuous 28-day cycle.

Treatment will continue until disease progression, unacceptable toxicity, or any other of the criteria for treatment discontinuation is met (Section 4.4). For patients who discontinue treatment for reasons other than disease progression, response assessments should be continued until disease progression is documented or until initiation of subsequent new anticancer therapy (whichever occurs first).

Patients will be followed for survival every 12 weeks (±2 weeks) until survival events (deaths) have been reported for at least 75% of enrolled patients in each Cohort, the patient withdraws consent, or the study is terminated early by the Sponsor.

Additional cohorts may be added in the future in case of new emerging data. This change will be implemented through a protocol amendment which will describe the rationale for the addition(s).

3.2. Scientific Rationale for Study Design

Please see Section 1.3.

3.3. Study Periods and Visits for Each Patient

The study periods / visits described in this section are defined for all patients. Please see the schedule of events for an outline of all assessments to be performed during each study period / visit.

For all patients, the Safety Assessment Period begins at the time informed consent has been documented and continues until at least 30 days after the last dose of futibatinib. After the 30-day Safety Follow-Up Visit (see below), patients who have not started treatment with a new anticancer therapy will be assessed for drug-related serious adverse events (SAEs) only.

For each patient, the Study Duration is defined as the time informed consent has been documented to the last day of Disease Assessment Follow-up / Survival Follow-up (see below).

3.3.1. Screening Period

The Screening Period is defined as the time informed consent has been documented to when they receive the first dose of futibatinib. Determination of eligibility is based on the entry criteria enumerated in Section 4. No protocol-specific procedures or assessments may be performed prior to documented consent, except for procedures that represent standard-of-care.

3.3.2. Treatment Period and End of Treatment Visit

Treatment discontinuation may occur for any of the reasons listed in Section 4.4. The treatment period is the time from first dose of futibatinib (Day 1) to the date of last dose of futibatinib. An end-of-treatment (EOT) visit must be performed within 7 days after the decision is made to discontinue futibatinib; at this visit, every effort should be made to perform the assessments outlined in the schedule of events. For patients who discontinue at a planned study visit, that visit may be considered the EOT visit if all assessments required at EOT are performed.

3.3.3. Safety Follow-Up Period and 30-Day Safety Follow-Up Visit

The Safety Follow-Up Period is the time from the date of last dose of study drug through the 30-Day Safety Follow-Up Visit, which must be performed 30 days (+7 days) following the last dose of study drug. If the patient starts new anticancer therapy within 30 days of the last dose of study drug, the 30-Day Safety Follow-Up Visit should be performed before the start of new anticancer therapy. Every effort should be made to perform the assessments outlined in the schedule of events. If the patient is unable to return to the study site, a follow-up phone call can

be made by the study site to collect any new safety information that occurred during the Safety Follow-up Period.

After the 30-Day Safety Follow-Up Visit (see below), patients who have not started treatment with a new anticancer therapy will be assessed for drug-related SAEs only.

3.3.4. Post-Discontinuation Considerations

Patients who discontinue without documented disease progression should continue to undergo response assessments according to the Schedule of Events (that is, every 8 weeks ±7 days) until progressive disease (PD) is documented, new anticancer therapy is initiated, the study is terminated, or the patient dies, withdraws consent, or is lost to follow-up).

3.3.5. Survival Follow-Up

Once a patient discontinues study treatment, regardless of the reason, Survival Follow-Up will begin, unless the patient withdraws consent or the study is terminated early by the Sponsor. During this period, the patient or family should be contacted for Survival Follow-Up every 12 weeks (±2 weeks) until survival events (deaths) have been reported for 75% of enrolled patients, patient withdraws consent or the study is terminated early by the Sponsor. In addition, all subsequent anticancer treatments will be recorded.

3.4. Study Completion and Study Extension

The study will be considered complete when:

- Survival events (deaths) have been reported for at least 75% of enrolled patients in either Cohort A, B, or C, whichever comes last; or
- The study is halted early for any reason.

Following Study Completion, patients deriving benefit from study drug in the opinion of the Investigator and Sponsor may be permitted to continue treatment with futibatinib in a Study Extension phase. The Sponsor will inform study sites when a Study Extention phase is initiated. During Study Extension, patients may receive treatment until withdrawal criteria are met and study drug is available.

All safety assessments are to be continued according to the Study Extension phase schedule (Table 3). Specifically, study extension data collection is to include, at a minimum:

- Study drug administration
- Study drug accountability
- Serious adverse events
- Non-serious AEs that are related to study drug or result in treatment discontinuation
- Any cases of pregnancy or overdose

3.5. Patient Enrollment

Eligibility must be verified prior to patient enrollment. Patients will be enrolled via an Interactive Voice/Web Response System (IXRS). The patient should receive the first dose of study drug within 3 days following enrollment.

3.6. End of Trial

The end of the trial will occur when all patients (including patients in the Study Extension phase, if any) have discontinued treatment and undergone all protocol-mandated assessments (including the 30-Day Safety Follow-Up Visit).

4. SELECTION AND WITHDRAWAL OF PATIENTS

Results of *FGFR* gene aberration status should be available before the patient undergoes any protocol-specific procedures. Waivers will not be granted for any of the eligibility criteria.

4.1. Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Provide documented informed consent (refer to Section 6.3)
2. ≥18 years of age (or meets the country's regulatory definition for legal adult age, whichever is greater)
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
4. Has recovered from the acute toxic effects of prior anticancer therapy to baseline or Grade 1 (except toxicities which are not clinically significant such as alopecia)
5. Known *FGFR* aberration status and tumor type that meet all of the criteria for one of the following cohorts:
   - **a. Cohort A**
     - i. Histologically confirmed, locally advanced, advanced, or metastatic solid tumors harboring a *FGFR1-4* rearrangement determined in tumor tissue using next-generation sequencing (NGS), fluorescence in situ hybridization (FISH), or other assays that can determine gene rearrangements in tumor tissues. Patients with primary brain tumor or iCCA are not eligible.
     - ii. Measurable disease per RECIST 1.1
     - iii. Had disease progression/recurrence after standard treatment for their advanced or metastatic cancer
   - **b. Cohort B**
     - i. Histologically confirmed, locally advanced, advanced, or metastatic gastric or GEJ adenocarcinoma harboring a FGFR2 amplification. The tumor must have an FGFR2/CEN10 ratio of ≥5 or an FGFR2 copy number ≥10 signals per cell determined in tumor tissue using NGS, FISH, or other assays that can determine gene amplifications in tumor tissues.
     - ii. Measurable disease per RECIST 1.1
     - iii. Received at least 2 prior systemic regimens for advanced/metastatic disease
     - iv. Experienced disease progression/recurrence during or after the most recent prior systemic treatment for advanced/metastatic gastric or GEJ cancer.
   - **c. Cohort C**
     - i. Confirmed MLN with a FGFR1 rearrangement as defined by WHO criteria
     - ii. Not a candidate for hematological stem cell transplant (HSCT) or relapsed after HSCT and donor lymphocyte infusion, and progressed and not a candidate for other therapies.
6. Has archival or fresh tumor tissue (preferably in block format) for Cohorts A and B and bone marrow tissue for Cohort C available to send to central laboratory.

7. Adequate organ function as defined by the following criteria:
    a. **Cohorts A and B:**
        i. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L
        ii. Platelet count ≥75,000/mm^3 (≥75 × 10^9/L)
        iii. Hemoglobin ≥9.0 g/dL
        iv. ALT and aspartate aminotransferase (AST) ≤ 3.0 × upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤5.0 × ULN.
        v. Total bilirubin ≤1.5 × ULN, or ≤3.0 × ULN for patients with Gilbert's syndrome.
        vi. Creatinine clearance (CrCl) (calculated or measured value): ≥40 mL/min. For calculated CrCl, use the Cockcroft-Gault formula (Section 6).
        vii. Phosphorus <1.5 ULN
    b. **Cohort C**
        i. ALT and AST ≤3.0 × ULN; if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤5.0 × ULN.
        ii. Total bilirubin ≤1.5 × ULN, or ≤3.0 × ULN for patients with Gilbert's syndrome.
        iii. CrCl (calculated or measured value): ≥40 mL/min. For calculated CrCl, use the Cockcroft-Gault formula (Section 6).
        iv. Phosphorus <1.5 ULN
8. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test prior to administration of the first dose of futibatinib. Female patients are not considered to be of child-bearing potential if they are post-menopausal (no menses for 12 months without an alternative medical cause) or permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
9. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 90 days after the last dose or longer based on local requirements.
10. Ability to take medications orally (feeding tube is not permitted).
11. Willing and able to comply with scheduled visits and study procedures.

4.2. Exclusion Criteria

A patient must not meet any of the following exclusion criteria to be eligible for participation in this study:

1. Currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the Investigator and the Sponsor's Medical monitor is required to establish eligibility.

2. History and/or current evidence of any of the following disorders:
    a. Non-tumor related alteration of the calcium-phosphorus homeostasis that is considered clinically significant in the opinion of the Investigator.
    b. Ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, or myocardia and lung, considered clinically significant in the opinion of the Investigator.
    c. Retinal or corneal disorder confirmed by retinal/corneal examination and considered clinically significant in the opinion of the Investigator.
3. Corrected QT interval using Fridericia's formula (QTcF) >470 msec. Patients with an atrioventricular pacemaker or other condition (for example, right bundle branch block) that renders the QT measurement invalid are an exception and the criterion does not apply.
4. Treatment with any of the following within the specified time frame prior to the first dose of futibatinib:
    a. Major surgery within 4 weeks (surgical incision should be fully healed)
    b. Radiotherapy for extended field within 4 weeks or limited field radiotherapy within 2 weeks
    c. A drug that has not received regulatory approval for any indication within 14 or 21 days of treatment for a nonmyelosuppressive or myelosuppressive agent, respectively
5. Received strong inhibitors or inducers of CYP3A4 within 2 weeks
6. Prior treatment with an FGFR inhibitor
7. A serious illness or medical condition(s) including, but not limited to, the following:
    a. Known acute systemic infection
    b. Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months
    c. History or current evidence of uncontrolled ventricular arrhythmia
    d. Chronic diarrhea diseases considered to be clinically significant in the opinion of the Investigator
    e. Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death
    f. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or futibatinib administration, or may interfere with the interpretation of study results, and in the judgment of the Investigator would make the patient inappropriate for entry into this study
8. Active central nervous system (CNS) metastasis and/or carcinomatous meningitis. Patients with previously treated brain metastases that are clinically and radiologically stable (for at least 4 weeks prior to enrollment) are eligible.

9. Known additional malignancy that is progressing or has required active treatment within the past 2 years. Patients with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
10. Pregnant or breastfeeding.

4.3. Screen Failure

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE after completion of the ICF.

Patients who do not meet the criteria for participation in this study (screen failure) may be rescreened a maximum of 3 times. Rescreened patients should be assigned the same patient identification code as for the initial screening.

4.4. Discontinuation of Treatment

A patient will be discontinued from all study drug for any of the following reasons:

1. Disease progression
2. Unacceptable AEs, or change in underlying condition such that the patient can no longer tolerate therapy, as evidenced by a dose delay >28 days from the scheduled start date of the next cycle or need for more than 2 dose reductions outlined in this protocol
3. Physician's decision, including need for other anticancer therapy not specified in the protocol or surgery or radiotherapy to the only site(s) of disease being followed in the study
4. Pregnancy
5. Termination of the study by the Sponsor
6. At the patient's request at any time irrespective of the reason

Patients who withdraw consent for further treatment may choose to remain on study; in such a case, all study evaluations should continue as outlined in this protocol. If the patient withdraws consent to all follow-up assessments, the patient should be considered to have discontinued the study as described in Section 4.5.

4.5. Withdrawal from the Study

A patient will be withdrawn from all study interventions and assessments (that is, discontinued from the study without follow-up) for any of the following reasons:

1. Death
2. Lost to follow-up

- A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
- The following actions must be taken if a patient fails to return to the clinic for a required study visit:
  - The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
  - Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
  - Should the patient continue to be unreachable, they will be considered to have withdrawn from the study.

3. Patient withdrawal of consent to further follow-up assessments, irrespective of the reason.

5. STUDY TREATMENT

5.1. Study Drug Administration

A study cycle is defined as 28 days. Futibatinib is supplied as 4 mg tablets and will be taken orally at a dose of 20 mg daily until the patient meets any of the administration discontinuation criteria (see Section 4.4).

Futibatinib should be administered under fasting conditions. It should be taken with a glass of water, on an empty stomach, at the same time each day. No food should be consumed for 2 hours prior and 1 hour after the dose of futibatinib, but patients may drink water during this period.

When a PK sample is collected, futibatinib should be administered on site after collection of the first PK sample.

In the event of a dosing delay up to 12 hours after the scheduled dosing time, the patient should still take that day's dose. If the dosing delay continues for >12 hours after the scheduled dosing time, or if the patient vomits after a dose, the patient should skip dosing for that day and not make up for it the following day.

5.2. Dose and Schedule Modifications

Stepwise dose reductions of 4 mg to 16 mg (first reduction) and 12 mg (second reduction) are permitted based on toxicities. If dose reduction fails to result in achieving the minimal criteria to resume treatment or, if toxicities occur which would necessitate reduction of the dose of futibatinib below 12 mg QD, the patient should be discontinued from futibatinib.

Following a dose reduction, if a benefit/risk assessment favors an increase of futibatinib dose up to the initial starting dose (20 mg QD), an agreement with the Sponsor's Medical monitor is required prior to the dose increase.

If toxicities related to the dose reduction do not recover based on the criteria defined below within 28 days after the last dose of futibatinib, the patient will be discontinued permanently from treatment (Section 4.4). If resumption criteria are met within 28 days of the last dose of futibatinib, the patient may resume futibatinib treatment at the appropriate dose level.

5.2.1. Dose Modifications for Nonhematologic Toxicities

Dosing modification guidelines for nonhematologic and ocular toxicities are provided in Table 6 and Table 7, respectively.

Recommendations for hyperphosphatemia management are provided in Table 8. These are suggested guidelines based on emerging data from studies evaluating *FGFR* inhibitors and studies of futibatinib (Appendix B).

Table 6: Dose Modifications for Related Nonhematologic Toxicities

Grade[a]	**Dose Interruption/Resumption**	**Dose Adjustment**
Grade 1 or 2	Maintain treatment at the same dose level	None
Grade 3	Withhold treatment until return to baseline or Grade ≤1	Reduce by 1 dose level from the previous level. For Grade 3 nausea, vomiting, and/or diarrhea lasting >72 hours despite optimal medical management require withhold of treatment and dose reduction by one level.
Grade 4	Discontinue treatment	Permanent discontinuation of futibatinib.
Grade 4 (lab abnormality AE)	Withhold treatment until return to baseline or Grade ≤1	Futibatinib will be permanently discontinued if assessed by the Investigator as life-threatening. If it is in the best interest of the patient to continue treatment in the opinion of the Investigator and after discussion with the Sponsor, the patient can continue treatment at a reduced dose level. However, futibatinib should first be held until toxicity returns to baseline or Grade ≤1.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase.

[a] Interrupt futibatinib if any toxicities are intolerable, regardless of the grade (including Grade 1 and 2). If or when the toxicity resolves to a tolerable state, consideration can be given to resuming futibatinib at the same dose if deemed appropriate or reduced by one dose level if needed.

Table 7: Dose Modifications for Related Ocular Toxicities

Grade and Definition	Study Drug Management[a]
Grade 1	If there is no evidence of ocular toxicity on ophthalmologic examination, continue futibatinib therapy at the same dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as central serous retinopathy (CSR)/ retinal pigment epithelial detachments (RPED), withhold futibatinib until signs and symptoms have resolved. If toxicity is reversible (complete resolution or stabilization and asymptomatic) in 4 weeks according to ophthalmologic examination, resume futibatinib therapy at the next lower dose level after consultation with the Sponsor's Medical monitor. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence then re-escalation can be considered in consultation with the Sponsor's Medical monitor.
Grade 2	Withhold futibatinib therapy. If there is no evidence of drug-related corneal or retinal pathology on ophthalmologic examination, withhold futibatinib until signs and symptoms have resolved. Resume futibatinib therapy at the next lower dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality, withhold futibatinib until signs and symptoms have resolved or stabilized. If toxicity is Grade 2 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks according to ophthalmologic examination, resume futibatinib therapy at the next lower dose level after consultation with the Sponsor's Medical monitor. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence then re-escalation can be considered in consultation with the Sponsor's Medical monitor.
Grade 3	If the toxicity is Grade 3, report as an SAE and consider permanent discontinuation of futibatinib. If the toxicity is Grade 3 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks and the patient is receiving clinical benefit, and the Investigator and the Sponsor's Medical monitor agree that re-starting drug is in the best interest of the patient, then futibatinib therapy may be resumed at 2 dose levels lower if appropriate. Monitor for recurrence using appropriate investigations every 1 to 2 weeks for a month and as clinically appropriate thereafter. For cases of recurrence, consider permanent discontinuation.
Grade 4	Permanently discontinue treatment with futibatinib. Report as an SAE and monitor resolution of the event until complete resolution, stabilization, or the patient is lost to follow-up or withdraws consent (whichever happens first).

[a] If a patient has been deriving benefit from treatment, and the Investigator can demonstrate that reintroduction of study drug is in the best interest of the patient considering the terminal nature of the disease, the drug may be reintroduced at a lower dose and/or intensity if the Sponsor's Medical monitor is in agreement with this assessment. With appropriate re-consenting, the patient can be re-treated with a 1- or 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the Investigator. The Investigator should also have the patient re-consent, explaining that reintroduction of study drug could lead to increased risk of recurrence.

Table 8: Recommendations for Hyperphosphatemia Management

Serum Phosphorus Result[a] **(mg/dL and mmol/L)**[b]	**Futibatinib Dose Interruption and Modification**[c, d, e, f] **Recommended Phosphate Binder for Management of Hyperphosphatemia**[f]
ULN < P <5.5 (mg/dL) ULN < P <1.78 (mmol/L)	No interruption, consider phosphate binder once serum phosphorus level is > ULN. Should serum phosphorus level rapidly increase within 1 week, consider early phosphate-lowering therapy; eg, Sevelamer tablets 800 mg three times per day [TID]. Reassess serum phosphate within 7 days.
5.5 ≤ P ≤7.0 (mg/dL) 1.78 ≤ P ≤2.26 (mmol/L)	No interruption, implement phosphate binder (monotherapy or in combination). Start with Sevelamer monotherapy (range from 800 mg TID to 2400 mg TID). Reassess serum phosphate within 7 days. Escalate Sevelamer or add treatment with acetazolamide 250 mg QD or TID and/or lanthanum carbonate (Fosrenol®) 1.0 g QD or TID, and further titration,[c] if phosphate level continues to increase.
7.0 < P ≤10.0 (mg/dL) 2.26< P ≤3.23 (mmol/L)	Dose reduce futibatinib to the next lower dose level and intensify phosphate-lowering therapy. Reassess serum phosphate within 7 days and at least once a week. If the serum phosphorus level has resolved to ≤5.5 mg/dL/1.78 mmol/L within 14 days after dose reduction, continue futibatinib at the reduced dose level. If the serum phosphorus level has not resolved to ≤5.5 mg/dL/1.78 mmol/L after 14 days, further reduce futibatinib from the last reduced dose level (or no lower than 12 mg QD). If the serum phosphorus level has not resolved to ≤5.5 mg/dL/1.78 mmol/L after 14 days of the second dose reduction of futibatinib (or no lower than 12 mg QD), interrupt dosing with futibatinib until it is resolved to ≤5.5 mg/dL/1.78 mmol/L before resuming futibatinib at the reduced dose prior to dose interruption.
P >10.0 (mg/dL) P >3.23 (mmol/L)	Interrupt futibatinib until serum phosphate has resolved to ≤5.5 mg/dL/1.78 mmol/L, then resume futibatinib at the next lower dose level and intensify phosphate-lowering therapy. Reassess serum phosphate within 7 days and at least once a week. If after 2 dose interruptions and 2 dose reductions the serum phosphorus level has not resolved to ≤5.5 mg/dL/1.78 mmol/L after 14 days, permanently discontinue futibatinib.

Abbreviations: P=phosphorus; QD=once a day; TID=three times a day; ULN=upper limit of normal

[a] Serum phosphorus will be tested 4 days (± 24 hours) after Day 1 of Cycle 1 to initiate early intervention for hyperphosphatemia if indicated.

[b] mmol/L=mg/dL x 0.3229 (conversion factor).

[c] Interrupt futibatinib if any toxicities are intolerable. If or when the toxicity resolves to a tolerable state, consideration can be given to resuming futibatinib at the same dose if deemed appropriate or reduced by one dose level if needed.

[d] Serum calcium levels should be assessed at the same time.

[e] Futibatinib will be permanently discontinued if ectopic mineralization or calcification associated with hyperphosphatemia and considered clinically significant are observed.

[f] Phosphate binders can be used as monotherapy or in combination. Please consult the drug package insert. Sevelamer should be preferably taken in the middle of meals, both tablets and powder, in order to improve gastrointestinal tolerance and compliance. If Sevelamer cannot be used, other phosphate binders or hyperphosphatemia treatment drugs can be used. Lanthanum carbonate should be taken instead just after meals—tablets of Fosrenol® are quite big, but can be cut if required. No dose adjustments are needed in patients with renal or hepatic impairment.

[g] Titrate the dose every 2-3 weeks until an acceptable serum phosphate level is reached.

5.2.2. Dose Modifications for Hematologic Toxicities

Criteria for dose interruption and resumption for hematologic toxicities for patients in Cohorts A and B are presented in Table 9. For patients in Cohort C, dose modifications will be made at the Investigator's discretion.

Table 9: Futibatinib Dose Interruption and Modification Criteria for Related Hematologic Toxicities for Patients in Cohorts A and B

CTCAE Grade (value)	Recommended dose modification any time during a cycle of futibatinib[a]
Anemia (Hgb)	
Grade 1 (Hgb < LLN - 10.0 g/dL)	Maintain dose level
Grade 2 (Hgb <10 – 8.0 g/dL)	Maintain dose level
Grade 3 (Hgb <8.0 - 6.5 g/dL)	Withhold dose until resolved to ≤ Grade 1 or baseline, • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Grade 4 (life-threatening consequences; urgent intervention indicated)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce 1 dose level
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC <1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC <1000 - 500/mm^3)	Maintain dose level
Grade 4 (ANC <500/mm^3)	Withhold dose until resolved to ≤ Grade 2 or baseline • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Febrile neutropenia (ANC <1000/mm^3 with a single temperature of ≥38.3°C [101°F] or a sustained temperature of ≥38° C [100.4°F])	Withhold dose until resolved, then reduce 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT <75,000 - 50,000/mm^3)	Maintain dose level
Grade 3 (PLT <50,000 - 25,000/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Grade 4 (PLT <25,000/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce 1 dose level

Abbreviations: ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; Hgb=hemoglobin; LLN=lower limit of normal; PLT=platelets

[a] Interrupt futibatinib if any toxicities are intolerable, regardless of the grade (including Grade 1 and 2). If or when the toxicity resolves to a tolerable state, consideration can be given to resuming futibatinib at the same dose if deemed appropriate or reduced by one dose level if needed.

5.2.3. Dose Modifications in Case of Induced Drug Liver Injury (Hy's Law)

Futibatinib will be permanently discontinued if liver function test abnormalities fulfill Hy's Law criteria defined as:

Concurrent observation of the following, with no other reason found to explain the findings (such as viral hepatitis A, B, or C, preexisting or acute liver disease, liver metastases, or another drug capable of causing the observed liver injury):

- Elevated aminotransferase enzymes of >3 x ULN
- Alkaline phosphatase (ALP) <2 x ULN
- Associated with an increase in bilirubin ≥2 x ULN

5.3. Treatment Compliance

Each patient will be instructed to comply with the dosing regimen of futibatinib.

Compliance with all study drug administration should be documented in the patient's source documents (Section 5.6.3).

5.4. Concomitant Medications and Therapies

5.4.1. Prohibited Medications and Therapies

Patients are not permitted to receive any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers, or antineoplastic endocrine therapy during the study treatment period.

Extended-field radiation therapy or palliative radiation to a focal site of measurable disease is also prohibited. If it is deemed in the best interest of the patient and after discussion between the Investigator and Sponsor's Medical monitor, it can be administered, but the patient will be censored for the primary endpoint analysis.

5.4.2. Concomitant Medications and Therapies Requiring Precautions

Supportive treatment is allowed based on available institutional or local guidelines.

Local or regional palliative cryotherapy or radiation, such as for bone pain or palliative surgery (non-antineoplastic intent), are permitted (provided the target lesion is not a site of measurable disease and is not indicative of disease progression). Study drug should be ceased a minimum of 2 days prior to administration of palliative treatment, and may be resumed 7 days after the procedure or when the patient has recovered from the side effects of the procedure.

The following medications/therapies may be given concomitantly under the following guidelines:

Hematologic Support: May be administered as medically indicated (that is, blood transfusions, granulocyte colony-stimulating factor, erythropoietin stimulating agents) according to the institutional site standards or American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2015).

Management of Diarrhea: Prophylactic treatment for diarrhea is permitted during the study if clinically indicated according to the institutional or published guidelines (Benson et al. 2004).

Management of Nausea/Vomiting: Antiemetics may be administered as clinically indicated according to institutional standards or ASCO guidelines (Hesketh et al. 2017).

5.4.3. Drug Interactions

The following information is based on results from in vitro studies and clinical pharmacology studies of drug interactions in humans. Futibatinib is a substrate of CYP3A and moderate-to-strong inhibitors or inducers of CYP3A have potential clinical drug-drug interactions with futibatinib. Caution is advised if these drugs are given concomitantly (see Appendix C , Classification of Substrates, Inhibitors, and Inducers of CYP Enzymes and Transporters).

Moderate and strong CYP3A inducers: The results of Study TAS-120-103 showed a strong CYP3A inducer decreased futibatinib AUC by approximately 64%. A moderate CYP3A inducer was predicted to decrease futibatinib AUC by approximately 48%.

Moderate and strong CYP3A inhibitors: The results of Study TAS-120-103 showed a strong CYP3A inhibitor increased futibatinib AUC by approximately 41%. A moderate CYP3A inhibitor was predicted to increase futibatinib AUC by approximately 20% to 40%.

Strong CYP3A inhibitors and inducers (see Appendix C) should be avoided or substituted with other concomitant therapies while receiving futibatinib, if possible. However, if concomitant use with a strong CYP3A inhibitor cannot be avoided, futibatinib dose reductions should be considered by the investigator, considering the patient's individual benefit/risk and discussed with the Sponsor. The patient should be closely monitored for any AEs. Please see Section 5.2 for recommended dose modifications.

Additionally, in vitro studies have shown potential drug-drug interactions may occur with concomitant use of futibatinib and those drugs that are P-gp or BCRP substrates/inducers. Futibatinib is a potential inhibitor of P-gp and BCRP, and a substrate of P-gp and BCRP in vitro. Futibatinib may alter the PK of P-gp and BCRP substrates. P-gp and BCRP inhibitors may affect the PK of futibatinib. Caution is advised if these drugs are given concomitantly.

5.5. Effective Contraception During Study

Female patients considered not to be of child-bearing potential must have a history of being postmenopausal (no menses for 12 months without an alternative medical cause), or hysterectomy that is clearly documented in the patient’s source documents.

For WOCBP, including female patients and partners of male patients, effective contraception is required during the study and for 90 days after the last dose of study drug, or longer if necessary based on local requirements. Effective contraception is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal

  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner with documentation of the success of the vasectomy
- Complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Male patients, unless sterile (vasectomy with post-procedure semen analysis), with partners who are WOCBP should use a male condom in combination with at least one of the effective contraception methods during the study and for 90 days or longer based on local requirements after the last dose of study drug. Donation of sperm or ova is not allowed during the study and for 90 days or longer based on local requirements following the last dose of study drug.

5.6. Study Drug Materials and Management

Futibatinib will be supplied by the Sponsor. Detailed information such as the requirements for accountability and disposal of study drug can be found in the Pharmacy Manual, which will be provided separately.

5.6.1. Description of Study Drug

Futibatinib will be provided as 4-mg tablets for oral use. Please refer to the IB for additional information.

5.6.2. Packaging and Labeling

Futibatinib will be packaged and labelled according to local laws and regulations.

5.6.3. Storage

Futibatinib tablets should be stored in accordance with the label.

5.6.4. Accountability

The Investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. All study drugs will be stored and disposed of according to the Sponsor's instructions. The dispensing of study drug to the patient and the return of study drug from the patient must be documented in the patient’s source documents. The patient will be provided a diary to record when they have taken the study drug each day. Patients must be instructed to return all original containers, whether empty or containing study drug.

At the conclusion of the study, all study drugs supplied by the Sponsor must be destroyed or returned to the designated depot, per the instructions provided in the Pharmacy Manual.

6. STUDY ASSESSMENTS

The Schedule of Events (Table 1 for Cohorts A and B, Table 2 for Cohort C, and Table 3 for Extension Phase) summarizes the frequency and timing of all applicable study assessments, including allowable windows for study visits and assessments / procedures. Documented informed consent must be provided before any study-related procedures are performed.

Any AEs directly associated with a screening procedure should be reported as described in Section 9.2.

Assessment	Details
Review of inclusion/exclusion criteria	See Section 4.1 and 4.2. Eligibility must be confirmed prior to first dose of study drug.
Demographics/medial history	Sex, age, clinical diagnosis, date and method of diagnosis, prior cancer therapy, relevant medical history (past and concurrent)
Baseline signs and symptoms	Signs and symptoms occurred after informed consent has been documented but before administration of first dose of futibatinib.
Physical examination	
Vital signs	Pulse rate, systolic and diastolic blood pressure, body temperature, and respiration rate. Any abnormal reading should be repeatedly immediately.
Height and body weight	Height is collected for the purpose of body mass index calculations at baseline only.
ECOG performance status	See Appendix A.
12-lead electrocardiogram	Single, resting, semirecumbent 12-lead electrocardiogram will be performed locally. Data collection includes RR interval (heart rate), QT interval, QTcF interval, and abnormal findings. The Investigator is responsible for interpreting and measuring electrocardiogram data.
Hematology	Red blood cell count, hemoglobin, hematocrit, platelets, white blood cell count with differential, neutrophils (ANC), lymphocytes, monocytes, eosinophils, basophils
Serum chemistry	AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, lactate dehydrogenase, inorganic phosphorus, triglyceride, total cholesterol, creatinine, urea or blood urea nitrogen, sodium, potassium, chloride, calcium (corrected value), magnesium, blood glucose, uric acid For a calculated creatinine clearance (CrCl) value, use the Cockcroft-Gault formula: Male CrCl (mL/min) = Body wt (kg)×(140-age)[72×serum creatinine (mg/dL)] Female CrCl (mL/min) = male CrCl×0.85
Coagulation	Prothrombin time-international normalized ratio, activated partial thromboplastin time, fibrinogen
Pregnancy test	Serum β human chorionic gonadotrophin (human chorionic stimulating hormone) test required for WOCBP
Ophthalmological examination	See Section 6.1
PK blood sampling	See Section 7.

Assessment	Details
Pharmacodynamic biomarker blood sampling	See Section 10
Efficacy assessments	See Section 8.
Concomitant medication/concomitant therapy	Including all medications / therapies administered from the time informed consent has been documented through 30 days after administration of the last dose of study drug or until the start of new anticancer therapy.
AE monitoring	All AEs will be collected from the time informed consent has been documented until Safety Follow-Up Visit is completed after the last dose of any study drug (safety follow-up) or until the start of new anticancer therapy, whichever is earlier. See Section 9.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CrCl=calculated creatinine clearance; ICF=informed consent form; QT = QT interval; QTcF = Fridericia's Correction Formula; RR=intra-beat; WOCBP=women of childbearing potential

6.1. Ophthalmological Examination

The cornea and conjunctiva are readily visible tissues and, therefore, abnormalities of the cornea and conjunctiva can usually be recognized via external ocular examination and routine slit lamp biomicroscopy. The retina is visible through fundoscopy after dilation of the pupil. Ophthalmologic examination will be performed by an ophthalmologist or qualified delegate at screening and 4-6 weeks after first dose; additional on-study evaluation as needed due to physician judgment and/or symptoms or signs of mineral deposits.

Each evaluation will encompass:

- External ocular examination
- Routine slit lamp biomicroscopy of anterior ocular structures, including the anterior and posterior chambers (Fluorescein or rose Bengal or other dyes used to evaluate the ocular surface can be used according to institutional guidelines and local clinical practice)
- Dilation of the pupil with direct/indirect fundoscopy per institutional guidelines and local clinical practice

6.2. Laboratory Assessments

All laboratory assessments will be performed locally. The laboratory must provide normal reference ranges for hematology, chemistry, and coagulation tests. If justified (eg, deterioration of the patient’s health conditions and/or distance from the clinical site) and allowed by the country and institution, laboratory tests performed by external laboratories may be used for the study. However, laboratory reference ranges and accreditation are required. All laboratory test results (internal or external) must be reviewed for clinical significance by the Investigator.

Any clinically significant events must be followed and reported as required by the protocol (please see Section 9.3.1).

6.3. Considerations during the COVID-19 pandemic

During the COVID-19 pandemic, patients will be enrolled at the Investigator's discretion considering patient's benefit and risk and the availability of staff at the study sites. The Sponsor will perform a risk assessment of the study on an ongoing basis and prioritize patient safety to ensure:

- The protection of patient safety, particularly if scheduled visits to the site are postponed
- The uninterrupted supply of drug to patients who continue to benefit from it, while assuring safety, even if they are encouraged to remain at home (guidance will be provided to the site)
- The collection of safety and efficacy data, even if patients cannot keep their scheduled visits to the study site.

The following considerations may be applied in accordance with individual site policies and guidelines from regulatory authorities (FDA 2021, EMA 2021). The Sponsor will continue to follow regulatory guidelines for any updates related to the COVID-19 pandemic. If planned on-site monitoring visits are no longer possible, the Sponsor will consider optimizing the use of central and/or remote monitoring programs to maintain oversight of study sites. Alternative approaches will be implemented to maintain patient safety and study data quality and integrity, such as enhanced central monitoring, telephone contact with the sites to review study procedures, patient status and study progress, or remote monitoring of individual enrolled patients, where appropriate and feasible.

- If a patient is unable to sign the informed consent in person, their consent may be obtained electronically or remotely via phone call or video call.
- If a patient is unable to attend a scheduled on-site study visit and/or complete any protocol-required study assessments, the Sponsor should be contacted for further review.
- To ensure compliance with the protocol-required laboratory tests and assessments, the possibility for these tests to be performed at a local qualified laboratory or facility will be evaluated. The results of any tests or assessments performed by a local laboratory or facility must be communicated to the Investigator and documented in the patient's source files and the eCRF.
- If it is not possible to have assessments performed at a local facility, the patient may be evaluated for safety via a phone call or video call, assuring the collection and follow-up of adverse events is documented in the patient's source file. All C1 assessments need to be performed. For C2 and beyond, a patient will not receive additional treatment without having laboratory and ECG assessments performed at least once during each cycle (eg, on C1D1).
- Response assessments will need to be performed, as often as the circumstances allow, according to the protocol. If the patient is not able to visit the study site, alternatively, a local qualified imaging facility can be used.

- The results, including the images obtained from all radiographic procedures, should be sent to the Investigator. The imaging facility used, the timepoints, and the Investigator's review of the images should be documented in the patient's source files and the eCRF.
- If a patient is diagnosed with COVID-19 or develops symptoms suggesting COVID-19, patients will be managed according to local guidelines. Symptomatic COVID-19 cases will be reported as AEs or SAEs; it is at the Investigator's discretion to report asymptomatic COVID-19 cases. In the case of patients diagnosed with COVID-19 (symptomatic or asymptomatic), patients can only continue treatment with futibatinib if the Investigator considers that there is an individual positive risk/benefit balance, and once the patient has fully recovered from the COVID-19 infection. The Sponsor should be made aware of the Investigator's decision.

7. PHARMACOKINETICS

The PK population will consist of all patients who received at least one dose of futibatinib and have evaluable PK data for analysis. Blood samples will be obtained from all patients at the timepoints listed in Table 10 and used to determine plasma futibatinib concentrations.

In the event that a patient interrupts treatment after the pre-dose sample is collected and restarts the treatment at a later date, a pre-dose sample should be collected.

Table 10: Pharmacokinetic Blood Sample Collection

Day of Study (Time Window)	**Collection Time Point (hours) in Relation to Futibatinib Administration (Time Window)**
Day 15 of Cycle 1 (± 3 days)	Pre-dose (from -30 min to just before dose)
	1 hour ±30 min post-dose
	3 hours ±30 min post-dose

8. EFFICACY EVALUATIONS

8.1. Cohorts A and B

8.1.1. Efficacy Criteria

For patients in Cohorts A and B, response assessments (including CT/MRI) will be performed by the Investigator/local radiologist according to RECIST 1.1 guidelines (Eisenhauer et al. 2009). Planned time points for all efficacy assessments are provided in the Schedule of Events.

Results of the local assessments, including response for target and non-target lesions and appearance of new lesions, will be the basis for the continuation or discontinuation of study drug decisions.

If the Investigator determines that a patient has developed clinical disease progression manifested by symptomatic deterioration but not supported by radiologic evidence of progression, the patient may stop treatment. Symptoms of clinical disease progression must be documented in the patient's source documents and must be reported as AEs. Every effort should be made to document objective disease progression even after discontinuation of treatment.

Note that patients who discontinue without documented disease progression should continue to undergo response assessments/scans according to the Schedule of Events until PD is documented, new anticancer therapy is initiated, the study is terminated, or consent is withdrawn.

8.1.2. Method of Imaging

The same method of assessment and same technique should be used to characterize each identified and reported lesion at each assessment timepoint. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of treatment. All measurements should be recorded in metric notation using a ruler or calipers.

Contrast-enhanced CT scans or MRIs are the preferred methods for response assessments. If a contrast agent is contraindicated in a patient, obtain a non-contrast chest CT and enhanced MRI of the abdomen (and pelvis if clinically indicated). A spiral CT should be performed using a ≤5 mm contiguous reconstruction algorithm. Images must be acquired of the chest and abdomen (and pelvis if clinically indicated or obtained at baseline visit) at each time point. Only CT scans and MRI may be used for tumor measurement.

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules or palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Ultrasound should not be used to measure tumor lesions that are clinically not easily accessible for overall response evaluation (eg, visceral lesions). Ultrasound is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. For additional guidance, refer to RECIST 1.1 specifications for standard anatomical radiological imaging.

8.1.3. Tumor Definitions

The following definitions are outlined according to RECIST 1.1 criteria:

Measurable Lesions: Only measurable lesions can be selected as target lesions.

- Measurable visceral lesions: Lesions that can be accurately measured in at least 1 dimension with the longest diameter (to be recorded) ≥10 mm by CT scan if using slice thickness of ≤5 mm, or at least double the slice thickness of the CT or MRI scan if the slice thickness is >5 mm.
- Measurable pathological lymph nodes: A malignant lymph node must be considered pathologically enlarged with high suspicion of metastasis and measure ≥15 mm in the short axis when assessed by CT scan. The short axis is defined as the longest linear dimension perpendicular to the node's longest diameter as assessed within the same plane that the scan was acquired.

Non-measurable Lesions: All non-measurable lesions can only be selected as non-target lesions.

- Small visceral metastatic lesions that have a longest dimension <10 mm, or if slice thickness is >5 mm, less than twice the slice thickness
- Abnormal and suspected metastatic lymph nodes that are ≥10 mm to <15 mm in the short axis
- Truly non-measurable lesions (eg, ascites and peritoneal carcinomatosis)

Target Lesions:

- All measurable lesions up to a maximum of 2 lesions/organ and 5 lesions in total, representative of all involved organs/tissues should be identified as target lesions
- Target lesions should be selected on the basis of their size (visceral lesion with the longest diameter and lymph node with the measurement of short axis), be representative of all involved organs/tissues, but in addition should be those that lend themselves to reproducible repeated measurements
- When recording tumor measurements, the longest diameter will be measured for each non-nodal target lesion. For measurable pathological lymph nodes that may be identified as target lesions, the short axis measurement will be combined with the measurements of non-nodal (ie, visceral lesion) target lesions. Therefore, in cases of CR when abnormal nodes have been used as target lesions, the sum of diameters will not reduce to a null value.
- Target lesions will be followed up and measured at each subsequent timepoint.
- The sum of the diameters for all target lesions will be calculated and recorded. The baseline sum will be used as a reference to further characterize any objective response assessment in the measurable dimension of the disease.
- Assign a measurement to all target lesions regardless of size. An option of "too small to measure" will be provided if a measurement cannot be assigned. A value of zero should only be assigned in the case of a CR.

- An option of "not assessable" for a lesion will only apply to lesions that cannot be read due to technical reasons including:
  - CT artifact
  - Patient positioning where the lesions are obstructed or cannot be seen
  - Lesions that may not be seen in their entirety due to CT slice thickness
- In cases where a lesion divides into 2 lesions, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- In cases where 2 lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Non-target Lesions:

- Non-target lesions include all non-measurable lesions and measurable lesions that have not been selected as target lesions.
- The primary lesion should always be classified as a non-target lesion irrespective of its size and whether or not it can be accurately measured.
- Lymph nodes that have a short axis <1 mm are considered non-pathological and should not be recorded.
- Any equivocal lesion without clear diagnosis (eg, uncharacteristic solitary lung nodule without biopsy, uncharacteristic thyroid mass lesion without fine needle aspiration) may be considered a non-target lesion if it cannot be differentiated from a benign lesion.
- All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, but their presence, absence, or unequivocal progression should be followed throughout the study.
- It is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (eg, multiple enlarged pelvic lymph nodes or multiple liver metastases).

8.1.4. Response Criteria

Efficacy evaluation will include the assessment of target and non-target responses as well as objective responses. Responses will be assessed as defined in the SAP.

8.1.4.1. Target and Non-Target Response Assessments

Assessments will be based on the definitions for target and non-target lesions described in Table 11.

Table 11: Target and Non-target Lesions

TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph node must have reduction in short axis to <10 mm
Partial Response (PR)	At least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Definitive new lesion presence also indicates progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, referencing the smallest sum diameters while on study.
NON-TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10-mm short axis)
Partial Response (PR)	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions (see following definition).

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease

Progression in Non-target Disease: There must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

8.1.4.2. Additional Criteria to Consider When Making Response Assessments

Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (ie, an increase in tumor burden representing an additional 73% increase in “volume” [which is equivalent to a 20% increase in the diameter of a measurable lesion]).

When effusions are known to be a potential adverse effect of treatment, cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is not mandatory, but might be performed to differentiate between response (or SD) and PD when substantial change of effusion and or ascites is noted.

If a patient is discontinued from the study before PD occurs and receives local or regional palliative radiotherapy during the follow-up period, the irradiation site must be omitted from the response assessment of the patient; however, if the site is observed to demonstrate disease progression, this case should be judged as PD.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

8.1.5. Objective Response Assessment

Assessments will be based on the definitions provided in Table 12 and Table 13. Since this is a non-randomized study, all responses (CR/PR) must be confirmed.

Table 12: Time Point Response for Patients with Target (±Non-target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Objective Response
CR	CR	No	CR
CR	Non-CR/Non-PD or Not all evaluated	No	PR
PR	Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease

Table 13: Time Point Response for Patients with Only Non-target Disease

Non-Target Lesions	New Lesions	Objective Response
CR	No	CR
Non-CR/Non-PD	No	SD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease

8.2. Cohort C

8.2.1. Efficacy Criteria

Efficacy will be assessed by evaluation of:

- Bone marrow histomorphology changes, standard cytogenetics, and *FGFR* molecular status
- Peripheral blood assessment (blood count) including potentially *FGFR* molecular status
- Positron emission tomography (PET) scan for fluorodeoxyglucose (FDG) avid lesions
- Imaging (CT/MRI) in case of presence of solid lesions
- Clinical assessment

If the Investigator determines that a patient has developed clinical disease progression manifested by symptomatic deterioration, the patient may stop treatment. Every effort should be made to document objective disease progression even after discontinuation of treatment.

8.2.2. Response Criteria

For patients in Cohort C, response will be determined based on disease presentation. Investigators will assess response based on the following response criteria:

- Treatment Response Criteria for MDS/MPN (Savona et al. 2015)
- Response Evaluation Criteria in Lymphoma (RECIL 2017) (Younes et al. 2017)
- International Working Group (IWG) Response Criteria for AML (Cheson et al. 2003)

A review of the response assessments will be conducted by an adjudication committee.

8.2.3. Response Definitions

Response will be determined based on Investigators' assessment of imaging, bone marrow, peripheral blood, and extramedullary disease. Assessments will be based on the definitions described in Table 14.

Table 14: Response Definitions for Cohort C

MLN Characteristic	MLN Only	Lymphoma Presentation	Leukemia Presentation
Response Criteria	**Savona 2015[a]**	**RECIL 2017[b]**	**Cheson 2003[c]**
Complete response (CR)	Must fulfill all criteria defined for CR	Must fulfill all criteria defined for CR	• Must fulfill all criteria defined for morphologic complete response • CR does not include: o Morphologic leukemia-free state o Complete response with incomplete hematological recovery (CRi), or o Cytologic complete response (CRc)
Partial response (PR)	Must fulfill all criteria defined for PR	Must fulfill all criteria defined for PR	Must fulfill all criteria defined for partial remission
Complete response with incomplete blood count recovery (CRi)	N/A	N/A	Must fulfill all criteria defined for CRi
Complete cytogenetic response (CCyR)	Resolution of previously present chromosomal abnormality known to be associated with MLN (eg. 8p11 translocation)	Must fulfill all criteria defined for CCyR (Savona 2015)[a]	Must fulfill all criteria defined for cytogenetic complete response (CRc) (Cheson 2003)[c] and CCyR (Savona 2015)[a]
Partial cytogenetic response (PCyR)	≥50% reduction of chromosomal abnormality known to be associated with MLN (eg. 8p11 translocation)	Must fulfill all criteria defined for PCyR (Savona 2015)[a]	Must fulfill all criteria defined for PCyR (Savona 2015)[a]
PD/Relapsed disease	Must fulfill all criteria defined for PD/relapsed disease	Must fulfill all criteria defined for PD/relapsed disease	Must fulfill all criteria defined for PD/relapsed disease

[a] Savona, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood. 2015.
[b] Younes, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol. 2017.
[c] Cheson, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003.

8.3. Efficacy Endpoints

The efficacy endpoints are provided in Table 4. Definitions of each endpoint are provided in Section 11.5.3.1.2 . For further information, refer to the SAP.

9. SAFETY EVALUATIONS

9.1. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study patient and does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. For this study, progression of the cancer under study is not considered an AE unless the Investigator deems it related to study drug.

All AEs will be collected from the time informed consent has been documented through 30 days after the last dose of any study drug (safety follow-up) or until the start of new antitumor therapy, whichever is earlier. Any untoward medical event that occurs after the safety follow-up is not considered an AE, unless the Investigator considers that the AE is related to the study drug.

Signs and symptoms of a preexisting disease should not be considered an AE, but should rather be considered baseline signs and symptoms. Clinically significant worsening of preexisting signs and symptoms is considered an AE.

9.2. Reporting of Adverse Events

9.2.1. Terms of Reported Adverse Events

All AEs will be documented in the eCRF according to the eCRF Completion Guidelines. Documentation should include onset and resolution/stabilization dates, severity/grade, relationship to study drug, and outcome of the event.

When a diagnosis for the reported signs or symptoms is known, the Investigator should report the diagnosis, not the symptoms, as the AE.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. In order to prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs.

9.2.2. Severity of Adverse Events

The NCI-CTCAE V5.0 will be used to grade the severity of AEs.

9.2.3. Causal Relationship with Study Drug

The causal relationship between an AE and study drug will be assessed using the following 2-point scale, taking into account the patient’s condition, medical history, concomitant medications, and the temporal relationship between study drug administration and onset of the event.

1. An AE is considered to be "Related" if the event follows a reasonable temporal sequence from administration of study drug and there is a reasonable possibility that at least one of the following conditions is true:
    - A positive dechallenge: This means that the event improves or resolves after the drug is stopped (temporarily or permanently).
    - A positive rechallenge: This means that the event reappears after the drug is restarted.
    - The event cannot be reasonably explained by the patient's clinical state and/or other therapies administered.
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, Stevens-Johnson syndrome).
2. An AE is considered to be "Not related" if there is no reasonable possibility that at least one of the following conditions is true:
    - The event occurred prior to study drug administration.
    - There is no reasonable possibility that the study drug caused the event. ("No reasonable possibility" means there is no evidence to suggest a causal relationship between the study drug and the AE)
    - The event does not follow a reasonable temporal sequence from administration of study drug and could have been produced by a documented preexisting condition, concomitant medication, or patient's clinical state.

9.2.4. Outcome of Adverse Events

Record the outcome of AEs as follows:

- Resolved
- Not resolved
- Fatal

9.2.5. Follow-up of Adverse Events

Any ongoing AEs should be followed until the earliest occurrence of one of the following:

- The AE has resolved or stabilized
- Completion of Safety Follow-Up Visit
- Start of new antitumor therapy
- Withdrawal of consent
- Death
- Other (eg, transfer to another hospital)

9.3. Laboratory Assessments

9.3.1. Reporting and Evaluation of Laboratory Test Results

All laboratory results must be reviewed by the Investigator. A new laboratory abnormality that has a clinical impact on a patient (including eg, resulting in study drug dose reduction, treatment delay, treatment discontinuation, or requirement of intervention) is considered an AE, unless it is considered part of clinical manifestations to a clinical diagnosis that is already reported as an AE.

All laboratory values that are out of the normal range are to be evaluated for their clinical impact before exposing the patient to the next dose of futibatinib.

The NCI-CTCAE V5.0 will be used to grade the severity of laboratory data.

9.3.2. Repeat Testing

Evaluation of any clinically significant laboratory test will be repeated, as clinically indicated, until the value returns to the baseline level or clinically stabilizes, or until another treatment is given.

9.4. Serious Adverse Events

9.4.1. Definitions of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
  - Death due to disease progression or relapse is not considered an SAE unless the Investigator deems it related to the study drug.
- Is life-threatening
  - The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. The following are not considered hospitalizations for the purposes of assessing seriousness (however, one of the other serious criteria may apply):
  - Emergency room visits <24 hours
  - Hospitalizations for pre-planned procedures
  - Hospitalization for study-related treatment and procedures
- Results in persistent or significant disability/incapacity, where disability is defined as a substantial disruption of a person’s ability to conduct normal life functions, either reported or defined as per clinical judgment.
- Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child).

- Is any other important medical event that based upon appropriate medical judgement may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above (eg, may not result in death, be life-threatening, or require hospitalization).

9.4.2. Reporting of Serious Adverse Events (within 24 hours)

All SAEs occurring from the time informed consent has been documented through the Safety Follow-up Visit (30 days after the last dose of study drug or discontinuation, whichever is earlier) must be reported to Sponsor's Pharmacovigilance group or its designee immediately and no later than 24 hours from the time the Investigator first becomes aware of the SAE.

Comprehensive information available at the time of initial reporting (including narrative description, medical history, and concomitant medications) needs to be provided with careful consideration regarding causality and serious criterion. The SAE reporting process and contact information are provided in supplement guidelines.

After the initial SAE notification to the Sponsor's Pharmacovigilance group or its designee, all follow-up SAE information will be submitted each time they become available (for example, clinical diagnosis, outcome, causality assessment, or results of specific investigations) on a follow-up SAE form.

Investigators are not obligated to actively seek SAEs after the 30-day Follow-up. However, if the Investigator learns of any SAE (including a death) at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study treatment or participation, the investigator must promptly notify the Sponsor.

The Investigator also must submit further information if it is required by the Sponsor or the director of the study site or an institutional review board (IRB)/independent ethics committee (IEC).

Every SAE should be followed until it has resolved, stabilized, or returned to baseline.

9.4.3. Reporting of Deaths (within 24 hours)

All deaths (except disease progression) occurring from the time informed consent has been documented through the Safety Follow-up Period (30 days after the last dose of study drug or discontinuation, whichever is earlier) must be reported immediately and no later than 24 hours from the time the Investigator first becomes aware of the death. The primary cause of the death should be reported as the SAE term, if available, and entered on the death page of the eCRF. Death due to disease progression is not a reportable event unless the Investigator deems it related to study drug. In the latter case, the event must be reported within 24 hours from the times the Investigator first becomes aware of the death.

9.5. Other Safety Information

9.5.1. Pregnancy

If a patient becomes pregnant while in the study, the study drug must be immediately discontinued. Pregnancy information in a female patient (or for the female partner of a male

patient) should be reported to Sponsor's Pharmacovigilance or designee via the Pregnancy Form as soon as possible from the time the Investigator first becomes aware of a pregnancy or its outcome.

New and/or corrected information regarding the pregnancy obtained after submitting the Pregnancy Form must be submitted on an updated Pregnancy Form to the Sponsor's Pharmacovigilance or designee. Pregnancies must be followed to outcome by the Investigator, even after study completion.

If the outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, it should be reported as an SAE to the Sponsor's Pharmacovigilance or designee. Live births will be followed up by the Investigator. Any information that may be associated with the study drug should be reported even after study completion.

9.5.2. Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not itself an AE, but it may result in an AE.

An overdose that results in an AE should be reported to Sponsor's Pharmacovigilance or designee within 24 hours from the time the Investigator first becomes aware of its occurrence.

10. BIOMARKER EVALUATION

10.1. Biomarker Assessments

10.1.1. Objectives and Background

Exploratory objectives of this study are to assess the possible impact of specific genetic alterations or other laboratory abnormalities on the efficacy of futibatinib.

Biomarkers will be tested using analytically validated assay at a central laboratory.

All biomarker assessments described in this section will be performed at the timepoints shown in the Schedule of Events; methods of sample collection and preparation will be described in a separate Laboratory Manual.

10.1.2. Assessment of *FGF/FGFR* Aberrations in Blood

A blood sample will be collected to assess *FGF/FGFR* aberrations in ctDNA as described in the Schedule of Events and where local regulations allow. In addition to assessing ctDNA as a pharmacodynamic biomarker, samples or a set of samples, will be used to investigate its possible utility as a complimentary or an alternative to tumor tissues for the future potential companion diagnostic development. Samples will be collected and stored, as per the Laboratory Manual, and analyzed in batches.

10.1.3. Tissue Samples

Archival or fresh tumor/bone marrow biopsy samples will be collected during screening to retrospectively confirm *FGFR* gene status at the Sponsor's designated central laboratories or for the purpose of a bridging study should companion diagnostics be warranted (fine needle aspiration is not acceptable). Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. The remaining samples may be stored at the Sponsor's designated central laboratories for up to 10 years after study completion for future testing or companion diagnostic development if warranted.

10.2. Sample Storage and Disposal

Samples or leftover samples will be stored for a maximum of 10 years following the completion of the study at central laboratories. These samples could be used to develop companion diagnostics and to investigate the genes or other biomarkers related to efficacy or resistance of futibatinib in the future. After the storage period ends, samples will be destroyed.

10.3. Analytical Procedures

Patients will be enrolled depending on local results but tissue samples will be collected and stored at central location for possible confirmatory testing, molecular profiling, and/or companion diagnostic development if warranted by the clinical response.

Analyzing plasma ctDNA will be conducted retrospectively in batches on an adequately validated assays at central lab(s).

The detailed analytical procedures will be described in the SAP for Biomarkers.

11. STATISTICAL CONSIDERATIONS

The statistical analysis methods will be documented in detail in the SAP.

11.1. Estimation of Sample Size

A total of approximately 155 patients will be enrolled in the study.

Cohort A

Approximately 100 patients with solid tumors harboring *FGFR* rearrangements will be enrolled in Cohort A. Sample size considerations are based on differentiating a null ORR of 10% with a target ORR of 25%. Assuming the true ORR is 25%, the study has over 90% power to reject the null hypothesis that the true ORR is ≤10%, considering a 2-sided alpha of 5%.

A 2-stage Simon design (Simon 1989) will be used for futility assessment, comparing a poor response of ≤10% vs a promising response of ≥25%, at a 5% 1-sided significance level and approximate 90% power. In Stage 1 (futility assessment), enrollment will include 35 patients and accrual will continue to Stage 2, if at least 4 (11.4%) of 35 patients respond (CR or PR).

If the Stage 1 futility boundary is exceeded, Stage 2 will be open and require at least 25 additional patients. To further provide a more precise estimate of objective response rate and a better evaluation of safety profile, a total of 100 patients will be enrolled.

The entire population in Cohort A (total of 100 patients) will be analyzed as specified in the objectives. Table 15 summarizes the 95% exact CI for the target ORRs ranging from 17% to 30% with a sample size of 100. At observed ORR = 17%, the lower bound of the 95% CI excludes 10%, which is the null hypothesis ORR rate. This translates to observing at least 17 responders out of 100 treated patients (ORR of 17.0% with 95% CI 10.2%-25.8%).

Table 15: Observed ORR with Exact 95% Confidence Interval (Cohort A)

ORR	95% Exact Confidence Interval
17%	[10.2% – 25.8%]
20%	[12.7%-29.2%]
25%	[16.9%-34.7%]
30%	[21.2%-40.0%]

Cohort B

Approximately 35 patients with gastric or GEJ cancer harboring *FGFR2* amplification will be enrolled in Cohort B. Sample size considerations are based on differentiating a historical control ORR of 10% or less, with a target ORR of 35%. Assuming the true ORR is 35%, the cohort has approximately 96% power to reject the null hypothesis that the true ORR is ≤10%, considering a 2-sided alpha of 5%. With a sample size of 35, observing at least 8 responders will have a 95% CI lower bound excluding 10% ORR of 23% with 95% CI (10.4%-40.1%)(Table 16).

Table 16: Observed ORR with Exact 95% Confidence Interval (Cohort B)

ORR	95% Exact Confidence Interval
23%	[10.4%-40.1%]
29%	[14.6%-46.3%]
37%	[21.5%-55.1%]

Cohort C

Approximately 20 patients with myeloid or lymphoid neoplasms harboring *FGFR1* rearrangements will be enrolled in Cohort C. Sample size considerations are based on differentiating a historical control CR rate of 10% or less with a target CR rate of 50%. Assuming the true CR rate is 50%, the cohort has over 95% power to reject the null hypothesis that the true CR rate is ≤10%, considering a 2-sided alpha of 5%.

Observing at least 6 responders out of 20 treated patients will have a 95% CI lower bound excluding 10% CR rate of 30% with 95% CI (11.9%-54.3%) (Table 17).

Table 17: Observed CR Rate with Exact 95% Confidence Interval (Cohort C)

CR Rate	95% Exact Confidence Interval
30%	[11.9%-54.3%]
40%	[19.1%-64.0%]
50%	[27.2%-72.8%]

11.2. Timing of Analysis

The Sponsor will review the data at the time Cohort A has the required number of patients (n=35) to determine if that particular cohort should continue. Additional interim analyses may be performed if required for regulatory purposes. Should Cohort A continue enrollment, the primary analysis for Cohort A will be carried out when all patients have been followed up for at least 6 months or have discontinued the study. For Cohort B and Cohort C, the primary analysis will be at the time when all patients have been followed up for at least 6 months or have discontinued the study in each cohort.

11.3. Analysis Populations

The analysis populations in the study are defined in Table 18.

Table 18: Definitions of Analysis Populations

Analysis Population	Definition
All Enrolled Population	All patients who provided documented informed consent in this study
All Treated Population/Full Analysis Set	All enrolled patients who received at least 1 dose of study drug
Pharmacodynamic/Biomarker Evaluable Set	All patients in the All Treated Population who have evaluable pharmacodynamic/biomarker data for analyses

11.4. Criteria for Handling of Patient Data

The criteria for handling of patient data are provided in the SAP.

11.5. Statistical Analyses

This section outlines the statistical methodology to be used to summarize the study results. A more detailed methodology for summary and statistical analyses of the data collected in this study are documented in the SAP. The SAP will be prepared as a separate document by the Sponsor.

11.5.1. Demographic and Baseline Characteristics

The number of patients in each study population and the reasons for exclusion will be summarized. In each analysis population, the distribution of main patient background, disease characteristics, and baseline laboratory values and clinical findings will be summarized. These patient attributes will be summarized using frequency distribution or descriptive statistics as appropriate.

11.5.2. Study Drug Administration

In the All Treated Population, the following analyses will be performed by dose level:

- Administration status
- The total dose, total duration of administration, and the number of administration cycles will be summarized by all treated patients/each intervention group.
- Status of administration completion
- The rate of administration completion will be presented by cycle.
- The presence or absence of study discontinuation and reasons for study discontinuation will be tabulated by cycle.
- Dose intensity
- Actual dose intensity and relative dose intensity in each patient will be calculated, and descriptive statistics will be presented.

11.5.3. Efficacy Analyses

All efficacy analysis will be performed using the All Treated Population

A description of each efficacy endpoint is provided in Table 4 and Table 5. See the SAP for more detailed information on the efficacy analyses.

11.5.3.1. Cohorts A and B

11.5.3.1.1. Primary Efficacy Analysis

Objective response rate is defined as the proportion of patients with objective evidence of CR or PR (per RECIST 1.1). The evaluation of ORR will be based on an independent central review of radiologic images. At the analysis stage, the best objective response will be assigned for each patient as the best response recorded after initiation of study drug and confirmed at least 4 weeks later. If applicable, responses recorded after disease progression or initiation of new anticancer treatment will be excluded. The exact 2-sided CI based on Clopper-Pearson methodology will be derived for ORR.

11.5.3.1.2. Secondary Efficacy Analyses

Duration of response is a key efficacy endpoint:

- Duration of response will only be evaluated in patients with an objective response of CR or PR. Patients who are alive and progression-free as of the analysis cut-off date will be censored at their last evaluable response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last response assessments prior to initiation of the subsequent anticancer therapy.

Additional efficacy endpoints include:

- Overall response rate and DCR based on Investigator assessment will be determined (per RECIST 1.1) as described for the primary analysis of ORR based on independent central review of radiologic images (Section 11.5.3.1.1).
- Progression-free survival will be estimated using the Kaplan-Meier method. Patients who die without a reported disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last response assessment. Patients who did not have any on-study assessments and did not die will be censored on the first dosing date. Patients who started any subsequent anticancer therapy without a prior reported progression will be censored at the last response assessment prior to initiation of the subsequent anticancer therapy.
- Overall survival will be analyzed in a similar manner to PFS. In the absence of confirmation of death or for patients who are alive as of the OS cut-off date, survival time will be censored at the last known date that the patient was alive.

11.5.3.2. Cohort C

11.5.3.2.1. Primary Analysis

Complete response rate defined as the proportion of patients who achieved a CR will be calculated and the exact 2-sided CI will also be derived using the Clopper Pearson methodology.

11.5.3.2.2. Secondary Analyses

The overall response, CR+CRi (leukemia presentation only), CCyR, and PCyR rates will be calculated and the exact 2-sided CIs will also be derived using the Clopper-Pearson methodology.

Duration of CR (only in patients who achieved a CR), duration of CR+CRi (only in patients who achieved a CR/CRi [leukemia presentation only]), and duration of response (only in patients with an objective response of CR, CRi [leukemia presentation only], or PR) will be estimated using the Kaplan-Meier method. Patients who are alive and progression-free as of the analysis cut-off date will be censored at their last evaluable response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last response assessments prior to initiation of the subsequent anticancer therapy.

Progression-free survival will be estimated using the Kaplan-Meier method. Patients who die without a reported disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last response assessment. Patients who did not have any on-study assessments and did not die will be censored on the first dosing date. Patients who started any subsequent anticancer therapy without a prior reported progression will be censored at the last response assessment prior to initiation of the subsequent anticancer therapy.

Relapse-free survival will only be evaluated in patients with an objective response of CR and measured from the first date of achieving CR until the first date of relapsed disease or death from any cause, whichever occurs first. Patients who die without a reported disease relapse will be considered to have relapsed on the date of their death. Patients who did not relapse or die will be censored on the date of their last response assessment. Patients who started any subsequent anticancer therapy without a prior reported relapse will be censored at the last response assessment prior to initiation of the subsequent anticancer therapy.

Event-free survival will be estimated only for patients with leukemia presentation using the Kaplan-Meier method. EFS is defined as the time from first dose of study drug to treatment failure, relapse after CR (if applicable), or death from any cause, whichever occurs first. For a patient with none of these events before the end of study follow-up, observation of EFS is censored at the date of last contact prior to the analysis cut-off date. If the patient does not achieve a CR, EFS is defined as the point of treatment failure or death, whichever comes first. Treatment failure for EFS is defined as PD in this study.

Overall survival will be analyzed in a similar manner to PFS. In the absence of confirmation of death or for patients who are alive as of the OS cut-off date, survival time will be censored at the last known date that the patient was alive.

11.5.4. Safety Analyses

The safety analysis will be performed using the All Treated Population.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities terminology and the severity of the toxicities will be graded according to the NCI-CTCAE V5.0, where applicable.

Concomitant medications will be coded according to the WHO Drug Dictionary for Concomitant Medication.

All AEs will be summarized (by incidence) and listed by the System Organ Class, preferred term, toxicity/severity grade, and causal relationship to futibatinib. In addition, separate summaries of SAEs and Grade 3 or 4 AEs will be presented.

For all AEs that occurred between the patient providing documented informed consent and the last day of the Safety Follow-up Period, lists of preferred AE terms, grade, onset date, actions, outcome of AE, date of outcome confirmed, causalities with the study drug, and comments on AEs will be listed by patient.

Hematological and chemistry laboratory parameters will be graded according to the NCI-CTCAE V5.0 where applicable. The worst severity grade, time to maximum Grade 3 or 4 value, and time to resolution (return to baseline grade or below) will be summarized.

Safety data (AEs and clinical laboratory results) will be summarized descriptively. A list of 12-lead electrocardiogram findings will be presented by patient.

11.5.5. Pharmacokinetic Analysis

The PK data obtained in this study will be combined with data from other studies in the clinical development program to develop a popPK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of futibatinib and to estimate measures of individual exposure (such as steady-state peak, trough and area under the plasma drug concentration-time curve). Model estimated exposures will be used for exposure-response analyses of selected efficacy and safety endpoints. The results of popPK and exposure-response analyses will be reported separately.

11.5.6. Pharmacodynamic/Biomarker Analysis

The exploratory pharmacodynamic/biomarker endpoints are described in Section 10.

Pharmacodynamic and biomarker data will be summarized descriptively using all patients in the Pharmacodynamic/Biomarker Evaluable Set who have evaluable data available.

12. ADMINISTRATIVE CONSIDERATIONS

12.1. Protocol Compliance

The Investigator must agree to comply with all aspects of the protocol. In the event that the Investigator is unable to continue the study and another suitable person is designated as the Investigator, the Sponsor must be notified in advance. The new Investigator must accept the responsibility in writing and be approved by the Sponsor and the IRB/IEC.

12.2. Protocol Deviations

The Investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study patients without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change and the reasons for it should be documented and submitted to the IRB/IEC and Sponsor.

The Investigator is to record any deviation from the protocol in the source documents, describing this departure and the circumstances under which it was required.

12.3. Protocol Amendments

All protocol amendments must be issued by the Sponsor, and signed and dated by the Investigator. Documentation of amendment approval by the Investigator and IRB/IEC must be provided to the Sponsor.

If the changes involve only logistic or administrative aspects of the study, these changes will be notified in writing by the Sponsor.

12.4. Study Termination

If the Sponsor and/or the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. The Sponsor also reserves the right to discontinue this study for administrative or discretionary reasons at any time.

12.5. Case Report Forms

The Investigator should complete all eCRFs in accordance with the eCRF Completion Guidelines. Data in the eCRFs shall be consistent with source documents.

In this study, all relevant personnel will receive electronic data capture access according to their roles in the study.

An eCRF should be completed for each screened and enrolled patient.

The Investigator, or assigned personnel, should verify the data and correct as necessary prior to approval of the eCRFs.

12.6. Access to Source Data/Documents

The Investigator and the site must make all study-related records available for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

12.6.1. Source Data/Documents

Source documents are original documents, data, and records such as hospital records, clinical and office charts, laboratory notes, memoranda, patient's evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfilm or magnetic media, X-ray, patient files, and records kept at the pharmacy, laboratories, and medical-technical departments involved in the study.

Specific details regarding source documents and source data to be recorded directly on the eCRFs for the study should be identified with the Investigator prior to and during the study.

12.6.2. Access to Source Data

The Sponsor's study monitor, or other representatives, should verify the entries in the eCRF and source documents to confirm the completeness and accuracy of the data. If there are any discrepancies between the entries in eCRFs and source documents, the monitor will query the Investigator.

12.7. Data Handling

All study information is confidential. The patient's and Investigator's personal data which may be included in the Sponsor's database shall be treated in compliance with all applicable laws and regulations.

When processing and archiving personal data pertaining to the Investigator and to the patients, the Sponsor or its representatives shall take all appropriate measures to safeguard and prevent access to these data by any unauthorized third party.

12.8. Responsibilities of Recordkeeping

12.8.1. Investigator and Study Site

The Investigator and the study site are responsible for the retention of all study documents according to institutional policies, local laws, and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guidelines. In multinational studies, non-United States sites will be considered non-Investigational New Drug (IND) sites. Non-IND sites will be required to follow local regulations and ICH Guidelines.

The Investigator and the study site agree to inform the Sponsor in writing of the intention to remove or destroy any study-related records. Prior to contacting the Sponsor, the Investigator and study site must ensure that the applicable regulatory requirements have been satisfied. The Sponsor will evaluate the requests from the Investigator and the study site and will provide authorization for destruction of such records in writing.

In the event that all retention of records requirements have been fulfilled, but the Sponsor requests that the Investigator and study site maintain the records for a longer period of time, additional arrangements will be made.

12.8.2. Sponsor

The Sponsor must retain all Sponsor-specific essential documents in conformance with the applicable regulatory requirements of the countries where the product is approved, and where the Sponsor intends to apply for approvals.

If the Sponsor discontinues the clinical development of the study drug, the Sponsor must maintain all Sponsor-specific essential documents in conformance with the applicable regulatory requirements.

12.9. Monitoring

The Sponsor and designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator and the site agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

12.10. Financial Disclosure

Financial disclosure for Investigators will be obtained and record keeping of financial records will be in accordance with local regulatory requirements. Investigators will provide the Sponsor with sufficient, accurate financial information upon the Sponsor’s request.

12.11. Compensation for Health Injury

The clinical study is insured according to applicable regulatory requirements. A copy of the Compensation Policy Document will be provided to the study site by the Sponsor.

In the case of a compensation claim, excluding claims that have arisen due to medical malpractice or negligence, the legally responsible person is clearly identified.

Sponsor should address the policies and payment procedures of compensation for the event of study-related injuries as the Compensation Policy Document.

When patients receive compensation, the policies and payment procedure of compensation should comply with the Compensation Policy Document.

12.12. Study Administrative Structure

The study organization details will be maintained in a supplement.

13. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will perform quality control and quality assurance procedures in accordance with the Sponsor's standard operating procedures (SOPs) to ensure the quality of the clinical study.

13.1. Quality Control

The Sponsor is responsible for controlling the quality of the clinical study according to the SOPs regarding study operation, monitoring, data collection and management, statistical analysis, and handling of safety information to verify that the study-related activities have been fulfilled.

13.2. Quality Assurance

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The Investigator and the site will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data and documents pertaining to the clinical study.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to ensure that these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP E6 Guidelines, and any applicable local regulatory requirements. The Investigator and the site should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

Any results arising from such inspections will be immediately communicated by the Investigator and the site to the Sponsor. The Investigator and the Sponsor will take corrective actions for all findings and observations found during audits and/or inspections. The auditors and inspectors will not disclose private information unless required by law.

14. ETHICS

14.1. Ethical Conduct of the Study

It is mandatory that all considerations regarding the protection of patients be carried out in accordance with the latest versions of the protocol, ICH GCP Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

14.2. Documented Informed Consent

The ICF(s) must be approved by the IRB/IEC before a patient's consent to any study-related activity. It must be in a language that the patient can read and understand. The ICF process should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP Guidelines, and applicable regulatory requirements. Each patient (or a legally acceptable representative) must give documented consent according to local requirements.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

There must be documentation in each patient's case history/medical record that informed consent was obtained prior to any study procedure being performed. Patients must be re-consented to the most current version of the ICF(s) during their participation in the study (including during survival follow-up).

14.3. Institutional Review Board/Independent Ethics Committee

The study must be approved by an appropriately constituted IRB/IEC, as required in the applicable local regulation such as ICH E6 Guidelines (Part 3), Code of Federal Regulations Title 21, part 56, and Ordinance of the Ministry of Health and Welfare No. 28, Chapter IV, Section 1 before the study is initiated. At the end of the study, the Investigator will notify the IRB/IEC of the conclusion of the study and its outcome.

15. PUBLICATION POLICY

15.1. Publication Policy

The Sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country or region.

The results of the study may be presented during scientific symposia and/or published in a scientific journal only after review by the Sponsor in accordance with the guidelines set forth in the applicable publication.

The Investigator(s) and the Sponsor will discuss and determine the presenter(s) or author(s) and timing of any presentation or publication related to this study and/or its results. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

15.2. Secondary Use of Data

The Sponsor maintains the right to secondary use of data in this study.

Secondary use of data describes the use of data from this study for other study/studies for purposes including, but not limited to, drug development and/or academic research. Secondary use of data also includes external offerings of study data to domestic and/or foreign organization(s), other companies and researcher(s), on a case by case basis.

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APPENDIX A. ECOG PERFORMANCE

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

From: Oken MM, Creech, RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

APPENDIX B. DIETARY GUIDELINES FOR TREATMENT OF HYPERPHOSPHATEMIA

The best way to limit phosphorus in the diet is to limit foods highest in phosphorus, including:

- Fast food, convenience foods, and processed foods, which may be full of phosphorus additives
- Beverages that contain phosphorus (look for the letters "phos" in the ingredient list)

Also, look for any ingredient that contains "phos" in the term such as:

- Calcium phosphate
- Disodium phosphate
- Phosphoric acid
- Monopotassium phosphate
- Sodium acid pyrophosphate
- Sodium tripolyphosphate

Listing of Some Lower and Higher Phosphorus Foods	
Higher Phosphorus Foods	**Lower Phosphorus Foods**
Milk, pudding, yogurt, soy milk, nondairy creamers and enriched rice milk	Unenriched rice milk
Processed cheeses and cheese spreads	A small amount of Brie or Swiss cheese
Hard cheeses, ricotta or cottage cheese, fat-free cream cheese	Regular or low-fat cream cheese
Ice cream or frozen yogurt	Sherbet, sorbet or frozen fruit pops
Soups made with higher phosphorus ingredients (milk, dried peas, beans, lentils)	Soups made with lower phosphorus ingredients (broth- or water-based with other lower phosphorus ingredients)
Whole grains, including whole-grain breads, crackers, cereal, rice and pasta	White bread, crackers, cereals, rice and pasta
Quick breads, biscuits, cornbread, muffins, pancakes or waffles	White dinner rolls, bread, bagels or English muffins
Dried peas (split, black-eyed), beans (black, garbanzo, lima, kidney, navy, pinto) or lentils	Green peas, green beans or wax beans
Processed meats (ie, bologna, ham and hot dogs), and meat, poultry or seafood with "phos" in the ingredients	All-natural lean beef, pork, lamb, poultry, seafood or other fish without "phos" in the ingredients
Organ meats, walleye, pollock or sardines	All-natural lean beef, pork, lamb, poultry, seafood or other fish without "phos" in the ingredients
Nuts and seeds	Popcorn or pretzels
Peanut butter and other nut butters	Jam, jelly or honey
Chocolate, including chocolate drinks	Jelly beans, hard candy, fruit snacks or gumdrops
Colas and pepper-type sodas, some flavored waters, bottled teas, some drink mixes (any with "phos" in the ingredients)	Lemon-lime soda, ginger ale, root beer, plain water or some drink mixes (any without "phos" in the ingredients)
Although a food or drink may be low in phosphorus, limitation of portion size and the number of servings you eat or drink each day may still be recommended.	

From: Rachael Majorowicz, R.D.N., L.D. (Feb, 2016). Why is a low-phosphorus diet useful in managing kidney disease? What foods contain phosphorus? https://www.mayoclinic.org/food-and-nutrition/expert-answers/faq-20058408.

APPENDIX C. CLASSIFICATION OF SUBSTRATES, INHIBITORS, AND INDUCERS OF CYP ENZYMES AND TRANSPORTERS

The classification below is based on the FDA Drug Development and Drug Interactions | Table of Substrates, Inhibitors and Inducers. Content current as of 03/10/2020. https://www.fda.gov

Example of CYP3A Inhibitors

Cytochrome P450 (CYP) Enzymes	Strong Inhibitors[a] ≥ 5-fold increase in AUC	Moderate inhibitors[b] ≥ 2 but < 5-fold increase in AUC
CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice,[c] indinavir and ritonavir, idelalisib, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil

[a] Strong inhibitors are drugs that increase the area under the concentration-time curve (AUC) of sensitive index substrates of a given metabolic pathway ≥5-fold.
[b] Moderate inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥2 to <5-fold.
[c] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

Example of CYP3A Inducers

Cytochrome P450 (CYP) Enzymes	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50%-80% decrease in AUC
CYP3A	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[a]	bosentan, efavirenz, etravirine, modafinil

[a] The effect of St. John's wort varies widely and is preparation-dependent.

Example of CYP3A Substrates

Cytochrome P450 (CYP) Enzymes	Sensitive substrates[a]	Moderate sensitive substrate[b]
CYP3A[c]	alfentanil, avanafil, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tacrolimus, ticagrelor, tipranavir, tolvaptan, triazolam, vardenafil	alprazolam, aprepitant, atorvastatin, colchicine, eliglustat, pimozide, rilpivirine, rivaroxaban, tadalafil

[a] Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction studies.
[b] Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction studies.
[c] Because a number of CYP3A substrates (eg, darunavir, maraviroc) are also substrates of MDR1 (P-gp), the observed increase in exposure could be due to inhibition of both CYP3A and MDR1 (P-gp).

Example of Inhibitors for P-gp and BCRP

Transporters	Gene	Inhibitor
P-gp[a]	*ABCB1*	Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP[b]	*ABCG2*	Curcumin, cyclosporine A, eltrombopag

[a] P-gp: (1) AUC fold-increase of digoxin ≥2 with co-administration and (2) in vitro inhibitor.

[b] BCRP: (1) AUC fold-increase of sulfasalazine ≥1.5 with co-administration and (2) in vitro inhibitor. Cyclosporine A and eltrombopag were also included, although the available DDI information was with rosuvastatin, where inhibition of both BCRP and OATPs may have contributed to the observed interaction.

Example of Substrates for P-gp and BCRP

Transporters	Gene	Substrate
P-gp[a]	*ABCB1*	Dabigatran, digoxin, fexofenadine
BCRP[b]	*ABCG2*	Rosuvastatin, sulfasalazine

[a] P-gp: (1) AUC fold-increase ≥2 with verapamil or quinidine co-administration and (2) in vitro transport by P-gp expression systems, but not extensively metabolized.

[b] BCRP: (1) AUC fold-increase ≥2 with pharmacogenetic alteration of ABCG2 (421C>A) and (2) in vitro transport by BCRP expression systems.

Taiho

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SIGNATURE PAGE

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Clinical Study Protocol

A PHASE 2 STUDY OF FUTIBATINIB IN PATIENTS WITH SPECIFIC *FGFR* ABERRATIONS

Futibatinib (TAS-120)

Protocol TAS-120-202

Issue Date: 08 November 2019 (Not implemented)

Amendment 1: 07 February 2020

IND Number: 145393

EudraCT Number: 2019-004084-49

Sponsor

Taiho Oncology, Inc.
101 Carnegie Center, Suite 101
Princeton, NJ 08540, USA

This clinical study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) Guidelines and applicable regulatory requirements.

PROTOCOL SYNOPSIS

Protocol Title:

A Phase 2 Study of Futibatinib in Patients with Specific *FGFR* Aberrations

Rationale:

Fibroblast growth factor receptor (*FGFR*) signaling plays a crucial role in cancer cell proliferation, migration, angiogenesis, and survival. Recent studies have uncovered increasing evidence that deregulated FGFRs can function as driving oncogenes in certain tumor types, maintaining the malignant properties of cancer cells. When FGFRs are amplified, rearranged, or undergo fusion, aberrant activation of downstream pathways results in mitogenic, mesenchymal, and antiapoptotic responses in cells. Therefore, FGFRs are attractive targets for therapeutic intervention in cancer treatment.

The Phase 2 study described in this protocol will evaluate the efficacy and safety of futibatinib in patients with *FGFR* aberrations in 3 distinct cohorts. Patients will be enrolled into 1 of 3 cohorts: patients with advanced, metastatic, or locally-advanced solid tumors harboring *FGFR* rearrangements (excluding primary brain tumors and intrahepatic cholangiocarcinoma [iCCA]); patients with gastric or gastro-esophageal junction (GEJ) cancer harboring *FGFR2* amplification; and patients with myeloid or lymphoid neoplasms harboring *FGFR1* rearrangements.

Study Objectives and Endpoints:

Cohorts A and B

Primary	
To evaluate the objective response rate (ORR) in patients with solid tumors harboring *FGFR* rearrangements or gastric cancer (including GEJ cancer) harboring *FGFR2* amplifications based on independent central review of radiologic images (IRC)	ORR, defined as the proportion of patients experiencing a best overall response of partial response (PR) or complete response (CR) (per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST 1.1]), based on IRC
Secondary	
• To evaluate ORR based on investigator assessment • To evaluate progression-free survival (PFS), disease control rate (DCR), duration of response (DOR), and overall survival (OS) • To assess safety and tolerability	• ORR, defined as the proportion of patients experiencing a best overall response of partial response of PR or CR (per RECIST 1.1), based on investigator assessment • DCR, defined as the proportion of patients experiencing a best overall response of stable disease (SD), PR, or CR (per RECIST 1.1), based on IRC • DOR defined as the time from the first documentation of response (CR or PR per RECIST 1.1 based on IRC) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first • PFS, defined as the time from first dose of study therapy to the date of death (any cause) or disease progression (based on IRC), whichever occurs first • OS, defined as the time from the date of first dose to the death date • Safety based on reported AEs and on-study laboratory parameters, graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events , Version 5.0 (NCI-CTCAE V5.0).
Exploratory	
• To assess the possible impact of genetic alterations or other laboratory abnormalities on the efficacy of futibatinib • To assess the population pharmacokinetics (3opPK) and exposure response	• Assessment of pharmacodynamic effects will be analyzed from circulating tumor DNA (ctDNA), tumor biopsy, and/or plasma samples. • PopPK and exposure response will be analyzed from blood samples collected during treatment.

Cohort C

Overall Objective The overall objective of Cohort C is to assess the clinical activity of futibatinib as monotherapy in the treatment of patients with myeloid/ lymphoid neoplasms (MLN) harboring *FGFR1* rearrangements.	
Primary	
To evaluate complete response rate	CR rate, defined as the proportion of patients who achieved a CR
Secondary	

• To evaluate:
  ○ ORR
  ○ CR + complete response with incomplete hematological recovery (CRi) rate
  ○ Complete or partial cytogenetic responses (CCcyR or PCyR) rate
  ○ Duration of CR
  ○ Duration of CR+CRi
  ○ DOR
  ○ Time-to-events
• To assess the safety and tolerability
	• ORR, defined as the proportion of patients who achieved a CR, CRi, or PR
	• CR+CRi rate, defined as the proportion of patients who achieved a CR or CRi
	• CCyR rate, defined as the proportion of patients who achieved CCyR
	• PCyR rate, defined as the proportion of patients who achieved PCyR
	• Duration of CR defined as the time from the first documentation of CR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• Duration of CR+CRi defined as the time from the first documentation of CR/CRi to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• DOR defined as the time from the first documentation of CR, CRi, or PR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• PFS, defined as the time from first dose of study therapy to the date of death (any cause) or disease progression, whichever occurs first
	• Relapse-free survival (RFS), defined as the time from the first documentation of CR to the first documentation of disease relapse or death due to any cause, whichever occurs first.
	• Event-free survival (EFS) (**leukemia presentation only**), defined as the time from first dose of study therapy to treatment failure, disease relapse after CR, or patient death from any cause.
	• OS, defined as the time from the date of first dose to the death date.
	• Safety based on reported AEs and on-study laboratory parameters, graded according to the NCI-CTCAE V5.0

Exploratory	
• To assess the pharmacodynamic effects of treatment with futibatinib • To assess the association of response and mechanisms of resistance in tumor tissue biopsies and/or blood • To assess the popPK and exposure response	• Changes in pharmacodynamic markers assessed in bone marrow tissue biopsies. • Exploratory association of tissue and/or blood markers with tumor efficacy endpoints and/or tumor resistance to futibatinib. • PopPK and exposure response will be analyzed from blood samples collected during treatment

Overall Design:

Study TAS-120-202 is an open-label, multinational, 3-arm Phase 2 study evaluating the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of futibatinib in patients with *FGFR* aberrations. Eligible patients will be assigned to 1 of 3 treatment cohorts based on diagnosis and *FGFR* gene aberration status.

Patients will receive futibatinib at an oral dose of 20 mg once a day on a continuous 28-day cycle. Treatment will continue until disease progression, unacceptable toxicity, or any other of the criteria for treatment discontinuation is met (Section 4.4). For patients who discontinue treatment for reasons other than disease progression, tumor assessments should be continued until radiologic disease progression is documented or until initiation of subsequent new anticancer therapy (whichever occurs first).

Patients will be followed for survival every 12 weeks (±2 weeks) until survival events (deaths) have been reported for 75% of enrolled patients, the patient withdraws consent, or the study is terminated early by the Sponsor.

Additional cohorts may be added in the future in case of new emerging efficacy data. This change will be implemented through a protocol amendment which will describe the rationale for the addition(s).

Number of Patients:

The study will enroll approximately 60 patients with advanced, metastatic, or locally-advanced solid tumor harboring *FGFR* rearrangements, except for primary brain tumor or iCCA); 35 patients with advanced, metastatic, or locally-advanced gastric or GEJ cancer harboring *FGFR2* amplification; and 20 patients with MLN harboring *FGFR1* rearrangements.

Entry Criteria:

Inclusion Criteria

1. Provide written informed consent
2. ≥18 years of age (or meets the country's regulatory definition for legal adult age, whichever is greater)
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
4. Has recovered from the acute toxic effects of prior anticancer therapy to baseline or Grade 1 (except toxicities which are not clinically significant such as alopecia)
5. Known *FGFR* aberration status and tumor type that meet all of the criteria for 1 of the following cohorts:
    a. Cohort A
        i. Histologically-confirmed, locally-advanced, advanced, or metastatic solid tumors harboring a *FGFR1-4* rearrangement determined in tumor tissue using next-generation sequencing (NGS), fluorescence in situ hybridization (FISH), or other assays that can determine gene rearrangements in tumor tissues. Patients with primary brain tumor or iCCA are not eligible.
        ii. Measurable disease per RECIST 1.1

iii. Had disease progression/recurrence after standard treatment for their advanced or metastatic cancer

b. Cohort B
   i. Histologically-confirmed, locally-advanced, advanced, or metastatic gastric or GEJ cancer harboring a *FGFR2* amplification. The tumor must have an *FGFR2*/CEN10 ratio of ≥5 or an *FGFR2* copy number ≥10 signals per cell determined in tumor tissue using NGS, FISH, or other assays that can determine gene amplification in tumor tissues.
   ii. Measurable disease per RECIST 1.1
   iii. Received at least 2 prior systemic regimens for advanced/metastatic disease
   iv. Experienced disease progression/recurrence during or after the most recent prior systemic treatment for advanced/metastatic gastric or GEJ cancer

c. Cohort C
   i. Confirmed MLN with a *FGFR1* rearrangement as defined by WHO criteria
   ii. Not a candidate for hematological stem cell transplant (HSCT) or relapsed after HSCT and donor lymphocyte infusion, and progressed and not a candidate for other therapies

6. Has archival or fresh tumor tissue (preferably in block format) available to send to central laboratory.
7. Adequate organ function as defined by the following criteria:
   a. Cohorts A and B:
      i. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L
      ii. Platelet count ≥ 75,000/mm^3 (≥ 75 × 109/L)
      iii. Hemoglobin ≥ 9.0 g/dL
      iv. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 × upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5.0 × ULN.
      v. Total bilirubin ≤ 1.5 × ULN, or ≤ 3.0 × ULN for patients with Gilbert's syndrome.
      vi. Creatinine clearance (CrCl) (calculated or measured value): ≥40 mL/min. For calculated CrCl, use the Cockcroft-Gault formula (Section 6).
      vii. Phosphorus <1.5 ULN
   b. Cohort C
      i. ALT and AST ≤ 3.0 × ULN; if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5.0 × ULN.
      ii. Total bilirubin ≤ 1.5 × ULN, or ≤ 3.0 × ULN for patients with Gilbert's syndrome.
      iii. CrCl (calculated or measured value): ≥40 mL/min. For calculated CrCl, use the Cockcroft-Gault formula (Section 6).
      iv. Phosphorus <1.5 ULN
8. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test prior to administration of the first dose of futibatinib. Female patients are not considered to be of child-bearing potential if they are post-menopausal, defined as no menses for 12 months without an alternative medical cause or permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
9. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 90 days after the last dose or longer based on local requirements.
10. Ability to take medications orally (feeding tube is not permitted).
11. Willing and able to comply with scheduled visits and study procedures.

Exclusion Criteria

1. Currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the investigator and Taiho Medical monitor is required to establish eligibility.
2. History and/or current evidence of any of the following disorders:
   a. Non-tumor related alteration of the calcium-phosphorus homeostasis that is considered clinically significant in the opinion of the Investigator
   b. Ectopic mineralization/calcification including, but not limited to, soft tissue, kidneys, intestine, or myocardia and lung, considered clinically significant in the opinion of the Investigator
   c. Retinal or corneal disorder confirmed by retinal/corneal examination and considered clinically significant in the opinion of the Investigator.
3. Corrected QT interval using Fridericia's formula (QTcF) >470 msec. Patients with an atrioventricular pacemaker or other condition (for example, right bundle branch block) that renders the QT measurement invalid are an exception and the criterion does not apply.
4. Treatment with any of the following within the specified time frame prior to the first dose of futibatinib:
   a. Major surgery within 4 weeks (surgical incision should be fully healed)
   b. Radiotherapy for extended field within 4 weeks or limited field radiotherapy within 2 weeks
   c. A drug that has not received regulatory approval for any indication within 14 or 21 days of treatment for a nonmyelosuppressive or myelosuppressive agent, respectively.
5. Received strong inhibitors and inducers of CYP3A4 within 2 weeks of first dose
6. Prior treatment with an FGFR inhibitor
7. A serious illness or medical condition(s) including, but not limited to, the following:
   a. Known acute systemic infection
   b. Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months
   c. History or current evidence of uncontrolled ventricular arrhythmia
   d. Chronic diarrhea diseases considered to be clinically significant in the opinion of the Investigator
   e. Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death
   f. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or futibatinib administration, or may interfere with the interpretation of study results, and in the judgment of the Investigator would make the patient inappropriate for entry into this study
8. Active central nervous system (CNS) metastasis and/or carcinomatous meningitis. Patients with previously treated brain metastases that are clinically and radiologically stable (for at least 4 weeks prior to enrollment) are eligible.
9. Known additional malignancy that is progressing or has required active treatment within the past 2 years. Patients with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
10. Pregnant or breastfeeding.

Evaluation Criteria:

Efficacy

Cohorts A and B

For patients in Cohorts A and B, on-site tumor assessments (including computed tomography [CT]/magnetic resonance imaging [MRI]) will be performed by the Investigator/local radiologist according to RECIST 1.1 guidelines). (Eisenhauer et al. 2009). Primary objective and additional secondary objectives will be assessed by an IRC.

Results of the local assessments, including response for target and non-target lesions and appearance of new lesions, will be the basis for the continuation or discontinuation of study therapy decisions.

Cohort C

Efficacy will be assessed based on investigators' assessment of imaging, bone marrow, peripheral blood, and extramedullary disease. Depending on the presentation response will be determined based on Treatment Response Criteria for MDS/MPN (Savona et al. 2015), Response Evaluation Criteria in Lymphoma (RECIL 2017) (Younes et al. 2017), and International Working Group (IWG) response criteria for AML (Cheson et al. 2003).

A review of the response assessments will be conducted by an adjudication committee.

Safety

The assessment of safety will be based on the incidence of treatment-emergent adverse events (TEAEs) and on-study laboratory parameters. Grading of TEAEs will be performed using NCI-CTCAE V5.0.

Pharmacokinetics

The PK population will consist of all patients who received futibatinib and have evaluable blood samples for analyses.

Pharmacodynamics

Genetic aberrations will be tested using analytically validated assay on NGS or similar technology at a central laboratory.

A blood sample will be collected to assess *FGF/FGFR* aberrations in ctDNA. In addition to assessing ctDNA as a pharmacodynamic biomarker, samples or a set of samples will be used to verify its utility as an alternative to tumor tissues for the potential companion diagnostic. Samples will be collected and stored, as per the laboratory manual, and analyzed in batches.

Archival or fresh tumor/bone marrow samples will be collected during screening to retrospectively confirm *FGFR* gene status at the Sponsor's designated central laboratories. The remaining samples may be stored at the Sponsor's designated central laboratories for up to 10 years after study completion for future testing.

Statistical Methods:

Determination of Sample Size

Approximately 60 patients with solid tumors harboring *FGFR* rearrangements will be enrolled in Cohort A. Sample size considerations (primary endpoint ORR) are based on a 2-stage Simon design, comparing a poor response of ≤ 10% vs a promising response of ≥ 25%, at a 5% 1-sided significance level and approximate 90% power.

- In Stage 1 (futility assessment), enrollment will include 35 patients and accrual will continue to Stage 2, if at least 4 (11.4%) of 35 patients respond (CR or PR).
- In Stage 2, if the Stage 1 futility boundary is exceeded, an additional 25 patients will be enrolled, for a total of at least 60 patients. With a total of 60 patients, if the observed ORR is 30%, the 95% exact confidence interval (CI) is (18.9%, 43.2%).

Approximately 35 patients with gastric or GEJ cancer harboring *FGFR2* amplification will be enrolled in Cohort B. Sample size considerations are based on differentiating a historical control ORR of 10% or less, with a target ORR of 35%. Assuming the true ORR is 35%, the cohort has approximately 96% power to reject the null hypothesis that the true ORR is ≤ 10%, considering a 2-sided alpha of 5%. With a sample size of 35, observing at least 8 responders will have a 95% CI lower bound excluding 10% (ORR of 23% with 95% CI [10.4% - 40.1%]).

Approximately 20 patients with MLN harboring *FGFR1* rearrangements will be enrolled in Cohort C. Sample size considerations are based on differentiating a historical control CR rate of 10% or less with a target CR rate of 50%. Assuming the true CR rate is 50%, the cohort has over 95% power to reject the null hypothesis that the true CR rate is ≤10%, considering a 2-sided alpha of 5%. Observing at least 6 responders out of 20 treated patients will have a 95% CI lower bound excluding 10% (CR rate of 30% with 95% CI (11.9% - 54.3%).

Interim Analysis

The Sponsor will review the data at the time Cohort A has the required number of patients to determine if the cohort should continue.

Efficacy Analyses

Cohorts A and B

Primary Efficacy Analysis

Objective response rate is defined as the proportion of patients with objective evidence of CR or PR. The primary evaluation of ORR will be based on an independent central review of radiologic images. At the analysis stage, the best objective response will be assigned for each patient as the best response recorded after initiation of study treatment and confirmed at least 4 weeks later. If applicable, responses recorded after disease progression or initiation of new anticancer treatment will be excluded. The exact 2-sided CI based on Clopper-Pearson methodology will be derived for ORR.

Secondary Efficacy Analyses

Overall response rate based on investigator assessment will be determined as decribed above for the primary analysis of ORR based on independent central review of radiologic images.

Disease control rate will be analyzed using the same methodology as ORR.

Duration of response will only be evaluated in patients with an objective response of CR or PR. Patients who are alive and progression-free as of the analysis cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy.

Progression-free survival will be estimated using the Kaplan-Meier method. Patients who die without a reported disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last tumor assessment. Patients who did not have any on-study assessments and did not die will be censored on the first dosing date. Patients who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy.

Overall survival will be analyzed in a similar manner to PFS. In the absence of confirmation of death or for patients who are alive as of the OS cut-off date, survival time will be censored at the last known date that the patient was alive.

Cohort C

Primary Analysis

Complete response rate defined as the proportion of patients who achieved a CR will be calculated and the exact 2-sided CI will also be derived using the Clopper Pearson methodology.

Secondary Analyses

The overall response, CR+CRi (leukemia presentation only), CCyR, and PCyR rates will be calculated and the exact 2-sided CIs will also be derived using the Clopper-Pearson methodology.

Duration of CR (only in patients who achieved a CR), duration of CR+CRi (only in patients who achieved a CR/CRi [leukemia presentation only]), and duration of response (only in patients with an objective response of CR, CRi [leukemia presentation only], or PR) will be estimated using the Kaplan-Meier method. Patients who are alive and progression-free as of the analysis cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy.

Progression-free survival will be estimated using the Kaplan-Meier method. Patients who die without a reported disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last tumor assessment. Patients who did not have any on-study assessments and did not die will be censored on the first dosing date. Patients who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy.

Relapse-free survival will only be evaluated in patients with an objective response of CR and measured from the first date of achieving CR until the first date of relapsed disease or death from any cause, whichever occurs first. Patients who die without a reported disease relapse will be considered to have relapsed on the date of their death. Patients who did not relapse or die will be censored on the date of their last tumor assessment. Patients who started any subsequent anti-cancer therapy without a prior reported relapse will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy.

Event-free survival will be estimated only for patients with leukemia presentation using the Kaplan-Meier method. EFS is defined as the time from first dose of study therapy to treatment failure, relapse after CR (if applicable), or death from any cause, whichever occurs first. For a patient with none of these events before the end of study follow-up, observation of EFS is censored at the date of last contact prior to the analysis cut-off date. If the patient does not achieve a CR, EFS is defined as the point of treatment failure or death, whichever comes first. Treatment failure for EFS is defined as PD in this study.

Overall survival will be analyzed in a similar manner to PFS. In the absence of confirmation of death or for patients who are alive as of the OS cut-off date, survival time will be censored at the last known date that the patient was alive.

Safety Analyses

The safety analysis will be performed using the All Treated Population.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities terminology and the severity of the toxicities will be graded according to the NCI-CTCAE V5.0, where applicable.

Concomitant medications will be coded according to the World Health Organization Drug Dictionary for Concomitant Medication.

All AEs will be summarized (by incidence) and listed by the System Organ Class, Preferred Term, toxicity/severity grade, and causal relationship to futibatinib. In addition, separate summaries of SAEs and Grade 3 or 4 AEs will be presented.

For all AEs that occurred between the signing of the ICF and the last day of the Safety Follow-up Period, lists of preferred AE terms, grade, onset date, actions, outcome of AE, date of outcome confirmed, causalities with the study drug, and comments on AEs will be listed by patient.

Hematological and chemistry laboratory parameters will be graded according to the NCI-CTCAE V5.0 where applicable. The worst severity grade, time to maximum Grade 3 or 4 value, and time to resolution (return to baseline grade or below) will be summarized.

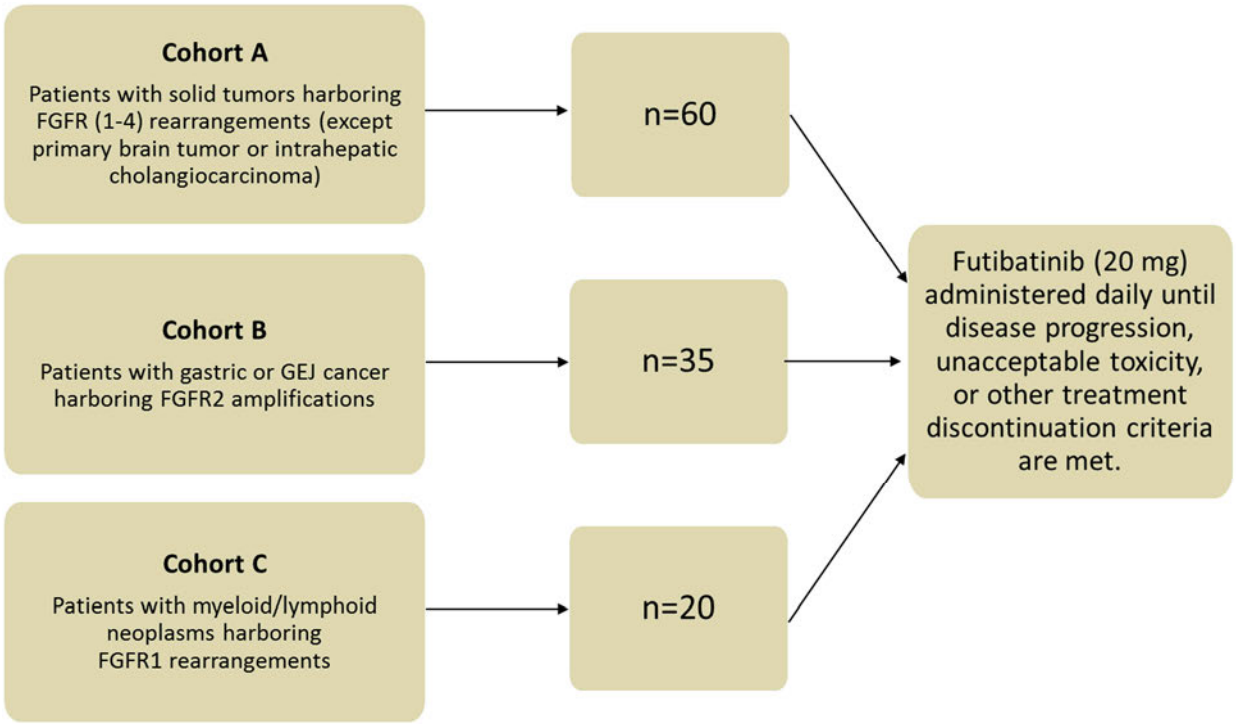
Safety data (AEs and clinical laboratory results) will be summarized descriptively. A list of 12-lead electrocardiogram findings will be presented by patient.

Pharmacodynamic and Pharmacokinetic Analyses

Pharmacodynamic and biomarker data will be summarized descriptively using all patients in the PD/Biomarker Evaluable Set who have evaluable data available.

PK analyses will be described in a separate Statistical Analysis Plan.

Study Schema



Schedule of Events

Evaluations on D1 of a cycle should be performed within 24 hours prior to dosing, unless otherwise noted. Procedures already performed during the screening period within 72 hours prior to dosing do not need to be repeated on C1D1. The End of Treatment (EOT) visit must be performed within 7 days after a decision is made to discontinue study treatment (for patients who discontinue at a planned study visit, that visit may be considered the EOT visit if all assessments required at EOT are performed). Required assessments for patients in Cohorts A and B are presented in Table 1 and for Cohort C in Table 2. Required assessments during the extension phase are presented in Table 3 for all cohorts.

Table 1: Schedule of Events (Cohorts A and B)

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Written informed consent	X										Written informed consent will be obtained prior to any study-related assessments or procedures.
Review eligibility criteria	X										
Demographics/medical history	X										
Review of baseline signs and symptoms	X										
Prior & concomitant medications, AE assessments	→	→	→	→	→	→	→	→	→		
Physical examination	X	X				X		X	X		Within 24 hours prior to dosing.
Vital signs	X	X				X		X	X		Heart rate, blood pressure, body temperature, and respiration rate.
Height and weight	X	X				X		X	X		Height at screening only.
ECOG performance status	X	X				X		X	X		Within 24 hours prior to dosing.
12-Lead electrocardiogram	X	X				X		X	X		
Hematology	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing. More frequent assessments may be performed if clinically indicated
Coagulation	X	X				X		X	X		Within 24 hours prior to dosing.
Chemistry (serum or plasma)	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing.

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Pregnancy test	X Within 7 days							X			Serum pregnancy test required for WOCBP. Additional testing may be required by local regulations.
Ophthalmological examination	X			See Note							Examination to be performed by an ophthalmologist or qualified delegate at screening, 4-6 weeks after first dose, and as indicated if symptoms or signs of mineral deposits.
PK blood sampling				See Note							Pre-dose (from -30 min to just before dose), 1 h±30 min post-dose, and 3 h±30 min post-dose
ctDNA blood samples	X							X			
Tumor tissue sample	X										Archival or fresh tumor biopsy
Tumor assessments (CT/MRI)	X						X	X	X	X	At baseline and the end of every 2 cycles ±7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever comes first). For patients who discontinue treatment for reasons other than radiographic disease progression, imaging will be performed at EOT, (if the prior scan was performed ≥9 weeks) and during Survival Follow-up until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first) unless patient withdraws consent.
Survival status										X	For all patients, unless patient withdraws consent or the study is terminated early by the Sponsor.

Table 2: Schedule of Events (Cohort C)

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Written informed consent	X										Written informed consent will be obtained prior to any study-related assessments or procedures.
Review eligibility criteria	X										
Demographics/medical history	X										
Review of baseline signs and symptoms	X										
Prior & concomitant medications, AE assessments	→										
Physical examination	X	X				X		X	X		Within 24 hours prior to dosing.
Vital signs	X	X				X		X	X		Heart rate, blood pressure, body temperature, and respiration rate.
Height and weight	X	X				X		X	X		Height at screening only.
ECOG performance status	X	X				X		X	X		Within 24 hours prior to dosing.
12-Lead electrocardiogram	X	X				X		X	X		
Hematology	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing. More frequent assessments may be performed if clinically indicated
Coagulation	X	X				X		X	X		Within 24 hours prior to dosing.
Chemistry (serum or plasma)	X	X	X	X	X	X		X	X		Within 24 hours prior to dosing.

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Pregnancy test	X Within 7 days							X			Serum pregnancy test required for WOCBP. Additional testing may be required by local regulations.
Ophthalmological examination	X			See Note							Examination to be performed by an ophthalmologist or qualified delegate. At screening, 4-6 weeks after first dose, and as indicated if symptoms or signs of mineral deposits.
PK blood sampling				See Note							Pre-dose (from -30 min to just before dose), 1 h±30 min post-dose, and 3 h±30 min post-dose
ctDNA blood samples	X							X			
Tumor tissue sample	X										Archival or fresh tumor biopsy
CT/MRI	X						X	X	X	X	At baseline and the end of every 2 cycles ±7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever comes first). For patients who discontinue treatment for reasons other than radiographic disease progression, imaging will be performed at EOT, (if the prior scan was performed ≥9 weeks) and during Survival Follow-up until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first) unless patient withdraws consent.
PET scan	X				See Note						PET scan to be performed at baseline then end of Cycle 1 if abnormal at baseline. Additional scans as required for response assessment.

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =28 days)						End of Treatment (+7 days)	Safety Follow-up 30 days after last dose (+7 days)	Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1				Cycle ≥2					
		D1 (±3 days)	D8 (±3 days)	D15 (±3 days)	D22 (±3 days)	D1 (±3 days)	End of Cycle (±7 days)				
Lymph node biopsy	X	See Note									Recommended at baseline if lymph node present at baseline and progression
Bone marrow biopsy	X	See Note									Biopsy to be performed at baseline and during treatment. Bone marrow biopsy should be performed in case of normalisation of peripheral blood count. In absence of peripheral blood count normalisation, biopsy to be performed every 6 months. Additional biopsies to be performed as clinically indicated.
Survival status										X	For all patients, unless patient withdraws consent or the study is terminated early by the Sponsor.

Table 3: Schedule of Events – Study Extension Phase: All Cohorts

	Treatment Period **At Least Every 3 Cycles**	**Safety Follow-up** **30 (+7) Days After last Dose**	**Notes**
Physical examination	X	X	Within 24 hours prior to dosing on D1
Vital signs	X	X	Heart rate, blood pressure, body temperature, and respiration rate.
Weight	X	X	
Ophthalmological examination	(X)	X	As needed due to local requirements, physician judgment, and/or symptoms or signs of mineral deposits.
ECOG performance status	X	X	Within 24 hours prior to dosing on D1
12-Lead electrocardiogram	X	X	
Hematology and coagulation	X	X	Within 24 hours prior to dosing on D1
Chemistry (serum or plasma)	X	X	Within 24 hours prior to dosing on D1
Pregnancy test		X	More frequently if required by local regulations.
Prior & concomitant medications, AE assessments	(X)	X	Collect from the time main informed consent is signed through 30 days after administration of the last dose of study therapy or until the start of new anticancer therapy, whichever is earlier.
Tumor assessments/imaging	(X)		All Cohorts: CT/MRI scans at baseline and the end of every 2 cycles ±7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever comes first). Cohort C only: bone marrow, PET, and other tumor assessments as clinically indicated.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ANC	Absolute neutrophil count
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BCR	Breakpoint cluster region (gene)
BCRP	Breast cancer resistance protein
CCA	Cholangiocarcinoma
CI	Confidence interval
CR	Complete response
CCyR	Complete cytogenetic response
CrCl	Creatinine clearance
CRi	Complete response with incomplete hematological recovery
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulatng tumor DNA
CYP	Cytochrome P450
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form

Abbreviation	Definition
EFS	Event-free survival
EOT	End of treatment/end of therapy
FGFR	Fibroblast growth factor receptor
FISH	Fluorescence in situ hybridization
GEJ	Gastro-esophageal junction
GCP	Good Clinical Practice
HSCT	Hematological stem cell transplant
iCCA	Intrahepatic cholangiocarcinoma
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Central Review Committee
MLN	myeloid/lymphoid neoplasms
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NGS	Next generation sequencing
ORR	Objective response rate
OS	Overall survival
PCyR	Partial cytogenetic response
PD	Progressive disease

Abbreviation	Definition
PFS	Progression free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetics
PR	Partial response
RECIL	Response Evaluation Criteria in Lymphoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
RFS	Relapse-free survival
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TOI	Taiho Oncology, Inc.
ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	Women of childbearing potential

1. INTRODUCTION

Futibatinib is a novel and selective small molecule irreversible, covalent inhibitor of fibroblast growth factor receptor (*FGFR*) 1–4 that is currently being tested in patient with different cancers.

Evolving knowledge of the molecular and genetic basis of cancer has led to refinements in the categorization of malignancies based on molecular markers. This, in turn, has led to changes in trial design, specifically tumor agnostic trials that enroll patients with the same genetic alterations but not the same histologic or anatomic tumor type. These trials are important because they provide insight into the importance of a genomic alteration across various histologic tumor types and allow for the development of more targeted therapies (Lacombe et al 2014).

1.1. Disease Background

FGFR signaling plays a crucial role in cancer cell proliferation, migration, angiogenesis, and survival. Recent studies have uncovered increasing evidence that deregulated *FGFRs* can function as driving oncogenes in certain tumor types, maintaining the malignant properties of cancer cells (Turner & Grose 2010). When *FGFRs* are amplified, rearranged, or undergo fusion, aberrant activation of downstream pathways results in mitogenic, mesenchymal, and antiapoptotic responses in cells. Therefore, FGFRs are attractive targets for therapeutic intervention in cancer (Turner & Grose 2010).

FGFR aberrations were found in 7.1% of cancers, with the majority being gene amplifications (66%), followed by mutations (26%) and rearrangements (8%) (Helsten et al. 2016).

Although they are rare, *FGFR2* fusions with multiple partners have been uncovered in many types of cancer, including cholangiocarcinoma (CCA), lung cancer, thyroid cancer, breast cancer, and prostate cancer (Wu et al. 2013; Gallo et al. 2015; Yoshihara et al. 2015). Of all the *FGFRs*, *FGFR2* shows the broadest range of fusion partners. Fusion genes have also been reported in bladder cancer and urothelial carcinoma (Williams et al. 2013; Loriot et al. 2019). It is clear that *FGFR* fusions are emerging as a new class of targetable fusions in solid tumors.

Amplification of *FGFR2* has been described in 4-10% of gastric cancer, particularly of the aggressive diffuse subtype (Deng et al. 2012; Kunii et al. 2008; Jung et al. 2012; Liu et al. 2014). Each year, approximately 990,000 people are diagnosed with gastric cancer worldwide, and about 738,000 people die from this disease (Ferlay et al. 2010), making gastric cancer the fourth most common cancer and the second most common cause of cancer death (Jemal et al. 2010). While the incidence of gastric cancer has been decreasing, the incidence of gastro-esophageal junction (GEJ) cancer doubled in Western countries from the 1970s to the 1990s, with rates stabilizing today (Buas & Vaughan, 2013).

In vitro, *FGFR2*-amplified gastric cancer cell lines have been shown to be selectively sensitive to the inhibitory effects of *FGFR* tyrosine kinase inhibitors (Kunii et al. 2008).

Myeloid and lymphoid neoplasms with abnormalities of the *FGFR1* gene have been recognized as a distinct disease group in the 2008 World Health Organization (WHO) classification of hematopoietic neoplasms (Bain et al. 2008). These myeloproliferative neoplasms are characterized by eosinophilia, lymphadenopathy, and a high incidence of T-cell non-Hodgkin lymphoma with progression to acute myeloid leukemia (MacDonald et al. 1995). They occur over a wide age range of 3 to 84 years, with a median of 44 years, and with a very slight male

predominance (male to female ratio of 1.2:1) (Jackson et al. 2010). This is a very rare disease, with fewer than 100 patients reported around the world (MacDonald et al. 2002; Jackson et al. 2010). There is a marked absence of curative treatments for these patients. Of the 4 FGFRs, FGFR2 and FGFR3 have been identified as having comparatively more frequent gene rearrangements (Courjal et al. 1997). However, although hematopoietic neoplasms with *FGFR1* rearrangements are uncommon entities, they are extremely aggressive and resistant to standard treatments. One of the most frequently observed cytogenetic abnormalities is t(8;22) (p11.2;q11.2). The t(8;22) abnormality results in an in-frame fusion of FGFR1 on 8p11 and the breakpoint cluster region (BCR) gene on 22q11. The resultant fusion proteins activate tyrosine kinases, which may result in the development of hematologic malignancies (Villafuerte-Gutiérrez et al. 2018).

This Phase 2 clinical trial will investigate the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of futibatinib in patients with tumors harboring specific *FGFR* aberrations. Patients will be enrolled into one of 3 cohorts: patients with solid tumors harboring *FGFR* rearrangements (excluding primary brain tumors and intrahepatic CCA [iCCA]); patients with gastric or GEJ cancer harboring *FGFR2* amplification; and patients with myeloid or lymphoid neoplasms (MLN) harboring *FGFR1* rearrangement.

1.2. Futibatinib (TAS-120)

1.2.1. Clinical Overview

As of 5 September 2019, a total of 460 subjects (41 healthy volunteers and 419 patients) have been treated with futibatinib across 4 clinical trials.

- Study 10059010 is an ongoing, Phase 1 study being conducted in Japan to evaluate the PK, safety, and preliminary efficacy of futibatinib in patients with advanced solid tumors administered futibatinib three times a week (doses 8 to 240 mg) or daily (QD, doses 8 to 120 mg). The most frequently reported treatment-emergent AEs (>20% of all patients at all dose levels) were hyperphosphatemia, decreased appetite, diarrhea, constipation, nausea, stomatitis, and vomiting. Adverse events were mainly Grade 1 or 2.
- Study TAS-120-101 is an ongoing, 3-part global study to evaluate the PK, safety, and efficacy of futibatinib administered 3 times a week (doses 8 to 200 mg) or QD (doses 4 to 24 mg):
    - Phase 1 Dose Escalation (completed with a total of 86 patients receiving either daily or 3-times-per-week dosing)
    - Phase 1 Dose Expansion, which includes additional cohorts in CCA, gliomas, urothelial carcinoma, and basket cohorts with *FGF/FGFR* aberrations
    - Phase 2 study initiated in April 2018, evaluating futibatinib at a QD dose of 20 mg, in patients with iCCA harboring *FGFR2* gene rearrangements
    - The most frequently reported treatment-emergent AEs (>20%) in patients administered futibatinib 20 mg QD (recommended Phase 2 dose) were hyperphosphatemia, diarrhea, constipation, nausea, dry mouth, increased ALT, increased AST, and fatigue.

- Study 10059020, a Phase 1, PK, and bioequivalence study in healthy adult males. This completed study compared two futibatinib formulations and found them to be biologically equivalent.
- Study TAS-120-102, a food effect study in healthy adult subjects. This completed study evaluated the effect of food on the PK of futibatinib under fasting or fed conditions and demonstrated that PK was affected by the consumption of a high-fat, high-calorie meal.

Efficacy has been observed in different tumor types:

- Solid tumors harboring *FGFR* rearrangements, including iCCA, head and neck, unknown primary, and gastric cancer
- Gastric cancer with *FGFR2* amplification
- MPN with *FGFR1* rearrangement
- Other solid tumors with different *FGFR* aberrations

Refer to the Investigator's Brochure for more detailed background information on futibatinib.

1.3. Summary of Study Rationale

Based on available preclinical and clinical data to date, the Sponsor concludes that the benefit-risk assessment results of futibatinib support the continued enrollment and treatment of patients in clinical trials and supports further investigation of futibatinib in tumors with *FGFR* aberrations.

The Phase 2 study described in this protocol will evaluate the efficacy and safety of futibatinib in patients with *FGFR* aberrations in 3 distinct cohorts.

Based on prior safety and efficacy experience in the broad Phase I dose escalation and expansion study a dose of 20 mg QD of futibatinib has been selected for use in this Phase 2 trial. The drug is administered continuously without interruption. Treatment cycles of 28 days will be used to define the protocol specified interval for tumor measurement and other interventions.

2. OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study are shown in Table 4 and Table 5.

Table 4: Objectives and Endpoints (Cohorts A and B)

Primary	
To evaluate the objective response rate (ORR) in patients with solid tumors harboring *FGFR* rearrangements or gastric cancer (including GEJ cancer) harboring *FGFR2* amplifications based on independent central review of radiologic images (IRC)	ORR, defined as the proportion of patients experiencing a best overall response of partial response (PR) or complete response (CR) (per Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST 1.1]), based on IRC
Secondary	
• To evaluate ORR based on investigator assessment • To evaluate progression-free survival (PFS), disease control rate (DCR), duration of response (DOR), and overall survival (OS) • To assess safety and tolerability	• ORR, defined as the proportion of patients experiencing a best overall response of partial response of PR or CR (per RECIST 1.1), based on investigator assessment • DCR, defined as the proportion of patients experiencing a best overall response of stable disease (SD), PR, or CR (per RECIST 1.1), based on IRC • DOR defined as the time from the first documentation of response (CR or PR per RECIST 1.1 based on IRC) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first • PFS, defined as the time from first dose of study therapy to the date of death (any cause) or disease progression (based on IRC), whichever occurs first • OS, defined as the time from the date of first dose to the death date • Safety based on reported AEs and on-study laboratory parameters, graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events, Version 5.0 (NCI-CTCAE V5.0),
Exploratory	
• To assess the possible impact of genetic alterations or other laboratory abnormalities on the efficacy of futibatinib • To assess the population pharmacokinetics (popPK) and exposure response	• Assessment of pharmacodynamic effects will be analyzed from circulating tumor DNA (ctDNA), tumor biopsy, and/or plasma samples. • PopPK and exposure response will be analyzed from blood samples collected during treatment.

Table 5: Objectives and Endpoints: Cohort C

Overall Objective The overall objective of Cohort C is to assess the clinical activity of futibatinib as monotherapy in the treatment of patients with MLN harboring *FGFR1* rearrangements.	
Primary	
To evaluate complete response (CR) rate	CR rate, defined as the proportion of patients who achieved a CR.
Secondary	

• To evaluate:
  o ORR
  o CR + complete response with incomplete hematological recovery (CRi) rate
  o Complete or partial cytogenetic responses (CCyR or PCyR) rate
  o Duration of CR
  o Duration of CR+CRi
  o DOR
  o Time-to-events
• To assess the safety and tolerability
	• ORR, defined as the proportion of patients who achieved a CR, CRi, or PR
	• CR+CRi rate, defined as the proportion of patients who achieved a CR or CRi
	• CCyR rate, defined as the proportion of patients who achieved CCyR
	• PCyR rate, defined as the proportion of patients who achieved PCyR
	• Duration of CR defined as the time from the first documentation of CR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• Duration of CR+CRi defined as the time from the first documentation of CR/CRi to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• DOR defined as the time from the first documentation of CR, CRi, or PR to the first documentation of objective tumor progression or death due to any cause, whichever occurs first
	• PFS, defined as the time from first dose of study therapy to the date of death (any cause) or disease progression, whichever occurs first
	• Relapse-free survival (RFS), defined as the time from the first documentation of CR to the first documentation of disease relapse or death due to any cause, whichever occurs first.
	• Event-free survival (EFS) (**leukemia presentation only**), defined as the time from first dose of study therapy to treatment failure, disease relapse after CR, or patient death from any cause.
	• OS, defined as the time from the date of first dose to the death date.
	• Safety based on reported AEs and on-study laboratory parameters, graded according to the NCI-CTCAE V5.0.

Exploratory	
• To assess the pharmacodynamic effects of treatment with futibatinib • To assess the association of response and mechanisms of resistance in tumor tissue biopsies and/or blood • To assess the popPK and exposure response	• Changes in pharmacodynamic markers assessed in bone marrow tissue biopsies. • Exploratory association of tissue and/or blood markers with tumor efficacy endpoints and/or tumor resistance to futibatinib. • PopPK and exposure response will be analyzed from blood samples collected during treatment

3. INVESTIGATIONAL PLAN

3.1. Overview of Study Design

Study TAS-120-202 is an open-label, multinational, 3-arm Phase 2 study evaluating the efficacy, safety, tolerability, PK, and pharmacodynamics of futibatinib in patients with *FGFR* aberrations. Eligible patients will be assigned to 1 of 3 treatment cohorts based on diagnosis and *FGFR* gene aberration status (Figure 1):

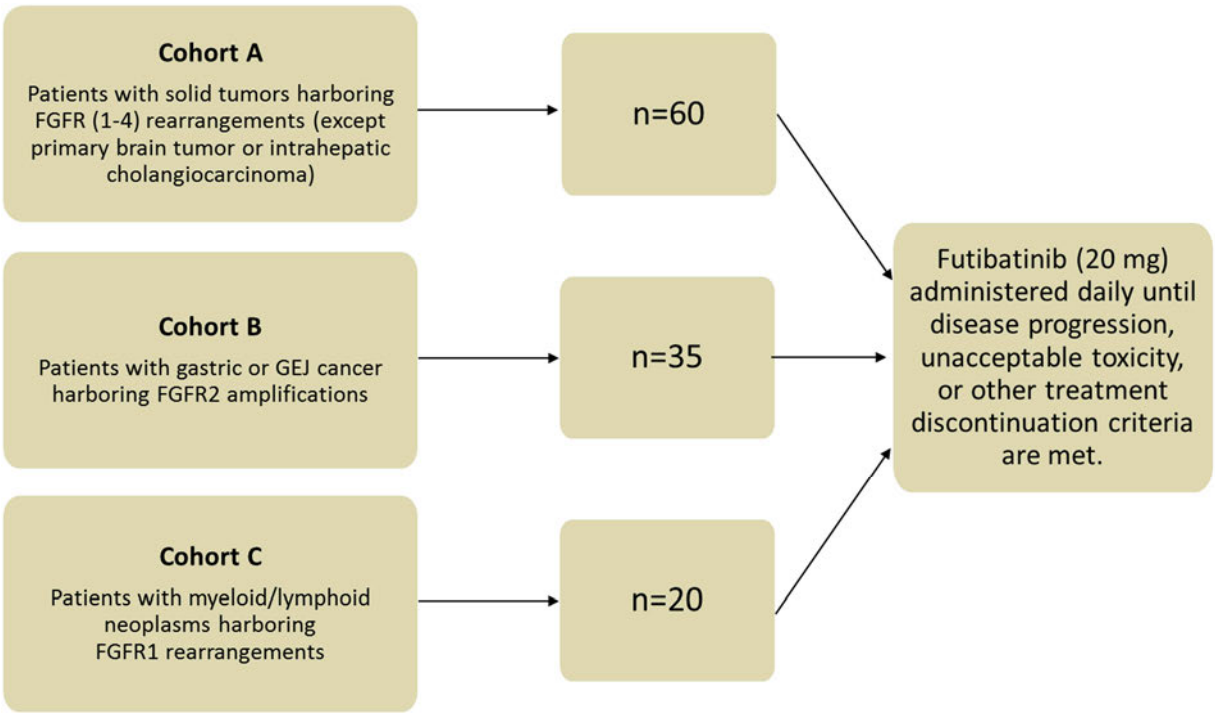

Figure 1: Study Schema

Patients will receive futibatinib at an oral dose of 20 mg once a day on a continuous 28-day cycle.

Treatment will continue until disease progression, unacceptable toxicity, or any other of the criteria for treatment discontinuation is met (Section 4.4). For patients who discontinue treatment for reasons other than disease progression, tumor assessments should be continued until disease progression is documented or until initiation of subsequent new anticancer therapy (whichever occurs first).

Patients will be followed for survival every 12 weeks (±2 weeks) until survival events (deaths) have been reported for 75% of enrolled patients, the patient withdraws consent, or the study is terminated early by the Sponsor.

Additional cohorts may be added in the future in case of new emerging data. This change will be implemented through a protocol amendment which will describe the rationale for the addition(s).

3.2. Scientific Rationale for Study Design

Please see Section 1.3.

3.3. Study Periods and Visits for Each Patient

The study periods / visits described in this section are defined for all patients. Please see the schedule of events for an outline of all assessments to be performed during each study period / visit.

For all patients, the Safety Assessment Period begins at the time the informed consent form (ICF) is signed and continues until at least 30 days after the last dose of futibatinib. After the 30-day Safety Follow-Up Visit (see below), patients who have not started treatment with a new anti-cancer therapy will be assessed for drug-related serious adverse events (SAEs) only.

For each patient, the Study Duration is defined as the time from day of ICF signature to the last day of Disease Assessment Follow-up / Survival Follow-up (see below).

3.3.1. Screening Period

The Screening Period is defined as the time from when the patient signs the ICF to when they receive the first dose of futibatinib. Determination of eligibility is based on the entry criteria enumerated in Section 4. No protocol-specific procedures or assessments may be performed prior to completion of the ICF, except for procedures that represent standard-of-care.

3.3.2. Treatment Period and End of Treatment Visit

Treatment discontinuation may occur for any of the reasons listed in Section 4.4. The treatment period is the time from first dose of futibatinib (Day 1) to the date of last dose of futibatinib. An end-of-treatment (EOT) visit must be performed within 7 days after the decision is made to discontinue futibatinib; at this visit, every effort should be made to perform the assessments outlined in the schedule of events. For patients who discontinue at a planned study visit, that visit may be considered the EOT visit if all assessments required at EOT are performed.

3.3.3. Safety Follow-Up Period and 30-Day Safety Follow-Up Visit

The safety follow-up period is the time from the date of last dose of study therapy through the 30-day safety follow-up visit, which must be performed 30 days (+7 days) following the last dose of study therapy. If the patient starts new anticancer therapy within 30 days of the last dose of study therapy, the 30-day safety follow-up visit should be performed before the start of new anticancer therapy. Every effort should be made to perform the assessments outlined in the schedule of events. If the patient is unable to return to the study site, a follow-up phone call can be made by the study site to collect any new safety information that occurred during the Safety Follow-up Period.

After the 30-day Safety Follow-Up Visit (see below), patients who have not started treatment with a new anti-cancer therapy will be assessed for drug-related serious adverse events (SAEs) only.

3.3.4. Post-Discontinuation Considerations

Patients who discontinue without documented disease progression should continue to undergo tumor assessments according to the Schedule of Events (that is, every 8 weeks ±7 days) until progressive disease (PD) is documented, new anticancer therapy is initiated, the study is terminated, or the patient dies, withdraws consent, or is lost to follow-up).

3.3.5. Survival Follow-up

Once a patient discontinues study treatment, regardless of the reason, survival follow-up will begin, unless the patient withdraws consent or the study is terminated early by the Sponsor. During this period, the patient or family should be contacted for survival follow-up every 12 weeks (±2 weeks) until survival events (deaths) have been reported for 75% of enrolled patients, patient withdraws consent or the study is terminated early by the Sponsor. In addition, all subsequent anticancer treatments will be recorded.

3.4. Study Completion and Study Extension

The study will be considered complete when:

- Survival events (deaths) have been reported for 75% of enrolled patients; or
- The trial is halted early for any reason.

Following Study Completion, patients deriving benefit from study therapy in the opinion of the Investigator and Sponsor may be permitted to continue treatment with futibatinib in a Study Extension phase. During Study Extension, patients may receive treatment until withdrawal criteria are met and study drug is available.

During this period, all safety assessments are to be continued according to the schedule in (Table 3). Specifically, study extension data collection is to include, at a minimum:

- Study drug administration;
- Study drug accountability;
- Serious adverse events;
- Non-serious AEs that are related to study treatment or result in treatment discontinuation; and
- Any cases of pregnancy or overdose.

3.5. Patient Enrollment

Eligibility must be verified prior to patient enrollment. Patients will be enrolled via an Interactive Voice/Web Response System (IXRS). The patient should receive the first dose of study therapy within 3 days following enrollment.

4. SELECTION AND WITHDRAWAL OF PATIENTS

Results of *FGFR* gene aberration status should be available before the patient undergoes any protocol-specific procedures. Waivers will not be granted for any of the eligibility criteria.

4.1. Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Provide written informed consent
2. ≥18 years of age (or meets the country's regulatory definition for legal adult age, whichever is greater)
3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
4. Has recovered from the acute toxic effects of prior anticancer therapy to baseline or Grade 1 (except toxicities which are not clinically significant such as alopecia)
5. Known *FGFR* aberration status and tumor type that meet all of the criteria for 1 of the following cohorts:

a. Cohort A
   i. Histologically-confirmed, locally-advanced, advanced, or metastatic solid tumors harboring a *FGFR1-4* rearrangement determined in tumor tissue using next-generation sequencing (NGS), fluorescence in situ hybridization (FISH), or other assays that can determine gene rearrangements in tumor tissues. Patients with primary brain tumor or intrahepatic cholangiocarcinoma are not eligible.
   ii. Measurable disease per RECIST 1.1
   iii. Had disease progression/recurrence after standard treatment for their advanced or metastatic cancer

b. Cohort B
   i. Histologically-confirmed, locally-advanced, advanced, or metastatic gastric or GEJ cancer harboring a *FGFR2* amplification. The tumor must have an FGFR2/CEN10 ratio of ≥5 or an *FGFR2* copy number ≥10 signals per cell determined in tumor tissue using NGS, FISH, or other assays that can determine gene amplifications in tumor tissues.
   ii. Measurable disease per RECIST 1.1
   iii. Received at least 2 prior systemic regimens for advanced/metastatic disease
   iv. Experienced disease progression/recurrence during or after the most recent prior systemic treatment for advanced/metastatic gastric or GEJ cancer

c. Cohort C
   i. Confirmed MLN with a *FGFR1* rearrangement as defined by WHO criteria
   ii. Not a candidate for hematological stem cell transplant (HSCT) or relapsed after HSCT and donor lymphocyte infusion, and progressed and not a candidate for other therapies.

6. Has archival or fresh tumor tissue (preferably in block format) available to send to central laboratory.
7. Adequate organ function as defined by the following criteria:

a. Cohorts A and B:

i. Absolute neutrophil count (ANC) ≥ 1.0×10^9/L
ii. Platelet count ≥ 75,000/mm^3 (≥ 75×10^9/L)
iii. Hemoglobin ≥ 9.0 g/dL
iv. ALT and aspartate aminotransferase (AST) ≤ 3.0 × upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5.0 × ULN.
v. Total bilirubin ≤ 1.5 × ULN, or ≤ 3.0 × ULN for patients with Gilbert's syndrome.
vi. Creatinine clearance (CrCl) (calculated or measured value): ≥40 mL/min. For calculated CrCl, use the Cockcroft-Gault formula (Section 6).
vii. Phosphorus < 1.5 ULN

b. Cohort C

i. ALT and AST ≤ 3.0 × ULN; if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤ 5.0 × ULN.
ii. Total bilirubin ≤ 1.5 × ULN, or ≤ 3.0 × ULN for patients with Gilbert's syndrome.
iii. CrCl (calculated or measured value): ≥40 mL/min. For calculated CrCl, use the Cockcroft-Gault formula (Section 6).
iv. Phosphorus <1.5 ULN

8. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test prior to administration of the first dose of futibatinib. Female patients are not considered to be of child-bearing potential if they are post-menopausal (no menses for 12 months without an alternative medical cause) or permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
9. Both males and females of reproductive potential must agree to use effective birth control during the study prior to the first dose and for 90 days after the last dose or longer based on local requirements.
10. Ability to take medications orally (feeding tube is not permitted).
11. Willing and able to comply with scheduled visits and study procedures.

4.2. Exclusion Criteria

A patient must not meet any of the following exclusion criteria to be eligible for participation in this study:

1. Currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study. If a patient is currently enrolled in a clinical trial involving non-approved use of a device, then agreement with the investigator and Taiho Medical monitor is required to establish eligibility.
2. History and/or current evidence of any of the following disorders:
   a. Non-tumor related alteration of the calcium-phosphorus homeostasis that is considered clinically significant in the opinion of the Investigator.
   b. Ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, or myocardia and lung, considered clinically significant in the opinion of the Investigator.

   c. Retinal or corneal disorder confirmed by retinal/corneal examination and considered clinically significant in the opinion of the Investigator.

3. Corrected QT interval using Fridericia's formula (QTcF) >470 msec. Patients with an atrioventricular pacemaker or other condition (for example, right bundle branch block) that renders the QT measurement invalid are an exception and the criterion does not apply.
4. Treatment with any of the following within the specified time frame prior to the first dose of futibatinib:
   a. Major surgery within 4 weeks (surgical incision should be fully healed)
   b. Radiotherapy for extended field within 4 weeks or limited field radiotherapy within 2 weeks
   c. A drug that has not received regulatory approval for any indication within 14 or 21 days of treatment for a nonmyelosuppressive or myelosuppressive agent, respectively
5. Received strong inhibitors and inducers of CYP3A4 within 2 weeks
6. Prior treatment with an FGFR inhibitor
7. A serious illness or medical condition(s) including, but not limited to, the following:
   a. Known acute systemic infection
   b. Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months
   c. History or current evidence of uncontrolled ventricular arrhythmia
   d. Chronic diarrhea diseases considered to be clinically significant in the opinion of the Investigator
   e. Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death
   f. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or futibatinib administration, or may interfere with the interpretation of study results, and in the judgment of the Investigator would make the patient inappropriate for entry into this study
8. Active central nervous system (CNS) metastasis and/or carcinomatous meningitis. Patients with previously treated brain metastases that are clinically and radiologically stable (for at least 4 weeks prior to enrollment) are eligible.
9. Known additional malignancy that is progressing or has required active treatment within the past 2 years. Patients with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
10. Pregnant or breastfeeding.

4.3. Screen Failure

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE after completion of the ICF.

Patients who do not meet the criteria for participation in this study (screen failure) may be rescreened a maximum of 3 times. Rescreened patients should be assigned the same subject identification code as for the initial screening.

4.4. Discontinuation of Treatment

A patient will be discontinued from all study therapy for any of the following reasons:

1. Disease progression
2. Unacceptable AEs, or change in underlying condition such that the patient can no longer tolerate therapy, as evidenced by a dose delay > 28 days from the scheduled start date of the next cycle or need for more than 2 dose reductions outlined in this protocol
3. Physician's decision, including need for other anticancer therapy not specified in the protocol or surgery or radiotherapy to the only site(s) of disease being followed in the study
4. Pregnancy
5. Termination of the study by the Sponsor, or
6. At the patient's request at any time irrespective of the reason.

Patients who withdraw consent for further treatment may choose to remain on study; in such a case, all study evaluations should continue as outlined in this protocol. If the patient withdraws consent to all follow-up assessments, the patient should be considered to have discontinued the study as described in Section 4.5.

4.5. Withdrawal from the Study

A patient will be withdrawn from all study interventions and assessments (that is, discontinued from the study without follow-up) for any of the following reasons:

1. Death
2. Lost to follow-up
    - A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
    - The following actions must be taken if a patient fails to return to the clinic for a required study visit:
        – The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the

assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.

- Before a patient is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

3. Patient withdrawal of consent to further follow-up assessments, irrespective of the reason.

5. STUDY TREATMENT

5.1. Study Drug Administration

A study cycle is defined as 28 days. Futibatinib is supplied as 4 mg tablets and will be taken orally at a dose of 20 mg daily until the patient meets any of the administration discontinuation criteria (see Section 4.4).

Futibatinib should be administered under fasting conditions. It should be taken with a glass of water, on an empty stomach, at the same time each day. No food should be consumed for 2 hours prior and 1 hour after the dose of futibatinib, but patients may drink water during this period.

When a PK sample is collected, futibatinib should be administered on site after collection of the first PK sample.

In the event of a dosing delay up to 12 hours after the scheduled dosing time, the patient should still take that day's dose. If the dosing delay continues for >12 hours after the scheduled dosing time, or if the patient vomits after a dose, the patient should skip dosing for that day and not make up for it the following day.

5.2. Dose and Schedule Modifications

Stepwise dose reductions of 4 mg to 16 mg (first reduction) and 12 mg (second reduction) are permitted based on toxicities. If dose reduction fails to result in achieving the minimal criteria to resume treatment or, if toxicities occur which would necessitate reduction of the dose of futibatinib below 12 mg QD, the patient should be discontinued from futibatinib.

Following a dose reduction, if a benefit/risk assessment favors an increase of futibatinib dose up to the initial starting dose (20 mg QD), an agreement with the Sponsor's medical monitor is required prior to the dose increase.

If toxicities related to the dose reduction do not recover based on the criteria defined below within 28 days after the last dose of futibatinib, the patient will be discontinued permanently from treatment (Section 4.4). If resumption criteria are met within 28 days of the last dose of futibatinib, the patient may resume futibatinib treatment at the appropriate dose level.

5.2.1. Dose Modifications for Nonhematologic Toxicities

Dosing modification guidelines for nonhematologic and ocular toxicities are provided in Table 6 and Table 7, respectively.

Recommendations for hyperphosphatemia management are provided in Table 8. These are suggested guidelines based on emerging data from studies evaluating *FGFR* inhibitors and studies of futibatinib.

Table 6: Dose Modifications for Related Nonhematologic Toxicities

Grade[a]	**Dose Interruption/Resumption**	**Dose Adjustment**
Grade 1 or 2	Maintain treatment at the same dose level	None
Grade 3	Withhold treatment until return to baseline or Grade ≤1	Reduce by 1 dose level from the previous level. For Grade 3 nausea, vomiting, and/or diarrhea lasting >72 hours despite optimal medical management require withhold of treatment and dose reduction by one level,
Grade 4	Discontinue treatment	Permanent discontinuation of futibatinib.
Grade 4 (lab abnormality AE)	Withhold treatment until return to baseline or Grade ≤1	Futibatinib will be permanently discontinued if assessed by the Investigator as life threatening. If it is in the best interest of the patient to continue treatment in the opinion of the Investigator and after discussion with the Sponsor, the patient can continue treatment at a reduced dose level. However, futibatinib should first be held until toxicity returns to baseline or Grade ≤1.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase.

[a] Interrupt futibatinib if any toxicities are intolerable, regardless of the grade (including Grade 1 and 2). If or when the toxicity resolves to a tolerable state, consideration can be given to resuming futibatinib at the same dose if deemed appropriate or reduced by one dose level if needed.

Table 7: Dose Modifications for Related Ocular Toxicities

Grade and Definition	Study Drug Management[a]
Grade 1	If there is no evidence of ocular toxicity on ophthalmologic examination, continue futibatinib therapy at the same dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as central serous retinopathy (CSR)/ retinal pigment epithelial detachments (RPED), withhold futibatinib until signs and symptoms have resolved. If toxicity is reversible (complete resolution or stabilization and asymptomatic) in 4 weeks according to ophthalmologic examination, resume futibatinib therapy at the next lower dose level after consultation with the medical monitor. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence then re-escalation can be considered in consultation with the medical monitor.
Grade 2	Withhold futibatinib therapy. If there is no evidence of drug-related corneal or retinal pathology on ophthalmologic examination, withhold futibatinib until signs and symptoms have resolved. Resume futibatinib therapy at the next lower dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality, withhold futibatinib until signs and symptoms have resolved or stabilized. If toxicity is Grade 2 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks according to ophthalmologic examination, resume futibatinib therapy at the next lower dose level after consultation with the medical monitor. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence then re-escalation can be considered in consultation with the medical monitor.
Grade 3	If the toxicity is Grade 3, report as a serious adverse event and permanently discontinue futibatinib. If, however, the toxicity is Grade 3 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks and the subject is having clinical benefit, and the investigator and the sponsor's medical monitor agree that re-starting drug is in the best interest of the patient, then futibatinib therapy may be resumed at 2 dose levels lower if appropriate. Monitor for recurrence using appropriate investigations every 1 to 2 weeks for a month and as clinically appropriate thereafter. For cases of recurrence consider permanent discontinuation.
Grade 4	Permanently discontinue treatment with futibatinib. Report as a serious adverse event and monitor resolution of the event until complete resolution, stabilization, or the patient is lost to follow-up or withdraws consent (which ever happens first).

[a] If a patient has been deriving benefit from treatment, and the investigator can demonstrate that re-introduction of study drug is in the best interest of the patient considering the terminal nature of the disease, the drug may be re-introduced at a lower dose and/or intensity if the Medical Monitor is in agreement with this assessment. With appropriate re-consenting, the patient can be retreated with a 1- or 2-dose level reduction as appropriate, along with appropriate clinical follow-up as designated by the investigator. The investigator should also have the patient re-consent, explaining that re-introduction of study drug could lead to increased risk of recurrence.

Table 8: Recommendations for Hyperphosphatemia Management

Serum Phosphorus Result[a] **(mg/dL and mmol/L)**[b]	**Grade**[c]	**Futibatinib Dose Interruption and Modification**[d, e, f] **Recommended Phosphate Binder for Management of Hyperphosphatemia**[g]
ULN < P <5.5 (mg/dL) ULN < P <1.78 (mmol/L)	Grade 1	No interruption, consider phosphate binder once serum phosphorus level is > ULN. Should serum phosphorus level rapidly increase within 1 week, consider early phosphate-lowering therapy; eg, Sevelamer tablets 800 mg three times per day [TID]. Re-assess serum phosphate within 7 days.
5.5 ≤ P ≤7.0 (mg/dL) 1.78 ≤ P ≤2.26 (mmol/L)	Grade 2	No interruption, implement phosphate binder (monotherapy or in combination), Start with Sevelamer monotherapy (range from 800 mg TID to 2400 mg TID). Re-assess serum phosphate within 7 days. Escalate Sevelamer or add treatment with acetazolamide 250 mg QD or TID and/or lanthanum carbonate (Fosrenol®) 1.0 g QD or TID, and further titration,[h] if phosphate level continues to increase.
7.0 < P ≤10.0 (mg/dL) 2.26< P ≤3.23 (mmol/L)	Grade 3	Dose reduce futibatinib to the next lower dose level and intensify phosphate lowering therapy. Re-assess serum phosphate within 7 days and at least once a week. If the serum phosphorus level has resolved to ≤ Grade 2 within 14 days after dose reduction, continue futibatinib at the reduced dose level. If the serum phosphorus level has not resolved to ≤ Grade 2 after 14 days, further reduce futibatinib from the last reduced dose level (or no lower than 12 mg QD). If the serum phosphorus level has not resolved to ≤ Grade 2 after 14 days of the second dose reduction of futibatinib (or no lower than 12 mg QD), interrupt dosing with futibatinib until it is resolved to ≤ Grade 2 before resuming futibatinib at the reduced dose prior to dose interruption.
P >10.0 (mg/dL) P >3.23 (mmol/L)	Grade 4	Interrupt futibatinib until it's resolved to ≤ Grade 2, then resume futibatinib at the next lower dose level and intensify phosphate lowering therapy. Re-assess serum phosphate within 7 days and at least once a week. If after 2 dose interruptions and 2 dose reductions the serum phosphorus level has not resolved to ≤ Grade 2 after 14 days, permanently discontinue futibatinib.

Abbreviations: P=phosphorus; QD=once a day; TID=three times a day; ULN=upper limit of normal

[a] Serum phosphorus will be tested 4 days (± 24 hours) after Day 1 of Cycle 1 to initiate early intervention for hyperphosphatemia if indicated.

[b] mmol/L=mg/dL x 0.3229 (conversion factor)

[c] This grading for the range of serum phosphorus levels will be used for the protocol.

[d] Interrupt futibatinib if any toxicities are intolerable, regardless of the grade (including Grade 1 and 2). If or when the toxicity resolves to a tolerable state, consideration can be given to resuming futibatinib at the same dose if deemed appropriate or reduced by one dose level if needed.

[e] Serum calcium levels should be assessed at the same time.

[f] Futibatinib will be permanently discontinued if ectopic mineralization or calcification associated with hyperphosphatemia and considered clinically significant are observed

[g] Phosphate binders can be used as monotherapy or in combination. Please consult the drug package insert. Sevelamer should be preferably taken in the middle of meals, both tablets and powder, in order to improve gastrointestinal tolerance and compliance. If Sevelamer cannot be used, other phosphate binders or hyperphosphatemia treatment drugs can be used. Lanthanum carbonate should be taken instead just after meals—tablets of Fosrenol® are quite big, but can be cut if required. No dose adjustments are needed in patients with renal or hepatic impairment

[h] Titrate the dose every 2-3 weeks until an acceptable serum phosphate level is reached.

5.2.2. Dose Modifications for Hematologic Toxicities

Criteria for dose interruption and resumption for hematologic toxicities for patients in Cohorts A and B are presented in Table 9. For patients in Cohort C, dose modifications will be made at the Investigator's discretion.

Table 9: Futibatinib Dose Interruption and Modification Criteria for Related Hematologic Toxicities for Patients in Cohorts A and B

CTCAE Grade (value)	Recommended dose modification any time during a cycle of futibatinib[a]
Anemia (Hgb)	
Grade 1 (Hgb < LLN - 10.0 g/dL)	Maintain dose level
Grade 2 (Hgb < 10 – 8.0 g/dL)	Maintain dose level
Grade 3 (Hgb < 8.0 - 6.5 g/dL)	Withhold dose until resolved to ≤ Grade 1 or baseline, • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Grade 4 (life threatening consequences; urgent intervention indicated)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce 1 dose level
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1500/mm^3)	Maintain dose level
Grade 2 (ANC < 1500 - 1000/mm^3)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm^3)	Maintain dose level
Grade 4 (ANC < 500/mm^3)	Withhold dose until resolved to ≤ Grade 2 or baseline, • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Febrile neutropenia (ANC < 1000/mm^3 with a single temperature of ≥ 38.3°C [101° F] or a sustained temperature of ≥ 38° C [100.4° F])	Withhold dose until resolved, then reduce 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75,000/mm^3)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm^3)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, • If resolved ≤7 days, then maintain dose level • If resolved >7 days, then reduce 1 dose level
Grade 4 (PLT < 25,000/mm^3)	Withhold dose until resolved to ≤ Grade 1 or baseline, then reduce 1 dose level

Abbreviations: ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; Hgb=hemoglobin; LLN=lower limit of normal; PLT=platelets.

[a] Interrupt futibatinib if any toxicities are intolerable, regardless of the grade (including Grade 1 and 2). If or when the toxicity resolves to a tolerable state, consideration can be given to resuming futibatinib at the same dose if deemed appropriate or reduced by one dose level if needed.

5.2.3. Dose Modifications in Case of Induced Drug Liver Injury (Hy's Law)

Futibatinib will be permanently discontinued if liver function test abnormalities fulfill Hy's Law criteria defined as:

Concurrent observation of the following, with no other reason found to explain the findings (such as viral hepatitis A, B, or C; preexisting or acute liver disease; liver metastases; or another drug capable of causing the observed liver injury):

- Elevated aminotransferase enzymes of >3 x ULN
- Alkaline phosphatase (ALP) <2 x ULN
- Associated with an increase in bilirubin ≥2 x ULN

5.3. Treatment Compliance

Each patient will be instructed to comply with the dosing regimen of futibatinib.

Compliance to all study medication administration should be documented in the patient's source documents (Section 5.6.3).

5.4. Concomitant Medications and Therapies

5.4.1. Prohibited Medications and Therapies

Patients are not permitted to receive any other investigational or any other anticancer therapy, including chemotherapy, immunotherapy, biological response modifiers, or antineoplastic endocrine therapy during the study treatment period.

Extended-field radiation therapy or palliative radiation to a focal site of measurable disease is also prohibited. If it is deemed in the best interest of the patient and after discussion between the Investigator and Medical Monitor, it can be administered, but the patient will be censored for the primary endpoint analysis.

5.4.2. Concomitant Medications and Therapies Requiring Precautions

Supportive treatment is allowed based on available institutional or local guidelines.

Local or regional palliative cryotherapy or radiation, such as for bone pain or palliative surgery (non-anti-neoplastic intent), are permitted (provided the target lesion is not a site of measurable disease and is not indicative of disease progression). Study therapy should be ceased a minimum of 2 days prior to administration of palliative treatment, and may be resumed 7 days after the procedure or when the patient has recovered from the side effects of the procedure.

The following medications/therapies may be given concomitantly under the following guidelines:

Hematologic Support: may be administered as medically indicated (that is, blood transfusions, granulocyte colony-stimulating factor, erythropoietin stimulating agents) according to the institutional site standards or American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2015).

Management of Diarrhea: Prophylactic treatment for diarrhea is permitted during the study if clinically indicated according to the institutional or published guidelines (Benson et al. 2004).

Management of Nausea/Vomiting: Antiemetics may be administered as clinically indicated according to institutional standards or ASCO guidelines (Hesketh et al. 2017).

5.4.3. Drug Interactions

The following information is based on results from in vitro studies and preliminary results from clinical pharmacology studies of drug interactions studies. Caution is advised if these drugs are given concomitantly (see Appendix C, Classification of Substrates, Inhibitors, and Inducers of CYP Enzymes and Transporters).

Cytochrome P450 (CYP) 3A inhibitors and inducers: CYP3A is involved in the metabolism of futibatinib. The preliminary clinical pharmacology results suggested that strong CYP3A inhibitor increase futibatinib exposure and that a strong CYP3A inducer decrease the exposure. CYP3A inhibitors and inducers may alter the concentration and activity of futibatinib.

CYP3A substrates: Futibatinib is a potential time-dependent inhibitor of CYP3A. However, preliminary clinical pharmacology result suggested that futibatinib had no significant effect on exposure of sensitive CYP3A substrate.

P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibitors: Futibatinib is a potential inhibitor of P-gp and BCRP. Futibatinib may alter the PK and activity of P-gp and BCRP substrates.

P-gp and BCRP substrates: Futibatinib is a substrate of P-gp and BCRP. P-gp and BCRP inhibitors may alter the concentration and activity of futibatinib.

5.5. Effective Contraception During Study

Female patients considered not to be of childbearing potential must have a history of being postmenopausal (no menses for 12 months without an alternative medical cause), or hysterectomy that is clearly documented in the patient's source documents.

For WOCBP, including female study participants and partners of male participants, effective contraception is required during the study and for 90 days after the last dose of study medication, or longer if necessary based on local requirements. Effective contraception is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable

- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner with documentation of the success of the vasectomy
- Complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Male patients, unless sterile (vasectomy with post-procedure semen analysis), with partners who are WOCBP should use a male condom in combination with at least one of the effective contraception methods during the study and for 90 days or longer based on local requirements after the last dose of study medication. Donation of sperm or ova is not allowed during the study and for 90 days or longer based on local requirements following the last dose of study drug.

5.6. Study Drug Materials and Management

Futibatinib will be supplied by the Sponsor. Detailed information such as the requirements for accountability and disposal of study drug can be found in the Pharmacy Manual, which will be provided separately.

5.6.1. Description of Study Drug

Futibatinib will be provided as 4-mg tablets for oral use. Please refer to the Investigator's Brochure for additional information.

5.6.2. Packaging and Labeling

Futibatinib will be packaged and labelled according to local laws and regulations.

5.6.3. Storage

Futibatinib tablets should be stored in accordance with the label.

5.6.4. Accountability

The Investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. All study drugs will be stored and disposed of according to the Sponsor's instructions. The dispensing of study drug to the patient and the return of study drug from the patient must be documented in the patient's source documents. Patients must be instructed to return all original containers, whether empty or containing study drug.

At the conclusion of the study, all study drugs supplied by the Sponsor must be destroyed or returned to the designated depot, per the instructions provided in the Pharmacy Manual.

6. STUDY ASSESSMENTS

The Schedule of Events (Table 1 for Cohorts A and B, Table 2 for Cohort C, and Table 3 for Extension Phase) summarizes the frequency and timing of all applicable study assessments, including allowable windows for study visits and assessments / procedures. Written informed consent must be provided before any study-related procedures are performed.

Any AEs directly associated with a screening procedure should be reported as described in Section 9.2.

Assessment	Details
Review of inclusion/exclusion criteria	See Section 4.1 and 4.2. Eligibility must be confirmed prior to first dose of study therapy.
Demographics/medial history	Sex, age, clinical diagnosis, date and method of diagnosis, prior cancer therapy, relevant medical history (past and concurrent).
Baseline signs and symptoms	Signs and symptoms occurred after signing of ICF but before administration of first dose of futibatinib.
Physical examination	
Vital signs	Pulse rate, systolic and diastolic blood pressure, body temperature, and respiration rate. Any abnormal reading should be repeatedly immediately.
Height and body weight	Height is collected for the purpose of body mass index calculations at baseline only.
ECOG performance status	See Appendix A.
12-lead electrocardiogram	Single, resting, semirecumbent 12-lead electrocardiogram will be performed locally. Data collection includes RR interval (heart rate), QT interval, QTcF interval and abnormal findings; the Investigator is responsible for interpreting and measuring electrocardiogram data.
Hematology	Red blood cell count, hemoglobin, hematocrit, platelets, white blood cell count with differential, neutrophils (ANC), lymphocytes, monocytes, eosinophils, basophils
Serum chemistry	AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, lactate dehydrogenase, inorganic phosphorus, triglyceride, total cholesterol, creatinine, urea or blood urea nitrogen, bicarbonate, sodium, potassium, chloride, calcium (corrected value), magnesium, blood glucose, uric acid For a calculated creatinine clearance (CrCl) value, use the Cockcroft-Gault formula: Male CrCl (mL/min) = Body wt (kg)×(140-age)[72×serum creatinine (mg/dL)] Female CrCl (mL/min) = male CrCl×0.85
Coagulation	Prothrombin time-international normalized ratio, activated partial thromboplastin time, fibrinogen
Pregnancy test	Serum β human chorionic gonadotrophin (human chorionic stimulating hormone) test required for WOCBP
Ophthalmological examination	See Section 6.1
PK blood sampling	See Section 7.

Assessment	Details
Pharmacodynamic biomarker blood sampling	See Section 10
Efficacy assessments	See Section 8.
Concomitant medication/concomitant therapy	Including all medications / therapies administered from the time ICF is signed through 30 days after administration of the last dose of study therapy or until the start of new anticancer therapy.
AE monitoring	All AEs will be collected from the time the ICF is signed through 30 days after the last dose of any study therapy (safety follow-up) or until the start of new antitumor therapy, whichever is earlier. See Section 9.

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; CrCl=calculated creatinine clearance; ICF=informed consent form; QT = QT interval; QTcF = Fridericia's Correction Formula; RR=intra-beat; WOCBP=women of childbearing potential

6.1. Ophthalmological Examination

The cornea and conjunctiva are readily visible tissues and, therefore, abnormalities of the cornea and conjunctiva can usually be recognized via external ocular examination and routine slit lamp biomicroscopy. The retina is visible through fundoscopy after dilation of the pupil. Ophthalmologic examination will be performed by an ophthalmologist or qualified delegate at screening and 4-6 weeks after first dose; additional on-study evaluation as needed due to physician judgment and/or symptoms or signs of mineral deposits.

Each evaluation will encompass:

- External ocular examination
- Routine slit lamp biomicroscopy of anterior ocular structures, including the anterior and posterior chambers (Fluorescein or rose Bengal or other dyes used to evaluate the ocular surface can be used according to institutional guidelines and local clinical practice)
- Dilation of the pupil with direct/indirect fundoscopy per institutional guidelines and local clinical practice

6.2. Laboratory Assessments

All laboratory assessments will be performed locally. The laboratory must provide normal reference ranges for hematology, chemistry, and coagulation tests. If justified (eg, deterioration of the patient's health conditions and/or distance from the clinical site) and allowed by the country and institution, laboratory tests performed by external laboratories may be used for the study. However, laboratory reference ranges and accreditation are required. All laboratory test results (internal or external) must be reviewed for clinical significance by the Investigator.

Any clinically significant events must be followed and reported as required by the protocol (please see Section 9.3.1).

7. PHARMACOKINETICS

The PK population will consist of all patients who received futibatinib and have evaluable blood samples for analysis. Blood samples will be obtained from all patients at the timepoints listed in Table 10 and used to determine plasma futibatinib concentrations.

In the event that a patient interrupts treatment after the pre-dose sample is collected and restarts the treatment at a later date, a pre-dose sample should be collected.

Table 10: Pharmacokinetic Blood Sample Collection

Day of Study (Time Window)	**Collection Time Point (hours) in Relation to Futibatinib Administration (Time Window)**
Day 15 of Cycle 1 (± 3 days)	Pre-dose (from -30 min to just before dose)
	1 hour±30 min post-dose
	3 hours±30 min post-dose

8. EFFICACY EVALUATIONS

8.1. Cohorts A and B

8.1.1. Efficacy Criteria

For patients in Cohorts A and B, on-site tumor assessments (including computed tomography [CT]/magnetic resonance imaging [MRI]) will be performed by the Investigator/local radiologist according to RECIST 1.1 guidelines (Eisenhauer et al. 2009). Primary objective and additional secondary objectives will be assessed by an IRC.

Results of the local assessments, including response for target and non-target lesions and appearance of new lesions, will be the basis for the continuation or discontinuation of study therapy decisions.

If the Investigator determines that a patient has developed clinical disease progression manifested by symptomatic deterioration but not supported by radiologic evidence of progression, the patient may stop treatment. Symptoms of clinical disease progression must be documented in the patient's source documents and must be reported as AEs. Every effort should be made to document objective disease progression even after discontinuation of treatment.

Note that patients who discontinue without documented disease progression should continue to undergo tumor assessments/scans according to the Schedule of Events until PD is documented, new anticancer therapy is initiated, the study is terminated, or consent is withdrawn.

8.1.2. Method of Imaging

The same method of assessment and same technique should be used to characterize each identified and reported lesion at each assessment timepoint. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of treatment. All measurements should be recorded in metric notation using a ruler or calipers.

Contrast-enhanced CT scans or MRIs are the preferred methods for tumor assessments. If a contrast agent is contraindicated in a patient, obtain a non-contrast chest CT and enhanced MRI of the abdomen (and pelvis if clinically indicated). A spiral CT should be performed using a ≤5 mm contiguous reconstruction algorithm. Images must be acquired of the chest and abdomen (and pelvis if clinically indicated or obtained at Baseline) at each time point. Only CT scans and MRI may be used for tumor measurement.

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules, palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Ultrasound should not be used to measure tumor lesions that are clinically not easily accessible for overall response evaluation (eg, visceral lesions). Ultrasound is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. For additional guidance, refer to RECIST 1.1 specifications for standard anatomical radiological imaging.

8.1.3. Tumor Definitions

Measurable Lesions: Only measurable lesions can be selected as target lesions.

- Measurable visceral lesions: Lesions that can be accurately measured in at least 1 dimension with the longest diameter (to be recorded) ≥10 mm by CT scan if using slice thickness of ≤5 mm, or at least double the slice thickness of the CT or MRI scan if the slice thickness is >5 mm.
- Measurable pathological lymph nodes: A malignant lymph node must be considered pathologically enlarged with high suspicion of metastasis and measure ≥15 mm in the short axis when assessed by CT scan. The short axis is defined as the longest linear dimension perpendicular to the node's longest diameter as assessed within the same plane that the scan was acquired.

Non-measurable Lesions: All non-measurable lesions can only be selected as non-target lesions.

- Small visceral metastatic lesions that have a longest dimension <10 mm, or if slice thickness is >5 mm, less than twice the slice thickness
- Abnormal and suspected metastatic lymph nodes that are ≥10 mm to <15 mm in the short axis
- Truly non-measurable lesions (eg, ascites and peritoneal carcinomatosis)

Target Lesions:

- All measurable lesions up to a maximum of 2 lesions/organ and 5 lesions in total, representative of all involved organs/tissues should be identified as target lesions
- Target lesions should be selected on the basis of their size (visceral lesion with the longest diameter and lymph node with the measurement of short axis), be representative of all involved organs/tissues, but in addition should be those that lend themselves to reproducible repeated measurements
- When recording tumor measurements, the longest diameter will be measured for each non-nodal target lesion. For measurable pathological lymph nodes that may be identified as target lesions, the short axis measurement will be combined with the measurements of non-nodal (ie, visceral lesion) target lesions. Therefore, in cases of CR when abnormal nodes have been used as target lesions, the sum of diameters will not reduce to a null value.
- Target lesions will be followed up and measured at each subsequent timepoint.
- The sum of the diameters for all target lesions will be calculated and recorded. The baseline sum will be used as a reference to further characterize any objective tumor assessment in the measurable dimension of the disease.
- Assign a measurement to all target lesions regardless of size. An option of "too small to measure" will be provided if a measurement cannot be assigned. A value of zero should only be assigned in the case of a CR.
- An option of "not assessable" for a lesion will only apply to lesions that cannot be read due to technical reasons including:

  - CT artifact
  - Patient positioning where the lesions are obstructed or cannot be seen
  - Lesions that may not be seen in their entirety due to CT slice thickness
- In cases where a lesion divides into 2 lesions, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.
- In cases where 2 lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Non-target Lesions:

- Non-target lesions include all non-measurable lesions and measurable lesions that have not been selected as target lesions.
- The primary lesion should always be classified as a non-target lesion irrespective of its size and whether or not it can be accurately measured.
- Lymph nodes that have a short axis <1 mm are considered non-pathological and should not be recorded.
- Any equivocal lesion without clear diagnosis (eg, uncharacteristic solitary lung nodule without biopsy, uncharacteristic thyroid mass lesion without fine needle aspiration) may be considered a non-target lesion if it cannot be differentiated from a benign lesion.
- All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, but their presence, absence, or unequivocal progression should be followed throughout the study.
- It is possible to record multiple non-target lesions involving the same organ as a single item on the electronic case report form (eCRF) (eg, multiple enlarged pelvic lymph nodes or multiple liver metastases).

8.1.4. Response Criteria

Efficacy evaluation will include the assessment of target and non-target tumor responses as well as objective responses. Responses will be assessed as defined in the Statistical Analysis Plan (SAP).

8.1.4.1. Target and Non-Target Response Assessments

Assessments will be based on the definitions for target and non-target lesions described in Table 11.

Table 11: Target and Non-target Lesions

TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph node must have reduction in short axis to <10 mm
Partial Response (PR)	At least a 30% decrease in the sum of diameters of the target lesions, taking as a reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of the target lesions, taking as a reference the smallest sum on study, including the baseline sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Definitive new lesion presence also indicates progression.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, referencing the smallest sum diameters while on study.
NON-TARGET LESIONS	
Lesions Response:	**Definition:**
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10-mm short axis)
Partial Response (PR)	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions (see following definition).

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease

Progression in Non-target Disease: There must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

8.1.4.2. Additional Criteria to Consider When Making Tumor Response Assessments

Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease (ie, an increase in tumor burden representing an additional 73% increase in “volume” [which is equivalent to a 20% increase in the diameter of a measurable lesion]).

When effusions are known to be a potential adverse effect of treatment, cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or SD is not mandatory, but might be performed to differentiate between response (or SD) and PD when substantial change of effusion and or ascites is noted.

If a patient is discontinued from the study before PD occurs and receives local or regional palliative radiotherapy during the follow-up period, the irradiation site must be omitted from the response assessment of the patient; however, if the site is observed to demonstrate disease progression, this case should be judged as PD.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

8.1.5. Objective Response Assessment

Assessments will be based on the definitions provided in Table 12 and Table 13. Since this is a non-randomized study, all responses (CR/PR) must be confirmed.

Table 12: Time Point Response for Patients with Target (±Non-target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Objective Response
CR	CR	No	CR
CR	Non-CR/Non-PD or Not all evaluated	No	PR
PR	Non-PD or Not all evaluated	No	PR
SD	Non-PD or Not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease

Table 13: Time Point Response for Patients with Only Non-target Disease

Non-Target Lesions	New Lesions	Objective Response
CR	No	CR
Non-CR/Non-PD	No	SD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease

8.2. Cohort C

8.2.1. Efficacy Criteria

Efficacy will be assessed by evaluation of:

- bone marrow histomorphology changes, standard cytogenetics, and *FGFR* molecular status
- peripheral blood assessment (blood count) including potentially *FGFR* molecular status
- PET scan for fluorodeoxyglucose (FDG) avid lesions
- imaging (CT/MRI) in case of presence of solid lesions
- clinical assessment

If the Investigator determines that a patient has developed clinical disease progression manifested by symptomatic deterioration, the patient may stop treatment. Every effort should be made to document objective disease progression even after discontinuation of treatment.

8.2.2. Response Criteria

For patients in Cohort C, response will be determined based on disease presentation. Investigators will assess response based on the following response criteria:

- Treatment Response Criteria for MDS/MPN (Savona et al. 2015)
- Response Evaluation Criteria in Lymphoma (RECIL 2017) (Younes et al. 2017)
- International Working Group (IWG) Response Criteria for AML (Cheson et al. 2003)

A review of the response assessments will be conducted by an adjudication committee.

8.2.3. Response Definitions

Response will be determined based on investigators' assessment of imaging, bone marrow, peripheral blood, and extramedullary disease. Assessments will be based on the definitions described in Table 14.

Table 14: Response Definitions for Cohort C

MLN Characteristic	MLN Only	Lymphoma Presentation	Leukemia Presentation
Response Criteria	**Savona 2015[a]**	**RECIL 2017[b]**	**Cheson 2003[c]**
Complete response (CR)	Must fulfill all criteria defined for CR	Must fulfill all criteria defined for CR	• Must fulfill all criteria defined for morphologic complete response • CR does not include: o morphologic leukemia-free state o complete response with incomplete hematological recovery (CRi), or o cytologic complete response (CRc)
Partial response (PR)	Must fulfill all criteria defined for PR	Must fulfill all criteria defined for PR	Must fulfill all criteria defined for partial remission
Complete response with incomplete blood count recovery (CRi)	N/A	N/A	Must fulfill all criteria defined for CRi
Complete cytogenetic response (CCyR)	Resolution of previously present chromosomal abnormality known to be associated with MLN (eg. 8p11 translocation)	Must fulfill all criteria defined for CCyR (Savona 2015)[a]	Must fulfill all criteria defined for cytogenetic complete response (CRc) (Cheson 2003)[c] and CCyR (Savona 2015)[a]
Partial cytogenetic response (PCyR)	≥50% reduction of chromosomal abnormality known to be associated with MLN (eg. 8p11 translocation)	Must fulfill all criteria defined for PCyR (Savona 2015)[a]	Must fulfill all criteria defined for PCyR (Savona 2015)[a]
PD/Relapsed disease	Must fulfill all criteria defined for PD/relapsed disease	Must fulfill all criteria defined for PD/relapsed disease	Must fulfill all criteria defined for PD/relapsed disease

[a] Savona, et al. An international consortium proposal of uniform response criteria for myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in adults. Blood. 2015.

[b] Younes, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol. 2017.

[c] Cheson, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol. 2003.

8.3. Efficacy Endpoints

The efficacy endpoints are provided in Table 15. Definitions of each endpoint are provided in Section 2.

All efficacy endpoints in Cohorts A and B will be determined based on assessments performed by the investigators and the central review committee. All efficacy endpoints in Cohort C will be determined based on assessments performed by the investigators and reviewed by a response adjudication committee.

Table 15: Efficacy Endpoints

Primary Endpoints	Secondary Endpoints
Cohorts A and B	
ORR based on independent central review	ORR based on Investigator assessment
	DCR
	DOR
	PFS
	OS
Cohort C	
CR rate	ORR
	CR+CRi, CCyR, and PCyR rates
	DOR and duration of CR and CR+CRi
	PFS, RFS, and EFS
	OS

Abbreviations:; CR=complete response; DCR=disease control rate; DOR=duration of response; ORR=objective response rate; OS=overall survival; PFS=progression-free survival

9. SAFETY EVALUATIONS

9.1. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study patient and does not necessarily have a causal relationship with the study drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. For this study, progression of the cancer under study is not considered an adverse event.

All AEs will be collected from the time the ICF is signed through 30 days after the last dose of any study therapy (safety follow-up) or until the start of new antitumor therapy, whichever is earlier. For all AEs that occur between signing ICF, there is no need to record those that are unrelated unless it is mandatory by local regulations. Any untoward medical event that occurs after the safety follow-up is not considered an AE, unless the Investigator considers that the AE is related to the study drug.

Signs and symptoms of a pre existing disease should not be considered an AE, but should rather be considered baseline signs and symptoms. Clinically significant worsening of pre existing signs and symptoms is considered an AE.

9.2. Reporting of Adverse Events

9.2.1. Terms of Reported Adverse Events

All AEs will be documented in the eCRF according to the eCRF Completion Guidelines. Documentation should include onset and resolution/stabilization dates, severity/grade, relationship to study drug, and outcome of the event.

When a diagnosis for the reported signs or symptoms is known, the Investigator should report the diagnosis, not the symptoms, as the AE.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient. In order to prevent reporting bias, patients should not be questioned regarding the specific occurrence of one or more AEs.

9.2.2. Severity of Adverse Events

The NCI-CTCAE V5.0 will be used to grade the severity of AEs.

9.2.3. Causal Relationship with Study Drug

The causal relationship between an AE and study drug will be assessed using the following 2-point scale, taking into account the patient’s condition, medical history, concomitant medications, and the temporal relationship between study drug administration and onset of the event.

1. An AE is considered to be "Related" if the event follows a reasonable temporal sequence from administration of study drug and there is a reasonable possibility that at least one of the following conditions is true:
    - A positive dechallenge: This means that the event improves or resolves after the drug is stopped (temporarily or permanently).
    - A positive rechallenge: This means that the event reappears after the drug is restarted.
    - The event cannot be reasonably explained by the patient's clinical state and/or other therapies administered.
    - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, Stevens-Johnson syndrome).
2. An AE is considered to be "Not related" if there is no reasonable possibility that at least one of the following conditions is true:
    - The event occurred prior to study drug administration.
    - There is no reasonable possibility that the study drug caused the event. ("no reasonable possibility" means there is no evidence to suggest a causal relationship between the study drug and the AE)
    - The event does not follow a reasonable temporal sequence from administration of study drug and could have been produced by a documented pre-existing condition, concomitant medication or patient's clinical state.

9.2.4. Outcome of Adverse Events

Record the outcome of AEs as follows:

- Resolved
- Not resolved
- Fatal

9.2.5. Follow-up of Adverse Events

Any ongoing AEs should be followed until the earliest occurrence of one of the following:

- The AE has resolved or stabilized
- Completion of safety follow-up visit
- Start of new antitumor therapy
- Withdrawal of consent
- Death
- Other (eg, transfer to another hospital)

9.3. Laboratory Assessments

9.3.1. Reporting and Evaluation of Laboratory Test Results

All laboratory results must be reviewed by the Investigator. A new laboratory abnormality that has a clinical impact on a patient (including eg, resulting in study drug dose reduction, treatment delay, treatment discontinuation or requirement of intervention) is considered an AE, unless it is considered part of clinical manifestations to a clinical diagnosis that is already reported as an AE.

All laboratory values that are out of the normal range are to be evaluated for their clinical impact before exposing the patient to the next dose of futibatinib.

The NCI-CTCAE V5.0 will be used to grade the severity of laboratory data.

9.3.2. Repeat Testing

Evaluation of any clinically significant laboratory test will be repeated, as clinically indicated, until the value returns to the baseline level or clinically stabilizes, or until another treatment is given.

9.4. Serious Adverse Events

9.4.1. Definitions of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
  - Death due to disease progression or relapse is not considered an SAE unless the investigator deems it possibly related to the study drug
- Is life-threatening
  - The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization to treat the AE.
- The following are not considered hospitalizations for the purposes of assessing seriousness (however, one of the other serious criteria may apply):
  - Emergency room visits < 24 hours;
  - Hospitalizations for preplanned procedures;
  - Hospitalization for study-related treatment and procedures.
- Results in persistent or significant disability/incapacity, where disability is defined as a substantial disruption of a person’s ability to conduct normal life functions, either reported or defined as per clinical judgment.
- Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child).

- Is any other important medical event that based upon appropriate medical judgement may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. (eg, may not result in death, be life-threatening, or require hospitalization).

9.4.2. Reporting of Serious Adverse Events (within 24 hours)

All SAEs occurring from the time the ICF is signed through the Safety Follow-up Period (30 days after the last dose of study treatment or discontinuation of the Safety Follow-up Period, whichever is earlier) must be reported to Sponsor's Pharmacovigilance group or its designee within 24 hours from the time the Investigator first becomes aware of the SAE.

Comprehensive information available at the time of initial reporting (including narrative description, medical history, and concomitant medications) needs to be provided with careful consideration regarding causality and serious criterion. The SAE reporting process and contact information are provided in supplement guidelines.

After the initial SAE notification to the Sponsor's Pharmacovigilance group or its designee, all follow-up SAE information will be submitted each time they become available (for example, clinical diagnosis, outcome, causality assessment, results of specific investigations) on a follow up SAE form.

The Investigator also must submit further information if it is required by the Sponsor or the director of the study site or an institutional review board (IRB)/independent ethics committee (IEC).

Every SAE should be followed until it has resolved, stabilized, or returned to baseline.

9.4.3. Reporting of Deaths (within 24 hours)

All deaths (except disease progression) occurring from the time the ICF is signed through the Safety Follow-up Period (30 days after the last dose of study treatment or discontinuation, whichever is earlier) must be reported within 24 hours from the time the Investigator first becomes aware of the death. The primary cause of the death should be reported as the SAE term, if available, and entered on the death page of the eCRF.

9.5. Other Safety Information

9.5.1. Pregnancy

If a patient becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information in a female patient (or for the female partner of a male patient) should be reported to Sponsor's Pharmacovigilance or designee via th Pregnancy Form as soon as possible from the time the Investigator first becomes aware of a pregnancy or its outcome.

New and/or corrected information regarding the pregnancy obtained after submitting the Pregnancy Form must be submitted on an updated Pregnancy Form to the Sponsor's Pharmacovigilance or designee. Pregnancies must be followed to outcome by the Investigator, even after study completion.

If the outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, it should be reported as an SAE to the Sponsor's Pharmacovigilance or designee. Live births will be followed up by the Investigator. Any information that may be associated with the study drug should be reported even after study completion.

9.5.2. Overdose

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE.

An overdose that results in an AE should be reported to Sponsor's Pharmacovigilance or designee within 24 hours from the time the Investigator first becomes aware of its occurrence.

10. BIOMARKER EVALUATION

10.1. Biomarker Assessments

10.1.1. Objectives and Background

Exploratory objectives of this study are to assess the possible impact of specific genetic alterations or other laboratory abnormalities on the efficacy of futibatinib.

Biomarkers will be tested using analytically validated assay at a central laboratory.

All biomarker assessments described in this section will be performed at the timepoints shown in the Schedule of Events; methods of sample collection and preparation will be described in a separate Laboratory Manual.

10.1.2. Assessment of *FGF/FGFR* Aberrations in Blood

A blood sample will be collected to assess *FGF/FGFR* aberrations in ctDNA as described in the Schedule of Events and where local regulations allow. In addition to assessing ctDNA as a pharmacodynamic biomarker, samples or a set of samples, will be used to investigate its possible utility as a complimentary or an alternative to tumor tissues for the future potential companion diagnostic development. Samples will be collected and stored, as per the Laboratory Manual, and analyzed in batches.

10.1.3. Tissue Samples

Archival or fresh tumor/bone marrow biopsy samples will be collected during screening to retrospectively confirm *FGFR* gene status at the Sponsor's designated central laboratories or for the purpose of a bridging study should companion diagnostics be warranted (fine needle aspiration is not acceptable). Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. The remaining samples may be stored at the Sponsor's designated central laboratories for up to 10 years after study completion for future testing or companion diagnostic development if warranted.

10.2. Sample Storage and Disposal

Samples or leftover samples will be stored for a maximum of 10 years following the completion of the study at central laboratories. These samples could be used to develop companion diagnostics and to investigate the genes or other biomarkers related to efficacy or resistance of futibatinib in the future. After the storage period ends, samples will be destroyed.

10.3. Analytical Procedures

Patients will be enrolled depending on local results but tissue samples will be collected and stored at central location for possible confirmatory testing, molecular profiling and/or companion diagnostic development if warranted by the clinical response.

Analyzing plasma ctDNA will be conducted retrospectively in batches on an adequately validated assays at central lab(s).

The detailed analytical procedures will be described in the SAP for Biomarkers.

11. STATISTICAL CONSIDERATIONS

The statistical analysis methods will be documented in detail in the SAP.

11.1. Estimation of Sample Size

A total of approximately 115 patients will be enrolled in the study.

Approximately 60 patients with solid tumors harboring *FGFR* rearrangements will be enrolled in Cohort A. Sample size considerations (primary endpoint ORR) are based on a 2-stage Simon design (Simon 1989), comparing a poor response of ≤ 10% vs a promising response of ≥ 25%, at a 5% 1-sided significance level and approximate 90% power.

- In Stage 1 (futility assessment), enrollment will include 35 patients and accrual will continue to Stage 2, if at least 4 (11.4%) of 35 patients respond (CR or PR).
- In Stage 2, if the Stage 1 futility boundary is exceeded, an additional 25 patients will be enrolled, for a total of approximately 60 patients. With a total of 60 patients, if the observed ORR is 30%, the 95% exact confidence interval (CI) is (18.9%, 43.2%).

Table 16: Observed ORR with Exact 95% Confidence Interval (Cohort A)

ORR	95% Exact Confidence Interval
20%	[10.8% - 32.3%]
25%	[14.7% - 37.9%]
30%	[18.9% - 43.2%]

Approximately 35 patients with gastric or GEJ cancer harboring *FGFR2* amplification will be enrolled in Cohort B. Sample size considerations are based on differentiating a historical control ORR of 10% or less, with a target ORR of 35%. Assuming the true ORR is 35%, the cohort has approximately 96% power to reject the null hypothesis that the true ORR is ≤10%, considering a 2-sided alpha of 5%. With a sample size of 35, observing at least 8 responders will have a 95% CI lower bound excluding 10% (ORR of 23% with 95% CI (10.4% - 40.1%).

Table 17: Observed ORR with Exact 95% Confidence Interval (Cohort B)

ORR	95% Exact Confidence Interval
23%	[10.4% - 40.1%]
29%	[14.6% - 46.3%]
37%	[21.5% - 55.1%]

Approximately 20 patients with myeloid or lymphoid neoplasms harboring *FGFR1* rearrangements will be enrolled in Cohort C. Sample size considerations are based on differentiating a historical control CR rate of 10% or less with a target CR rate of 50%.

Assuming the true CR rate is 50%, the cohort has over 95% power to reject the null hypothesis that the true CR rate is ≤10%, considering a 2-sided alpha of 5%.

Observing at least 6 responders out of 20 treated patients will have a 95% CI lower bound excluding 10% (CR rate of 30% with 95% CI (11.9% - 54.3%).

Table 18: Observed CR Rate with Exact 95% Confidence Interval (Cohort C)

CR Rate	95% Exact Confidence Interval
30%	[11.9% - 54.3%]
40%	[19.1% - 64.0%]
50%	[27.2% - 72.8%]

11.2. Planned Interim Analysis

The Sponsor will review the data at the time Cohort A has the required number of patients to determine if that particular cohort should continue.

11.3. Analysis Populations

The analysis populations in the study are defined in Table 19.

Table 19 Definitions of Analysis Populations

Analysis Population	Definition
All Enrolled Population:	All patients who signed the ICF in this study
All Treated Population/Full Analysis Set:	All enrolled patients who received at least 1 dose of study drug
Pharmacodynamic/Biomarker Evaluable Set:	All patients in the All Treated Population who have evaluable pharmacodynamic/biomarker data for analyses

11.4. Criteria for Handling of Patient Data

The criteria for handling of patient data are provided in the SAP.

11.5. Statistical Analyses

11.5.1. Demographic and Baseline Characteristics

The number of patients in each study population and the reasons for exclusion will be summarized. In each analysis population, the distribution of main patient background, disease characteristics, and baseline laboratory values and clinical findings will be summarized. These patient attributes will be summarized using frequency distribution or descriptive statistics as appropriate.

11.5.2. Study Drug Administration

In the All Treated Population, the following analyses will be performed by dose level:

- Administration status
- The total dose, total duration of administration and the number of administration cycles will be summarized by all treated patients/each intervention group.
- Status of administration completion
- The rate of administration completion will be presented by cycle.
- The presence or absence of study discontinuation and reasons for study discontinuation will be tabulated by cycle.
- Dose intensity
- Actual dose intensity and relative dose intensity in each patient will be calculated, and descriptive statistics will be presented.

11.5.3. Efficacy Analyses

All efficacy analysis will be performed using the All Treated Population

A description of each efficacy endpoint is provided in Table 15. See the SAP for more detailed information on the efficacy analyses.

11.5.3.1. Cohorts A and B

11.5.3.1.1. Primary Efficacy Analysis

Objective response rate is defined as the proportion of patients with objective evidence of CR or PR. The evaluation of ORR will be based on an independent central review of radiologic images. At the analysis stage, the best objective response will be assigned for each patient as the best response recorded after initiation of study treatment and confirmed at least 4 weeks later. If applicable, responses recorded after disease progression or initiation of new anticancer treatment will be excluded. The exact 2-sided CI based on Clopper-Pearson methodology will be derived for ORR.

11.5.3.1.2. Secondary Efficacy Analyses

Overall response rate based on investigator assessment will be determined as decribed above for the primary analysis of ORR based on independent central review of radiologic images (Section 11.5.3.1.1).

Disease control rate will be analyzed using the same methodology as ORR

Duration of response will only be evaluated in patients with an objective response of CR or PR. Patients who are alive and progression-free as of the analysis cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy.

Progression-free survival will be estimated using the Kaplan-Meier method. Patients who die without a reported disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last tumor assessment. Patients who did not have any on-study assessments and did not die will be censored on the first dosing date. Patients who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy.

Overall survival will be analyzed in a similar manner to PFS. In the absence of confirmation of death or for patients who are alive as of the OS cut-off date, survival time will be censored at the last known date that the patient was alive.

11.5.3.2. Cohort C

11.5.3.2.1. Primary Analysis

Complete response rate defined as the proportion of patients who achieved a CR will be calculated and the exact 2-sided CI will also be derived using the Clopper Pearson methodology.

11.5.3.2.2. Secondary Analyses

The overall response, CR+CRi (leukemia presentation only), CCyR, and PCyR rates will be calculated and the exact 2-sided CIs will also be derived using the Clopper-Pearson methodology.

Duration of CR (only in patients who achieved a CR), duration of CR+CRi (only in patients who achieved a CR/CRi [leukemia presentation only]), and duration of response (only in patients with an objective response of CR, CRi [leukemia presentation only], or PR) will be estimated using the Kaplan-Meier method. Patients who are alive and progression-free as of the analysis cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy.

Progression-free survival will be estimated using the Kaplan-Meier method. Patients who die without a reported disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last tumor assessment. Patients who did not have any on-study assessments and did not die will be censored on the first dosing date. Patients who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy.

Relapse-free survival will only be evaluated in patients with an objective response of CR and measured from the first date of achieving CR until the first date of relapsed disease or death from any cause, whichever occurs first. Patients who die without a reported disease relapse will be considered to have relapsed on the date of their death. Patients who did not relapse or die will be censored on the date of their last tumor assessment. Patients who started any subsequent anti-cancer therapy without a prior reported relapse will be censored at the last tumor assessment prior to initiation of the subsequent anti-cancer therapy.

Event-free survival will be estimated only for patients with leukemia presentation using the Kaplan-Meier method. EFS is defined as the time from first dose of study therapy to treatment failure, relapse after CR (if applicable), or death from any cause, whichever occurs first. For a patient with none of these events before the end of study follow-up, observation of EFS is censored at the date of last contact prior to the analysis cut-off date. If the patient does not achieve a CR, EFS is defined as the point of treatment failure or death, whichever comes first. Treatment failure for EFS is defined as PD in this study.

Overall survival will be analyzed in a similar manner to PFS. In the absence of confirmation of death or for patients who are alive as of the OS cut-off date, survival time will be censored at the last known date that the patient was alive.

11.5.4. Safety Analyses

The safety analysis will be performed using the All Treated Population.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities terminology and the severity of the toxicities will be graded according to the NCI-CTCAE V5.0, where applicable.

Concomitant medications will be coded according to the WHO Drug Dictionary for Concomitant Medication.

All AEs will be summarized (by incidence) and listed by the System Organ Class, preferred term, toxicity/severity grade, and causal relationship to futibatinib. In addition, separate summaries of SAEs and Grade 3 or 4 AEs will be presented.

For all AEs that occurred between the signing of the ICF and the last day of the Safety Follow-up Period, lists of preferred AE terms, grade, onset date, actions, outcome of AE, date of outcome confirmed, causalities with the study drug, and comments on AEs will be listed by patient.

Hematological and chemistry laboratory parameters will be graded according to the NCI-CTCAE V5.0 where applicable. The worst severity grade, time to maximum Grade 3 or 4 value, and time to resolution (return to baseline grade or below) will be summarized.

Safety data (AEs and clinical laboratory results) will be summarized descriptively. A list of 12-lead electrocardiogram findings will be presented by patient.

11.5.5. Pharmacokinetic Analysis

The concentration vs time data obtained in this study will be combined with data from other studies in the clinical development program to develop a Pop PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of futibatinib and to estimate measures of individual exposure (such as steady-state peak, trough and area under the plasma drug concentration-time curve). Model estimated exposures will be used for exposure-response analyses of selected efficacy and safety endpoints. The results of Pop PK and exposure response analyses will be reported separately.

11.5.6. Pharmacodynamic/Biomarker Analysis

The exploratory pharmacodynamic/biomarker endpoints are described in Section 10.

Pharmacodynamic and biomarker data will be summarized descriptively using all patients in the Pharmacodynamic/Biomarker Evaluable Set who have evaluable data available.

12. ADMINISTRATIVE CONSIDERATIONS

12.1. Protocol Compliance

The Investigator must agree to comply with all aspects of the protocol. In the event that the Investigator is unable to continue the study and another suitable person is designated as the Investigator, the Sponsor must be notified in advance. The new Investigator must accept the responsibility in writing and be approved by the Sponsor and the IRB/IEC.

12.2. Protocol Deviations

The Investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study patients without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change and the reasons for it should be documented and submitted to the IRB/IEC and Sponsor.

The Investigator is to record any deviation from the protocol in the source documents, describing this departure and the circumstances under which it was required.

12.3. Protocol Amendments

All protocol amendments must be issued by the Sponsor, and signed and dated by the investigator. Documentation of amendment approval by the Investigator and IRB/IEC must be provided to the Sponsor.

If the changes involve only logistic or administrative aspects of the study, these changes will be notified in writing by the Sponsor.

12.4. Study Termination

If the Sponsor and/or the Investigator should discover conditions arising during the study that indicate it should be terminated, an appropriate schedule for termination will be instituted. The Sponsor also reserves the right to discontinue this study for administrative or discretionary reasons at any time.

12.5. Case Report Forms

The Investigator should complete all eCRFs in accordance with the eCRF Completion Guidelines. Data in the eCRFs shall be consistent with source documents.

In this study, all relevant personnel will receive electronic data capture access according to their roles in the study.

An eCRF should be completed for each screened and enrolled patient.

The Investigator, or assigned personnel, should verify the data and correct as necessary prior to approval of the eCRFs.

12.6. Access to Source Data/Documents

The Investigator and the site must make all study-related records available for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

12.6.1. Source Data/Documents

Source documents are original documents, data, and records such as hospital records, clinical and office charts, laboratory notes, memoranda, patient's evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfilm or magnetic media, X-ray, patient files, and records kept at the pharmacy, laboratories, and medical-technical departments involved in the study.

Specific details regarding source documents and source data to be recorded directly on the eCRFs for the study should be identified with the Investigator prior to and during the study.

12.6.2. Access to Source Data

The Sponsor's study monitor, or other representatives, should verify the entries in the eCRF and source documents to confirm the completeness and accuracy of the data. If there are any discrepancies between the entries in eCRFs and source documents, the monitor will query the Investigator.

12.7. Data Handling

All study information is confidential. The patient's and Investigator's personal data which may be included in the Sponsor's database shall be treated in compliance with all applicable laws and regulations.

When processing and archiving personal data pertaining to the Investigator and to the patients, the Sponsor or its representatives shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

12.8. Responsibilities of Recordkeeping

12.8.1. Investigator and Study Site

The Investigator and the study site are responsible for the retention of all study documents according to institutional policies, local laws, and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Guidelines. In multinational trials, non-United States sites will be considered non-Investigational New Drug (IND) sites. Non-IND sites will be required to follow local regulations and ICH Guidelines.

The Investigator and the study site agree to inform the Sponsor in writing of the intention to remove or destroy any study-related records. Prior to contacting the Sponsor, the Investigator and study site must ensure that the applicable regulatory requirements have been satisfied. The Sponsor will evaluate the requests from the Investigator and the study site and will provide authorization for destruction of such records in writing.

In the event that all retention of records requirements have been fulfilled, but the Sponsor requests that the Investigator and study site maintain the records for a longer period of time, additional arrangements will be made.

12.8.2. Sponsor

The Sponsor must retain all Sponsor-specific essential documents in conformance with the applicable regulatory requirements of the countries where the product is approved, and where the Sponsor intends to apply for approvals.

If the Sponsor discontinues the clinical development of the study drug, the Sponsor must maintain all Sponsor-specific essential documents in conformance with the applicable regulatory requirements.

12.9. Monitoring

The Sponsor and designee will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator and the site agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

12.10. Financial Disclosure

Financial disclosure for investigators will be obtained and record keeping of financial records will be in accordance with local regulatory requirements. Investigators will provide the Sponsor with sufficient, accurate financial information upon the Sponsor’s request.

12.11. Compensation for Health Injury

The clinical study is insured according to applicable regulatory requirements. A copy of the Compensation Policy Document will be provided to the study site by the Sponsor.

In the case of a compensation claim, excluding claims that have arisen due to medical malpractice or negligence, the legally responsible person is clearly identified.

Sponsor should address the policies and payment procedures of compensation for the event of study-related injuries as the Compensation Policy Document.

When patients receive compensation, the policies and payment procedure of compensation should comply with the Compensation Policy Document.

12.12. Study Administrative Structure

The study organization details will be maintained in a supplement.

13. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will perform quality control and quality assurance procedures in accordance with the Sponsor's standard operating procedures (SOPs) to ensure the quality of the clinical study.

13.1. Quality Control

The Sponsor is responsible for controlling the quality of the clinical study according to the SOPs regarding study operation, monitoring, data collection and management, statistical analysis, and handling of safety information to verify that the study-related activities have been fulfilled.

13.2. Quality Assurance

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Authorized representatives of the Sponsor, a regulatory authority, or an IRB/IEC may visit the site to perform audits or inspections, including source data verification. The Investigator and the site will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data and documents pertaining to the clinical study.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to ensure that these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP E6 Guidelines, and any applicable local regulatory requirements. The Investigator and the site should contact the Sponsor immediately if contacted by a regulatory agency regarding an inspection.

Any results arising from such inspections will be immediately communicated by the investigator and the site to the Sponsor. The Investigator and the Sponsor will take corrective actions for all findings and observations found during audits and/or inspections. The auditors and inspectors will not disclose private information unless required by law.

14. ETHICS

14.1. Ethical Conduct of the Study

It is mandatory that all considerations regarding the protection of patients be carried out in accordance with the latest versions of the protocol, ICH GCP Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

14.2. Written Informed Consent

The ICF(s) must be approved by the IRB/IEC before patient's sign consent for any study-related activity. It must be in a language that the patient can read and understand. The ICF process should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP Guidelines, and applicable regulatory requirements. Each patient (or a legally acceptable representative) must give written consent according to local requirements.

The Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient.

There must be documentation in each patient's case history/medical record that informed consent was obtained prior to any study procedure being performed. Patients must be re-consented to the most current version of the ICF(s) during their participation in the study (including during survival follow-up).

14.3. Institutional Review Board/Independent Ethics Committee

The study must be approved by an appropriately constituted IRB/IEC, as required in the applicable local regulation such as ICH E6 Guidelines (Part 3), Code of Federal Regulations Title 21, part 56, and Ordinance of the Ministry of Health and Welfare No. 28, Chapter IV, Section 1 before the study is initiated. At the end of the study, the Investigator will notify the IRB/IEC of the conclusion of the study and its outcome.

15. PUBLICATION POLICY

15.1. Publication Policy

The Sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and regulatory authorities of any country or region.

The results of the study may be presented during scientific symposia and/or published in a scientific journal only after review by the Sponsor in accordance with the guidelines set forth in the applicable publication.

The Investigator(s) and the Sponsor will discuss and determine the presenter(s) or author(s) and timing of any presentation or publication related to this study and/or its results. Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

15.2. Secondary Use of Data

The Sponsor maintains the right to secondary use of data in this study.

Secondary use of data describes the use of data from this study for other study/studies for purposes including, but not limited to, drug development and/or academic research. Secondary use of data also includes external offerings of study data to domestic and/or foreign organization(s), other companies and researcher(s), on a case by case basis.

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APPENDIX A. ECOG Performance

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

From: Oken MM, Creech, RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55.

APPENDIX B. DIETARY GUIDELINES FOR TREATMENT OF HYPERPHOSPHATEMIA

The best way to limit phosphorus in the diet is to limit foods highest in phosphorus, including:

- Fast food, convenience foods, and processed foods, which may be full of phosphorus additives
- Beverages that contain phosphorus (look for the letters "phos" in the ingredient list)

Also, look for any ingredient that contains "phos" in the term such as:

- Calcium phosphate
- Disodium phosphate
- Phosphoric acid
- Monopotassium phosphate
- Sodium acid pyrophosphate
- Sodium tripolyphosphate

Listing of Some Lower and Higher Phosphorus Foods	
Higher Phosphorus Foods	**Lower Phosphorus Foods**
Milk, pudding, yogurt, soy milk, nondairy creamers and enriched rice milk	Unenriched rice milk
Processed cheeses and cheese spreads	A small amount of Brie or Swiss cheese
Hard cheeses, ricotta or cottage cheese, fat-free cream cheese	Regular or low-fat cream cheese
Ice cream or frozen yogurt	Sherbet, sorbet or frozen fruit pops
Soups made with higher phosphorus ingredients (milk, dried peas, beans, lentils)	Soups made with lower phosphorus ingredients (broth- or water-based with other lower phosphorus ingredients)
Whole grains, including whole-grain breads, crackers, cereal, rice and pasta	White bread, crackers, cereals, rice and pasta
Quick breads, biscuits, cornbread, muffins, pancakes or waffles	White dinner rolls, bread, bagels or English muffins
Dried peas (split, black-eyed), beans (black, garbanzo, lima, kidney, navy, pinto) or lentils	Green peas, green beans or wax beans
Processed meats (ie, bologna, ham and hot dogs), and meat, poultry or seafood with "phos" in the ingredients	All-natural lean beef, pork, lamb, poultry, seafood or other fish without "phos" in the ingredients
Organ meats, walleye, pollock or sardines	All-natural lean beef, pork, lamb, poultry, seafood or other fish without "phos" in the ingredients
Nuts and seeds	Popcorn or pretzels
Peanut butter and other nut butters	Jam, jelly or honey
Chocolate, including chocolate drinks	Jelly beans, hard candy, fruit snacks or gumdrops
Colas and pepper-type sodas, some flavored waters, bottled teas, some drink mixes (any with "phos" in the ingredients)	Lemon-lime soda, ginger ale, root beer, plain water or some drink mixes (any without "phos" in the ingredients)
Although a food or drink may be low in phosphorus, limitation of portion size and the number of servings you eat or drink each day may still be recommended.	

From: Rachael Majorowicz, R.D.N., L.D. (Feb, 2016). Why is a low-phosphorus diet useful in managing kidney disease? What foods contain phosphorus? https://www.mayoclinic.org/food-and-nutrition/expert-answers/faq-20058408.

APPENDIX C. CLASSIFICATION OF SUBSTRATES, INHIBITORS, AND INDUCERS OF CYP ENZYMES AND TRANSPORTERS

The classification below is based on the FDA Draft Guidance for Industry, Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications, October 2017. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf)

Example of CYP3A Inhibitors

Cytochrome P450 (CYP) Enzymes	Strong Inhibitors[a] ≥ 5-fold increase in AUC	Moderate inhibitors[b] ≥ 2 but < 5-fold increase in AUC
CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice,[c] indinavir and ritonavir, idelalisib, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil

[a] Strong inhibitors are drugs that increase the area under the concentration-time curve (AUC) of sensitive index substrates of a given metabolic pathway ≥5-fold.

[b] Moderate inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥2 to <5-fold.

[c] The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

Example of CYP3A Inducers

Cytochrome P450 (CYP) Enzymes	Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC
CYP3A	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort[a]	bosentan, efavirenz, etravirine, modafinil

[a] The effect of St. John's wort varies widely and is preparation-dependent.

Example of Inhibitors for P-gp and BCRP

Transporters	Gene	Inhibitor
P-gp[a]	*ABCB1*	Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP[b]	*ABCG2*	Curcumin, cyclosporine A, eltrombopag

[a] P-gp: (1) AUC fold-increase of digoxin ≥2 with co-administration and (2) in vitro inhibitor.

[b] BCRP: (1) AUC fold-increase of sulfasalazine ≥1.5 with co-administration and (2) in vitro inhibitor. Cyclosporine A and eltrombopag were also included, although the available DDI information was with rosuvastatin, where inhibition of both BCRP and OATPs may have contributed to the observed interaction.

Example of Substrates for P-gp and BCRP

Transporters	Gene	Substrate
P-gp[a]	*ABCB1*	Dabigatran, digoxin, fexofenadine
BCRP[b]	*ABCG2*	Rosuvastatin, sulfasalazine

[a] P-gp: (1) AUC fold-increase ≥2 with verapamil or quinidine co-administration and (2) in vitro transport by P-gp expression systems, but not extensively metabolized.

[b] BCRP: (1) AUC fold-increase ≥2 with pharmacogenetic alteration of ABCG2 (421C>A) and (2) in vitro transport by BCRP expression systems.

Taiho

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