Mayo Clinic Comprehensive Cancer Center

MC200402 Phase II Study of FGFR Inhibitor Futibatinib in Combination with Anti-PD-1 Antibody Pembrolizumab in Patients with Advanced or Metastatic Hepatocellular Carcinoma with FGF19 Expression

Sponsor/Principal Investigator: [redacted]

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Statistician: [redacted]

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Drug Availability:

Supplied Investigational Agents: futibatinib (TAS-120)

Commercial Agents: pembrolizumab

√Study contributor(s) not responsible for patient care

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/ interruptions/ adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Lead Site Clinical Study Coordinator	[redacted]
Lead Site Clinical Data Coordinator	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Laboratory Contacts for Correlative Studies	[redacted]
Serious Adverse Event Reporting	[redacted]

*No waivers of eligibility allowed

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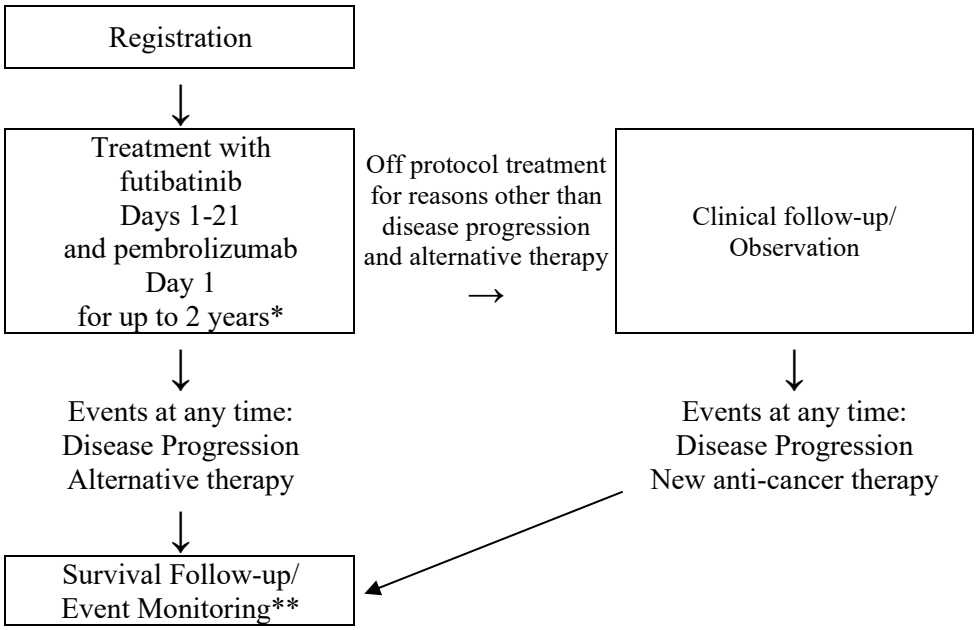
Schema



*When patients complete Cycle 9, the cycle length can be increased to 6 weeks with imaging every other cycle (~12 weeks)

**NOTE: Survival follow-up/Event Monitoring will cease for all patients as of 31Aug2025

Cycle = 21 days ±3 days for Cycles 1-9

Cycle = 42 days ±7 days for Cycles 10 and beyond

Generic name: futibatinib (TAS-120) Brand name(s): n/a Availability: Supplied by Taiho Pharmaceuticals	Generic name: pembrolizumab Brand name(s): Keytruda® Availability: Commercial

1.0 Background

1.1 Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer. It is the sixth most common cancer worldwide and the fourth leading cause of cancer death.[1] Between 1990 and 2015, the incidence of this specific disease has increased significantly owing mainly to changing age structure and population growth.[1] Patients often present with advanced disease when first diagnosed. The natural history of untreated advanced HCC has a dismal 3-year survival of approximately 28%.[2] Even with recent advances in systemic treatments, median overall survival (OS) ranges from 10.7 to 13.6 months.[3,4] Since 2007, sorafenib, an oral multikinase inhibitor, has been established as first line systemic therapy for patients with advanced HCC. This is based on the results of a phase III clinical trial (SHARP) where Llovet and colleagues randomized 602 patients to sorafenib or placebo.[3] Patients on the sorafenib arm demonstrated an improvement in OS (10.7 versus 7.9 months; hazard ratio (HR), 0.69; 95% CI, 0.55-0.87; P<0.001). Kudo and colleagues demonstrated non-inferiority of lenvatinib, another oral multikinase inhibitor, in comparison to sorafenib in patients with untreated advanced HCC.[4] In this phase III trial, 954 patients were randomly assigned to lenvatinib or sorafenib. The median OS were 13.6 and 12.3 months, respectively (HR 0.92, 95% CI 0.79-1.06). More recently, atezolizumab, an anti-PD-L1 antibody, in combination with bevacizumab, a monoclonal anti-VEGF antibody, showed superior outcomes (67.2% OS at 12 months vs. 54.6% with sorafenib), which led to FDA approval of the combination as the first-line systemic treatment for advanced HCC. Second line treatments include multikinase inhibitors cabozantinib and regorafenib, the anti VEGF antibody ramucirumab, and the anti PD1 antibodies nivolumab and pembrolizumab.[5] However, toxicity often limits the use of these agents and responses with these therapies are often measured in months. Majority if not all of patients will progress. Thus, there is a large unmet need for novel tailored treatments in HCC.

1.2 FGF-19 expression and role of FGFR4 inhibitor in HCC

Fibroblast growth factor (FGF) and fibroblast growth factor receptor (FGFR) signaling system is involved in broad biological processes including embryogenesis, angiogenesis, tissue homeostasis and cancer progression.[6] The FGF family consists of 22 members with FGF-19 functioning as a secreted endocrine signal that regulates many metabolic processes such as phosphate, glucose, and lipid metabolism.[7] Emerging data suggest FGF-19 is a potential HCC driver[8,9] with exclusive binding to FGFR4 in the presence of co-receptor klotho-β.[10] FGF-19 overexpression in HCC occurs via several mechanisms including amplification of the FGF19/CCND1 locus on chromosome 11q13.3 (5% of cases[9,11,12]) and epigenetic alterations[13] (23%). Aberrant expression of FGF-19 in transgenic mice has been shown to promote liver proliferation, dysplasia and tumor formation by enhancing expression of α-fetoprotein(AFP).[14] Furthermore, recombinant FGF-19 promotes proliferation and invasive ability of HCC cells while knockdown of FGF-19 or FGFR4 inhibits proliferation and invasion as well as induces apoptosis of HCC cells.[15] The binding of FGF-19 to FGFR4 form a homodimer receptor complex in the presence of klotho-β leading to downstream signaling pathways including Ras-Raf-ERK/2MAPK and PI3K-Akt.[16,17] Several studies have shown FGF-19 amplification was independently associated with shorter survival and higher risk of recurrence with poor prognostic factors including microvascular invasion and high AFP.[12,18,19]

A number of pan-FGFR inhibitors are under development in different phases of clinical trials in different disease types including LY2874455 (NCT01212107), AZD4547 (NCT02965378), infigratinib (NCT01004224), erdafitinib (NCT02365597), PRN1371

(NCT02608125), ASP5878 (NCT02038673). Kim and colleagues recently published results of the phase I trial using BLU-554 (fisogatinib) with accompanying IHC essay for FGF19 expression in advanced HCC.[20] This drug showed an overall response rate of 17% with 1 complete response and 10 partial responses. This data was encouraging but the level of IHC positivity was not correlated with response or genomic amplification of the FGF19 locus.

Futibatinib is a novel and highly selective irreversible pan-FGFR inhibitor. In the phase I dose-escalation study, 460 patients with solid tumor harboring FGF amplifications or FGFR aberrations showed manageable toxicity and had reasonable clinical activity.[21] The recommended phase 2 dose was 20mg daily. The most frequently reported treatment-related adverse events include hyperphosphatemia, diarrhea, dry mouth, nausea, and stomatitis. Currently, there is no clinical data on the efficacy of futibatinib alone or the combination of futibatinib and immunotherapy in HCC.

1.3 Role of checkpoint inhibitors (CPI) in HCC

The role of cytotoxic immune response against a tumor requires a complex and evolving interaction between several immune cells. T-cell activation requires antigen-specific receptor signaling in addition to a second costimulatory signal;[22] the lack of this latter signal may lead to unresponsive state known as clonal anergy.[23] The first signal involves the binding of T-cell receptor to a peptide presented by major histocompatibility complex (MHC) of antigen presenting cells (APCs). The second important costimulatory signal involves the interaction between B7 (CD80/86) on the APCs and CD28 on T cells. The combination of signaling leads to T-cell proliferation, cytokine release and upregulation of immune response. CD28, cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), inducible costimulator (ICOS) and BTLA (B and T lymphocyte attenuator) are homologous costimulatory receptors that regulate T-cell activation and tolerance.[24] Other costimulatory receptors include CD137, OX40, CD27, LAG3, TIM3.[25] CTLA-4 competes with CD28 for B7 binding with higher affinity. There are two PD-1 ligands, PD-L1 and PD-L2 that bind PD-1 receptor. Whereas CD28 signaling leads to T-cell activation and survival, CTLA-4 and PD-1 signaling inhibit T-cell responses.[24]

Preclinical work has demonstrated chronic inflammation in the liver as seen in viral hepatitis B (HBV), hepatitis C (HCV) and autoimmune hepatitis appears to promote a microenvironment that favors T cell exhaustion.[26] Comparing to liver biopsies from normal individuals, patients with chronic inflammatory conditions contained increased numbers of PD-1 expressing lymphocytes, PD-L1 on intrahepatic Kupffer cells and liver sinusoidal endothelial cells. It is suggested that high antigen load and high frequencies of infected liver cells seen in HBV infected patients result in persistent antigen exposure and the expression of co-inhibitory molecules such as PD-1, CTLA-4, LAG-3, etc,[27] leading to a less effective immune response capable of controlling the infection. Additionally, other factors seen in chronic inflammatory conditions include increased levels of IL-10, TGF-ß, increased frequency of Tregs as well as impaired antigen presentation.[28–32] Altogether, these factors contribute to an immunosuppressive environment associated with chronic inflammation that fosters the development and growth of HCC. Multiple studies, both in vitro and in vivo, have shown by blocking the inhibitory receptor pathways, the function of specific CD8+ T cells can be restored.[33–37] Using anti-PD-1 or anti-PD-L1 mAb in HBV murine models also showed clearance of HBV in vivo.[33,35]

One of the first immunotherapies studied in HCC was tremelimumab, a human IgG2 monoclonal antibody (mAb) that blocks CTLA-4, one of many inhibitory receptors that interfere with T cell activation. In a pilot phase II clinical trial involving 20 HCV-related

HCC patients with advanced tumor that had relapsed or progressed on at least one previous therapy, 3 of 17 evaluable patients had confirmed partial response with one patient having clinical benefit that lasted to 15.8 months.[38] It was also notable that 3 patients had transient complete viral response during follow up. Adverse events included transient grade 3 transaminitis occurring in 45% of patients after first dose. Since then, several clinical trials involving PD-1 inhibitors have shown clinical activity in HCC and are FDA approved for use.[39,40] Pembrolizumab has been evaluated in the 2nd line in HCC in phase II and phase III clinical trials with common toxicities including increased AST (13.3%), bilirubin (7.5%), fatigue and pruritus, as well as immune-related (18.3%) adverse events. These include hypothyroidism, hyperthyroidism and pneumonitis. The FDA approved dose for pembrolizumab is 200mg IV every 3 weeks or 400mg IV every 6 weeks.

1.4 Rationale for combining FGFR4 inhibitor and PD-1 inhibitor

Patients with advanced HCC have a dismal prognosis. Despite the recent approval of the combination atezolizumab and bevacizumab, this combination showed a confirmed response rate of only 27.3% by conventional RECIST 1.1 and 33.2% by mRECIST criteria. The median PFS is 6.8 months. There is currently no biomarker to predict response in these patients. Furthermore, the implementation of this combination as the new standard of care front line therapy has significantly changed the sequencing of treatments of HCC, as many of the currently approved therapies were not tested in ICP experienced patients. Thus, this poses the important question whether every patient with advanced HCC should receive this combination and whether there is a role for continuing ICP in combination with other agents in the second line setting.

FGFR4 inhibitors appeared to have activity in HCC, however, duration of response is similar to that of single agent CPI in the second line setting, inclusive of patients with negative FGF19 expression.[20] Combining FGFR inhibitors with CPI appeared synergistic. Previously, FGFR-altered cancers have been correlated with non-T-cell-inflamed microenvironment.[42] Palakurthi and colleagues confirmed this finding in genetically engineered mice showing significant decrease in T and natural killer cells, increased regulatory T cells, and exhaustion marker-positive T cells.[43] The combination of erdafitinib with anti-PD-1 leads to decrease infiltration of immunosuppressive TAMs, increased NK and B cells and higher proliferative, activated T and NK cells. Furthermore, the combination resulted in significant increase in both T-cell fraction and clonality resulting in improved survival. This provides a strong rationale for combining the use of futibatinib with anti-PD-1 antibody.

As of Amendment 4, we have expanded this trial to allow most patients with metastatic hepatocellular carcinoma (HCC) regardless of FGF19 expression at baseline. Our rationale for including patients with no known FGF19 expression by IHC at registration (but will be tested retrospectively) is three-fold: 1) In the current study, of 36 patients screened for FGF19 by IHC, we observed no FGF19 expression in only 5 patients (13%); 2) single agent FGFR inhibitor has demonstrated activity in those with no FGF19 expression as evidenced by Kim and colleagues who noted stable disease in 16 patients (50%) out of 32 patients[20]; and 3) we have enrolled 11 patients with FGF19 expression with a total target goal of 22 evaluable patients.

The treatment landscape for HCC is rapidly evolving. Since the conception of this protocol, another regimen has been approved in the first line setting (tremelimumab and durvalumab), which demonstrated improvement in survival for patients with advanced unresectable HCC. Furthermore, recently, we have received matured data from the IMbrave150 regimen which showed that patients are staying on treatment longer than ever,

and little is known of their liver function at the end of treatment. In clinical practice, we are observing patients with worsening bilirubin levels above clinical trial criteria or rapid decompensation of their cirrhosis making it difficult to enroll patients in the second line and later.

In an effort to improve recruitment to test our hypothesis, the protocol is being amended to reflect the changing treatment landscape. By adjusting the eligibility criteria, we hope to enroll advanced HCC patients in any line of systemic therapy who are not eligible for the standard first line treatments (e.g., due to history of varices with bleeding risks, or having portal vein invasion of disease) including IMbrave150 or STRIDE regimens based on the criteria listed in the respective clinical trials. We will continue to test for FGF19 tissue retrospectively, which would allow us to explore the efficacy signal of this combination in patients with FGF19 expression.

We therefore hypothesize that futibatinib in combination with anti-PD-1 antibody in patients with or without FGF19 expression will improve progression free survival in advanced HCC patients. This will be the first biomarker driven clinical trial combining CPI with pan-FGFR inhibitor. These results are expected to have an important positive impact because they will provide evidence guided understanding and indication of the use of FGFR inhibitor with a CPI in HCC.

1.5 Correlatives

1.51 Cell free DNA (cfDNA)

Detection of cancer specific mutations from the peripheral blood is an area of active investigation in many different types of cancers. An accumulating body of literature confirms an excellent correlation between mutations found in cancer tissues and mutations detected in cfDNA from the same patients.[47] Changes in cfDNA also correlate well with tumor marker dynamics in serial sampling, suggesting that cfDNA mutant allele fraction changes reflect changes in disease burden over time and treatment. Plasma based DNA mutation detection should therefore provide longitudinal changes in the representative genomic landscape of the malignancy in a non-invasive manner, overcoming the two major limitations of tissue based DNA mutation analysis (invasiveness and limited sampling from a genetically heterogeneous tumor).[48–50] In this protocol we will explore the utility of cfDNA as a marker to assess treatment response in advanced HCC.

1.52 3-D cell cultures (organoids) and microfluidic device

Preclinical tumor models are important tools to study cancer biology, develop novel therapeutics, and provide information for treatment decisions. However currently available tumor models such as cell lines, transgenic mice and patient-derived xenograft (PDX) models have inherent limitations that can adversely affect the translation of preclinical findings to the clinic. Patient-derived tumor organoids and microfluidic devices are 3-D cell cultures which enable the establishment of *ex vivo* tumor models from scant core-needle biopsy specimen in a timely manner. These tumor organoids recapitulate both phenotypes and genotypes of the donor tumo.r[67] The laboratory of [redacted] at our institution has successfully established such tumor organoids and device from core-biopsy tumor specimens donated by patients with metastatic hepatocellular carcinoma and hepatocytes, respectively. The established tumor organoids were ready for drug screening and related molecular studies within 4-6 weeks of the biopsy. Though the concordance between treatment effect in tumor organoids and the clinical benefit observed in the donor patients has been reported, the role of tumor organoids has not been prospectively evaluated in clinical trials of patients with advanced hepatocellular carcinoma. Here, we aim: 1) to determine if drug response from a parallel

ex vivo trial using patient-derived tumor organoids correlates with clinical response to futibatinib and pembrolizumab; and 2) to characterize the tumor microenvironment in antitumor immune response and resistance to this combination of therapy.

1.53 Patient Reported Outcomes/Quality of Life (PROQOL)

To understand the quality of life changes while on study treatment, we will have patients complete an EORTC-QLQ-C30, a series of 30 items that has been previously validated. The EORTC-QLQ-C30 is used to assess patient quality of life for patients with cancer. This questionnaire will be completed prior to treatment on Day 1 of the first cycle and prior to treatment on Day 1 of the 4th cycle to correspond with imaging results.

1.6 Study Design

This is a single-arm, two-stage, phase II trial to assess the efficacy of futibatinib plus pembrolizumab in advanced hepatocellular carcinoma for patients with FGF19 expression. Patients will receive futibatinib 20 mg daily Days 1-21 and will receive pembrolizumab 200 mg Day 1 of each 21 day cycle per current clinical standard of care. Patient will receive treatment until disease progression or unacceptable toxicities. Patients will undergo restaging scans every 3 cycles. Subjects will be monitored for adverse events from the beginning of the study drug to 28 days after the last dose. We will collect blood samples for determination of cell free DNA at baseline, after 3 and 6 cycles, and at progression. We will collect tumor biopsy specimens before treatment initiation to develop patient derived tumor organoid.

Once patient has completed 9 cycles of treatment, the cycle length can be extended to 6 weeks with futibatinib daily Days 1-42 and pembrolizumab 400mg Day 1 of each 42 day cycle (as currently approved by FDA). Restaging will be done every other cycle (~12 weeks). Patient will continue to receive treatment until disease progression or unacceptable adverse events.

2.0 Goals

2.1 Primary Goal

Determine the efficacy of combination of futibatinib and pembrolizumab in patients with advanced HCC and high FGF19 expression using progression free survival (PFS) at 6 months.

2.2 Secondary Goals

2.21 Assess the safety and tolerability of futibatinib and pembrolizumab combination through adverse event monitoring.

2.22 Determine the overall objective response rate (ORR) and overall survival (OS) of patients with advanced HCC treated with futibatinib and pembrolizumab combination.

2.23 Assess change in overall health-related quality of life, as measured by the global health domain of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30) between baseline and at time of first-restaging scan.

2.3 Exploratory Objectives

2.31 To evaluate the prognostic effect of baseline cfDNA.

2.32 To determine whether the change in cfDNA at 2 months of treatment from baseline is associated with PFS and OS.

2.33 To correlate drug response in patient derived organoids with clinical response and characterize the tumor microenvironment.

3.0 Patient Eligibility

3.1 Registration – Inclusion Criteria

3.11 Age ≥18 years

3.12 Adequate tissue for FGF19 testing by mRNA or IHC.

3.13 Disease characteristics:

Radiologically or pathologically confirmed hepatocellular carcinoma (HCC) that is not eligible for curative resection, transplantation, or ablative therapies.

NOTE: Prior radiation, chemoembolization, radioembolization, or other local ablative therapies or hepatic resection are permitted.

3.14 Measurable disease by any imaging modality as defined by RECIST 1.1 criteria (See Section 11.0) in at least one site not previously treated with radiation or liver directed therapy (including bland, chemo- or radio-embolization, or ablation)
NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease; disease that is measurable by physical examination only is not eligible.

3.15 ECOG Performance Status (PS) 0, 1 or 2 (Appendix I).

3.16 The following laboratory values obtained ≤15 days prior to registration:

- Absolute neutrophil count (ANC) ≥1500/mm^3
- Hemoglobin ≥8.0 g/dL
- Platelet count ≥75,000/mm^3
- Albumin ≥2.5 g/dL
- Alanine aminotransferase (ALT) and aspartate transaminase (AST) ≤2.5 × ULN (or ≤5 × ULN for patients with liver metastasis)
- Total bilirubin ≤2 × ULN
- Phosphorus ≤1.5 × ULN
- Calcium ≤1.5 × ULN
- PT/INR/aPTT ≤1.5 × ULN OR if patient is receiving anticoagulant therapy then INR or aPTT is within target range of therapy
- Calculated creatinine clearance ≥40 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{\textbf{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\frac{\textbf{(140 - age)(weight in kg)(0.85)}}{\text{(72)(serum creatinine in mg/dL)}}$

3.17 Child-Pugh scores of ≤7 (Child-Pugh A or B7) (See Appendix II)

3.18 BCLC stage A, B, or C (See Appendix III)

3.19a Negative pregnancy test done ≤7 days prior to registration, for persons of childbearing potential only.

3.19b Willing to use an adequate method of contraception (see Appendix IV) from Registration through 120 days after the last dose of study medication
NOTE: Only for a) persons of childbearing potential or b) persons able to father a child with partners of childbearing potential)

3.19c Able to swallow oral medication.

3.19d Provide written informed consent.

3.19e Willingness to provide mandatory blood specimens for correlative research (see Section 14.0).

3.19f Willingness to provide mandatory tissue specimens for correlative research (see Section 17.0).

3.19g Willingness and the ability to comply with scheduled visits (including geographical proximity), treatment plans, laboratory tests, and other study procedures.

3.19h Ability to complete questionnaires by themselves or with assistance.

3.2 Registration - Exclusion Criteria

3.21 Known standard therapy for the patient's disease that is potentially curative or definitely capable of extending life expectancy.

3.22 Eligible for first-line treatment with IMbrave150 or STRIDE regimens.

3.23 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant persons
- Nursing persons
- Persons of childbearing potential who are unwilling to employ adequate contraception

3.24 Any of the following prior therapies:

- Surgery ≤4 weeks prior to registration
- Radiotherapy for extended field ≤4 weeks prior to registration or limited field radiotherapy ≤2 weeks prior to registration
- Systemic anticancer therapy ≤2 weeks prior to registration
  NOTE: Prior immunotherapy is allowed unless patient discontinued due to Grade 4 AE
- Live vaccine ≤30 days prior to registration
- Prior treatment with FGFR inhibitor
- Received strong inhibitors and inducers and sensitive substrates of CYP3A4 ≤2 weeks prior to registration
- Received a drug that has not received regulatory approval for any indication as follows:
  - ≤2 weeks prior to registration for nonmyelosuppressive agents or
  - ≤4 weeks prior to registration for myelosuppressive agents

3.25 History and/or current evidence of any of the following disorders:

- Retinal or corneal disorder confirmed by retinal/corneal examination and considered clinically significant in the opinion of the Investigator
- Pneumonitis or interstitial lung disease within ≤3 years prior to registration

3.26 Active CNS metastasis and/or carcinomatous meningitis.
NOTE: Patients with previously treated brain metastases that are clinically and radiologically stable (for at least 4 weeks prior to enrollment) are eligible.

3.27 Corrected QT interval using Fridericia's formula (QTcF) >480 msec.
NOTE: 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.

3.28 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

3.29a Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm.

3.29b History or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

Notes:

- Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
- Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible.
- Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
    - Must **not** have ocular manifestations
    - Rash must cover less than 10% of body surface area (BSA)
    - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
    - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

3.29c Known active human immunodeficiency virus (HIV) infection (defined as patients who are not on anti-retroviral treatment and have detectable viral load and CD4+ <500/ml).
NOTE: HIV-positive patients who are well controlled on anti-retroviral therapy are allowed to enroll.

3.29d 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.

3.29e Uncontrolled intercurrent illness including, but not limited to:

- Ongoing or active severe infection
  NOTE: Must be afebrile >7 days to be eligible. Patient may be eligible if fever is present and infection has been ruled out or fever is related to tumor.
- Psychiatric illness/social situations that would limit compliance with study requirements.

3.29f Clinically significant or uncontrolled cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study treatment administration, New York Heart Association Class III and IV congestive heart failure, and uncontrolled arrhythmia
NOTE: Participants with pacemaker or with atrial fibrillation and well controlled heart rate are allowed.

3.29g Other active malignancy <6 months prior to registration.
EXCEPTIONS: Non-melanotic skin cancer, papillary thyroid cancer, or carcinoma-in-situ of the cervix, or others curatively treated and now considered to be at less than 30% risk of relapse are eligible.

3.29h Prior organ transplantation.

4.0 Test Schedule

4.1 Test schedule for Hepatocellular Carcinoma (HCC)

Tests and procedures[1]	Screening	Active Monitoring Phase							Obs
	≤21 days prior to registration	After Reg prior to C1D1 Tx	Cycle 1 Days 8, 15	End of every cycle	End of every 3 cycles (Cycles 1-9)[2]	End of every 2 cycles (Cycles 10+)[3]	End of treatment	Safety follow-up: 30 days post treatment	Clinical follow-up[4]
Window			±3 days	±3 days	±7 days	±7 days	±7 days	±7 days	±7 days
History and exam, Wt, PS	X		X	X			X	X	X
Height	X								
Adverse event assessment[5]	X	X	X	X	X	X	X	X	
Pregnancy test[6]	X								
Hematology group: CBC /w diff	X[7]		X	X			X	X	
Chemistry group[8]	X[9]		X	X			X	X	
TSH	X			X			X	X	
Ophthalmologic testing[10]	X				X[11]	X[12]			
Nutrition consult[13]			X						
FGF19 testing[R]		X[14]							
AFP, AFP-L3 %[15]	X				X	X			

Cycle = 21 days ±3 days for Cycles 1-9; Cycle = 42 days ±7 days for Cycles 10+; R= Research funded (See Section 19.0)

[1] All tests and procedures should be performed as needed for clinical care at treating physician's discretion.

[2] End of Cycles 3, 6, 9 (NOTE: Imaging schedule may be adjusted by treating oncologist as necessary for clinical care.)

[3] End of Cycles 11, 13, 15, etc. (NOTE: Imaging schedule may be adjusted by treating oncologist as necessary for clinical care.)

[4] Observation: every 9 weeks until disease progression, new anti-cancer therapy, death, withdrawal from clinical follow-up, or a maximum of 18 month post registration.

[5] AEs must be assessed at every cycle; Baseline AE collection for eligibility should be done after patient signs main study consent

[6] For persons of childbearing potential only: Must be done ≤7 days prior to registration and repeated prior to C1D1 if >7 days between registration and treatment.

[7] Eligibility requires ≤15 days prior to Registration

[8] Chemistry: comprehensive metabolic panel (CMP) (80053) plus phosphorus (84100)

[9] Eligibility requires ≤15 days prior to Registration

[10] Must include external ocular exam; routine slit lamp biomicroscopy of anterior ocular structures include the anterior and posterior chambers; dilation of the pupil with direct/indirect fundoscopy per institutional guidelines; must be done ≤6 months prior to treatment and 2 months after first dose of futibatinib and every 2 months until 6 months after first dose, and every 3 months thereafter and urgently at any time for visual symptoms.

[11] Every 2 months for first 6 months and every 3 months until 3 months after last dose of futibatinib; Order at any time if clinically indicated.

[12] Every 3 months until 3 months after last dose of futibatinib; Order at any time if clinically indicated

[13] Nutrition consult may be done one time at anytime after starting treatment as needed. (This exam is part of expanded patient care.)

[14] Testing may be done on archived tissue at any time after registration – not required to be prior to C1D1 (see Section 17.0)

[15] Performed in all HCC patients at baseline

Tests and procedures[1]	Screening	Active Monitoring Phase							Obs
	≤21 days prior to registration	After Reg prior to C1D1 Tx	Cycle 1 Days 8, 15	End of every cycle	End of every 3 cycles (Cycles 1-9)[2]	End of every 2 cycles (Cycles 10+)[3]	End of treatment	Safety follow-up: 30 days post treatment	Clinical follow-up[4]
Clinical tumor genomic testing[16]		X							
Tumor measurement[17]	X[18]				X[19]	X[20]	X		X
Tumor biopsy	X[21R]								
Research blood specimens[22R]		X			X[23]		X		
Research tissue specimens [24R]	X						X		
Patient medication diary (Appendix V)[25]				X			X		
Patient questionnaire booklets (Appendix VII)		X			X[26]		X		

Cycle = 21 days ±3 days for Cycles 1-9; Cycle = 42 days ±7 days for Cycles 10+; R= Research funded (See Section 19.0)

[16] Clinical testing – Note: Molecular analysis including next generation sequencing (NGS) to be done per clinical practice – should be ordered/tested any time prior to end of treatment and results should be uploaded in Medidata Rave® when available

[17] To be performed per Mayo Clinic Cancer Center guidelines – For HCC usually CT chest/abdomen/pelvis or CT chest and MRI abdomen/pelvis; NOTE: If pseudoprogression is suspected at any time, repeat imaging after two more cycles of treatment.

[18] Can be performed ≤28 days prior to registration

[19] To be performed about every 9 weeks (or 3 cycles), ≤7 days prior to planned Day 1 of Cycles 4, and 7 or as clinically indicated

[20] To be performed about every 12 weeks, ≤7 days prior to planned Day 1 of Cycles 10, 12, 14 etc., or as clinically indicated

[21] Research biopsy should be done after registration and prior to treatment on C1D1. Research biopsy may be omitted after discussion with PI, (e.g., if it is not medically feasible, or exceeds lab capacity, or other reason).

[22] Research blood specimens to be collected on Cycle 1 Day 1 (or any time between registration and Cycle 1 Day 1), end of Cycle 3 and end of treatment (see Section 14.0)

[23] End of Cycle 3 only

[24] Research tissue specimens to be collected during research biopsy any time between registration and prior to treatment on C1D1 (see Section 17.0). Biopsy can be omitted for patients for whom investigator deems it unsafe.

[25] The diary must begin the day the patient starts taking the medication, and must be completed per protocol and returned to the treating institution at each visit.

[26] End of Cycle 3, prior to C4 only.

4.2 Survival Follow-up/Event Monitoring

NOTE: Survival Follow-up/Event Monitoring on this study will cease as of 31Aug2025.

NOTE: Timelines are approximate and not meant to represent exact dates.

	Survival Follow-up		
	q. 6 months	Death	New Primary
Survival Follow-up[1]	X	X	At each occurrence

1. If a patient is still alive 5 years after registration, no further follow-up is required.

5.0 Grouping Factor

Enrollment Group: Safety run-in vs. phase II

6.0 Registration Procedures

6. Registration (Step 1)

To register a patient, access the Mayo Clinic Research Registration Application web page at [redacted] The registration application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, contact Research Registration at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the Mayo Clinic Office of Clinical Trials web page [redacted] nd detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact Mayo Clinic Research Registration Office [redacted] If the patient was fully registered, the Research Site Management staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.2 Verification of materials

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.3 Documentation of IRB approval

Documentation of IRB approval must be on file in the Research Site Management Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with the Research Site Management Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Research Site Management Office is no longer necessary.

6.4 Patient Permissions

At the time of registration, the following will be recorded:

- Patient is or is not willing to complete questionnaires as part of this study
- Patient has/has not given permission for Mayo Clinic to have access to his/her recurrence/progression clinical sample(s) for research testing as part of this study.

6.5 Correlative Research

6.51 Mandatory

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.1, 17.0).

6.52 Banking

At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research on cancer at Mayo Clinic.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.
- Patient has/has not given permission for Mayo Clinic to place coded genetic and medical information in secure databases for future research
- Patient has/has not given permission for Mayo Clinic to contact him/her for future research opportunities

6.6 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic under the supervision of a medical oncologist.

6.7 Treatment start

Treatment cannot begin prior to registration and must begin ≤7 days after registration.

6.8 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.9a Baseline symptoms

All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9b Ophthalmology consult required

An ophthalmologist has seen the patient and confirms the patient is a suitable candidate for this study.

6.9c Study drug

Study drug is available on site.

6.9d Blood draw kits

Blood draw kit is available on site for sites outside of Rochester, MN.

6.9e Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

7.1 Treatment Schedule

Patients may receive treatment on this trial for up to 2 years until disease progression, unacceptable adverse events, or patient refusal.

7.11 Treatment medication table – Cycles 1-9

Agent	Dose Level	Route	Day	ReRx
futibatinib	20 mg*	oral	Once daily on Days 1-21	Q3w
pembrolizumab	200 mg	IV	1	Q3w

Cycle length = 21 days ±3 days

*Investigator may start patients at lower dose (16mg) if clinically indicated (e.g., patient history of diarrhea) after discussion with PI

Once patients have completed Cycle 9, the cycle length can be increased to 6 weeks with imaging every other cycle (~12 weeks).

7.12 Treatment medication table – Cycles 10 and beyond

Agent	Dose Level	Route	Day	ReRx
futibatinib	20 mg	oral	Once daily on Days 1-42	Q6w
pembrolizumab	400 mg	IV	1	Q6w

Cycle length = 42 days ±7 days

7.13 Futibatinib

Futibatinib is an oral agent taken once daily by mouth with water with or without food. Futibatinib should be taken at the same time every day.

On Day 1 of each cycle, the futibatinib dose should be held until at least 30 minutes after pembrolizumab infusion.

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.

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.

7.14 Pembrolizumab

Pembrolizumab is given by IV infusion over 30 minutes (-5 or +10)

Pembrolizumab should be administered according to institutional guidelines for premedication and standard clinical care.

Pembrolizumab should be administered prior to futibatinib dose on Day 1.

7.2 Biopsies

If research biopsy material has already been obtained under IRB 17-003174 for this patient, then no additional research biopsy is needed specifically for this trial.

Tissue for FGF-19 testing can be from archived tissue or clinical biopsy as needed.

7.3 Return to consenting institution

For this protocol, the patient must return to the consenting institution for evaluation at least every 21 days ±3 days during treatment for first 9 cycles. Beginning with Cycle 10 patients must return at least every 42 days ±7 days.

7.4 Treatment by local medical doctor (LMD)

Treatment with futibatinib by a local medical doctor (LMD) is not allowed.

7.5 Safety Run-in for first six patients

Patients will receive futibatinib and pembrolizumab combination. The safety profile of both agents has been previously evaluated individually[21,40]. To ensure the safety of this combination, we will perform a safety run-in with 6 patients. If there are 2 or more patients out of 6 who developed excessive toxicity during first cycle, the trial will be temporarily closed for enrollment to allow the study team to convene and discuss the best next steps.

7.51 For this protocol, excessive toxicity will be defined as follows:

Adverse event at least possibly related to the study medication	**Definition using CTCAE v5.0**
Any*	Grade 3 resulting in treatment interruption of both drugs for more than 21 days
Blood and lymphatic system disorders: Anemia	Grade 3 lasting >3 days
Any*	Grade 4
Investigations: Absolute neutrophil count decreased	Grade 4 lasting >7 days
Any	Grade 5
Gastrointestinal disorders • Diarrhea • Nausea • Vomiting	Grade 3 lasting >3 days with optimal supportive care

*Exceptions for: anemia, absolute neutrophil count; transient laboratory values without clinical manifestation; bowel obstruction resulting in hospitalization as a consequence of disease; which will not count as excessive toxicity

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to manage mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

Special Considerations

- The treating investigator may reduce/withhold/discontinue a patient's dose for an AE of any grade/duration where s/he believes it to be in the best interests of the patient.
- In patients who have met the criteria for permanent discontinuation, resumption of futibatinib may be considered if the patient is deriving clinical benefit and has fully recovered from the related event after consulting with PI.
- Any consideration to modification of the above dose modification guidelines should be discussed with the Principal Investigator for approval or disapproval in advance.

→ ***ALERT:*** ***ADR reporting may be required for some adverse events (See Section 10.0)*** ←

8.1 Dose Levels (Based on Adverse Events in Tables 8.*2* and 8.3)

Dose Level	Futibatinib (TAS-120)	Pembrolizumab Cycles 1-9	Pembrolizumab Cycles 10+
1*	20 mg	200 mg q3w	400mg q6w
-1	16 mg	--	--
-2	12 mg	--	--

*Dose level 1 refers to the starting dose.
Patients may be started at dose -1 if clinically indicated after discussion with PI

NOTE: If either of futibatinib or pembrolizumab is discontinued, the patient can continue on the other drug, unless specified otherwise in the dose modification tables. If both are discontinued, the patient will go to survival follow-up (Section 4.2).

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) current version 5.0* unless otherwise specified*** ← ←

[redacted]

8.2 Dose Modifications for Futibatinib

8.21 Dose Modifications for Futibatinib for Expected Adverse Events

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION**
Blood and lymphatic system disorders	Anemia Grade 3	Omit 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	Omit dose until resolved to ≤Grade 1 or baseline
Blood and lymphatic system disorders	Febrile neutropenia	Omit dose until resolved, then reduce 1 dose level
Eye disorders	Eye disorders - Other, specify - retinal pigment epithelial detachment (RPED)	Continue at current dose and continue periodic ophthalmic evaluation: • If resolved ≤14 days to ≤Grade 1, then maintain dose level • If resolved >14 days to ≤Grade 1, then omit dose until resolved, then resume at same dose level or a lower dose
Gastrointestinal disorders	Diarrhea Grade 2	Omit futibatinib dose until resolved to ≤Grade 1 or baseline
	Grade 3	Omit dose until further evaluation and cause is determined If resolved within 21 days, and deemed related to futibatinib, then reduce 1 dose level
Gastrointestinal disorders	Mucositis oral Grade 3	If AE persists despite optimal supportive care: Omit futibatinib dose until resolved to ≤Grade 1 or baseline
Gastrointestinal disorders	Nausea Grade 3	If AE persists despite optimal supportive care (See Section 9.0): Omit futibatinib dose until resolved to ≤Grade 1 or baseline
Gastrointestinal disorders	Vomiting Grade 3	If AE persists despite optimal supportive care (See Section 9.0): Omit futibatinib dose until resolved to ≤Grade 1 or baseline
Investigations	Alanine aminotransferase increased >5 x ULN AND Aspartate aminotransferase increased >5 x ULN AND Blood bilirubin increased ≥3 x ULN	Omit futibatinib for up to 14 days until resolved to ≤Grade 1 or baseline, then restart at same dose level If related to futibatinib then reduce 1 dose level
Investigations	For ALT >20 x ULN, and AST >20 x ULN, or Blood bilirubin increased >10 x ULN	Permanently discontinue futibatinib

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION**
Investigations	Hyperphosphatemia Grade 3 Serum phosphorus level >7 - ≤10 mg/dL	Dose reduce futibatinib to the next lower dose level and initiate or intensify phosphate lowering therapy (See Section 9.0 for management suggestions) 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), omit dosing with futibatinib until it is resolved to ≤Grade 2 before resuming futibatinib at the reduced dose prior to dose interruption.
Investigations	Hyperphosphatemia Grade 4 Serum phosphate >10 mg/dL	Omit futibatinib until it is 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
Investigations	Neutrophil count decreased Grade 4	Omit 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
Investigations	Platelet count decreased Grade 3	Omit 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	Omit dose until resolved to ≤Grade 1 or baseline, then reduce 1 dose level
Skin and subcutaneous tissue disorders	Palmar-plantar erythrodysesthesia syndrome Grade 3	Omit dose until resolved to ≤Grade 1 or baseline • If resolved ≤21days, then maintain dose level • If resolved >21 days, then reduce 1 dose level
	Rash, maculopapular	Omit dose until resolved to ≤Grade 1 or baseline • If resolved ≤21 days, then maintain dose level • If resolved >21 days, then reduce 1 dose level
All others not specified above and at least possibly related to futibatinib	Grade 3	Omit dose until resolved to ≤Grade 1 or baseline Reduce by 1 dose level from the previous level
	Grade 4 (nonlab)	Discontinue futibatinib

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	ACTION**
	Grade 4 lab abnormalities	Omit dose until resolved to ≤Grade 1 or baseline 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

** Use the following to describe actions in the Action column:

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- **Discontinue** = The specified drug(s) are totally stopped.

NOTE: Interrupt futibatinib if any adverse events are intolerable, regardless of the grade (including Grade 1 and 2). If or when the adverse event 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

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events >Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles.

8.3 Dosage Modifications for Pembrolizumab

There are no dose reductions for pembrolizumab.

Holding and discontinuation of pembrolizumab should follow clinical practice and most current product information.

9.0 Ancillary Treatment/Supportive Care

9.1 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Volume 33, No 28 (October 1), 2015: pp. 3199-3212 (WBC growth factors) AND Journal of Clinical Oncology, Volume 37, No 15 (May 20), 2019: pp. 1336-1351 (darbepoetin/epoetin).

9.3 Antiemetics

Antiemetics may be used at the discretion of the attending physician.

9.4 Diarrhea/Colitis

All events of diarrhea or colitis should be thoroughly evaluated for more common etiologies other than immune-induced effects.
NOTE: Futibatinib can cause non-immune-related diarrhea which can be managed clinically.

- For events of significant duration or severity or associated with signs of systemic inflammation or acute-phase reactants, check for immune-related colitis.
  - 9.41 Grade 1- without abdominal pain/or blood in stool and symptoms. Infectious etiologies should be ruled out. Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. Patients may be managed symptomatically (e.g., loperamide). Instruct patients to report any increase in stools.
  - 9.42 Grade 2- without abdominal pain/or blood in stool and symptoms <1 week, and resolve to Grade 0 or 1. Continue to monitor. Infectious etiologies should be ruled out. Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology. Patients may be managed symptomatically (e.g., loperamide). Instruct patients to report any increase in stools.
  - 9.43 Grade 2- with symptoms >1 week despite optimal supportive care, considersteroid therapy –first choice is budesonide at 12 mg once daily (if unable to obtain budesonide and/or patent continues to have diarrhea after 72 hours of use start systemic steroids at 0.5 mg/kg/day prednisone or equivalent- can be given in two doses- especially for patients that have nocturnal diarrhea).
    ** Infectious etiologies should be ruled out. Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology.
  - 9.44 Grade 3 or greater- despite optimal supportive care including loperamide, and with other etiologies ruled out consider systemic steroids at 1-2 mg/kg/day prednisone or equivalent (may be given in two daily doses- especially for patients that have nocturnal diarrhea).
    ** Assess for dehydration. Patients may require hospitalization for IV

steroids (1-2 mg/kg/day methylprednisolone). Discontinue medications that may exacerbate colitis (e.g., NSAIDS) while investigating etiology.

** Once patients have improvement of symptoms to Grade 0 or 1 taper of steroids should occur over at least 1 month. If patients have been started on budesonide in addition to systemic steroids, start tapering the prednisone FIRST.

Do NOT administer loperamide in patients with ≥Grade 3 diarrhea until etiology is known as it may cause toxic megacolon and/or perforation.

If at any time patients experience diarrhea with the following symptoms: fever or abdominal pain patients should have a CT scan of the abdomen to rule out perforation. Emergent surgical evaluation should be performed if perforation is found. If a patient has bloody diarrhea, a Gastroenterology consult should be obtained. A Gastroenterology consult should be obtained if provider is considering infliximab for treatment of colitis.

For all patients- assess hydration status and monitor electrolytes, including magnesium.

9.5 Hyperphosphatemia Management Recommendations

Serum Phosphorus Result[a] (mg/dL and mmol/L)[b]	**Management Suggestions[d,e,f]**
ULN <P <5.5 mg/dL ULN <P <1.78 mmol/L	If not already done, implement dietary restrictions and consider consultation with nutritionist. Re-assess serum phosphate within 7 days
5.5 mg/dL ≤P ≤7.0 mg/dL 1.78 ≤P ≤2.26 mmol/L	Consider phosphate binder (monotherapy or in combination)[g] 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	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	Omit 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 Result[a] (mg/dL and mmol/L)[b]	Management Suggestions[d,e,f]
	serum phosphorus level has not resolved to ≤Grade 2 after 14 days, permanently discontinue futibatinib

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)
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 is 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.

9.6 Ocular Toxicity

9.61 Retinal Pigment Epithelial Detachment (RPED)

Futibatinib can cause RPED, which may cause symptoms such as blurred vision.

Median time to first onset of RPED is generally 40days.

Perform a comprehensive ophthalmological examination, including OCT of the macula,prior to initiation of therapy, every 2 months for the first 6 months, and every 3 months thereafter. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of futibatinib.

Withhold or reduce the dose of futibatinib if not resolved to ≤Grade 1 within 14 days of symptom onset.

9.62 Dry Eye/Corneal Keratitis

Per standard clinical care, treat patients with ocular demulcents as needed.

9.7 Liver considerations

9.71 Hepatobiliary disorders

In an integrated data analysis (as of 01 October 2020), treatment-related AEs of ALT increased, AST increased, and blood bilirubin increased were observed in patients who received futibatinib at a dose of 20 mg QD.

If any of the following parameters are reported, testing should be repeated at least twice a week until resolution to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade ≤1 or baseline before initiation of treatment, and then at least weekly until either initiation of re-treatment or until stabilization:

- Bilirubin >2 × ULN
- NCI CTCAE Grade ≥3 ALT or AST elevation
- NCI CTCAE Grade >2 bilirubin and any NCI CTCAE Grade ≥2 ALT or AST elevation

9.72 Hepatic impairment

Futibatinib PK was evaluated in subjects with mild, moderate, and severe hepatic impairment and healthy matched control subjects following administration of 20mg futibatinib. While exposure was higher in subjects with hepatic impairment, the magnitude of exposure change did not correspond with severity of impairment and was not considered clinically relevant. No dose modification is needed in patients with impaired hepatic function.

Patients with existing hepatic impairment should be monitored per standard clinical care while taking futibatinib.

9.8 Side effect management for immune-related adverse events

These are to be regarded as guidelines for managing adverse events that occur with therapy and should not replace clinical judgement (e.g., patients with Grade 1 rash may require systemic steroids). Follow clinical standard of care for all events related to pembrolizumab.

General recommendations.

Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.

For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation.

If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper).

More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events when these events are not responding to systemic steroids.

With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.

Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

9.9a Concomittant Medications

Consider more frequent monitoring for adverse reactions associated with concomitantly administered drugs that are sensitive substrates of P-gp or BCRP and reduce the dose of these drugs per their Prescribing Information.

Futibatinib may increase exposure of drugs that are substrates of P-gp or BCRP as an inhibitor of P-gp and BCRP.

10.0 Adverse Event (AE) Monitoring and Reporting

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

Adverse events are collected from the time the patient signs the main study consent until a minimum of 30 days after the last dose of study drug.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

10.01 Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHAT form:	WHERE to send:
[redacted]	[redacted]
[redacted]	[redacted]

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0 A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:
[redacted]

- Identify the grade and severity of the event using the CTCAE version 5.0.
- Determine whether the event is expected or unexpected (see Section 10.2).
- Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
- Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
- Determine if other reporting is required (see Section 10.5).

NOTE: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

NOTE: *The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure. Refer to protocol or IB for reporting needs.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE is clearly related to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

*Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

CTCAE System Organ Class (SOC)	**Adverse event/ Symptoms**	**CTCAE Grade at which the event will not be reported in an expedited manner[1]**
Blood and lymphatic system disorders	Anemia	≤Grade 4
Gastrointestinal disorders	Diarrhea	≤Grade 3
	Nausea	≤Grade 3
	Vomiting	≤Grade 3
General disorders and administrations site conditions	Fatigue	≤Grade 3
	Malaise	≤Grade 3
Investigations	Lymphocyte count decreased	≤Grade 4
	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood cell count decreased	≤Grade 4

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard **expedited** adverse events reporting requirements must be followed.

The following hospitalizations are **not** considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalization prior to signing main study consent
- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug

- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry
- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.

10.4 Expedited Reporting Requirements for IND Agents

10.41 Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

Expedited AE reporting t timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General reporting instructions

The Mayo IND and/or MCCC Compliance will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form [redacted] for investigational agents or commercial/investigational agents on the same arm.

Submit to NCCN via email [redacted]

AND

Submit to Taiho Oncology Inc. Pharmacovigilance contact information for IIT sites to report SAEs (**email preferred**):

[redacted]

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in Table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously

reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:

If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report form [redacted] he Mayo Clinic Compliance Unit will review and process the submission to the Mayo Clinic IRB and work with the IND Coordinator for submission to FDA.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND requires expedited reporting within 24-hours.

Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND requires expedited reporting within 24-hours.

Reportable categories of Death

1. Death attributable to a CTCAE term.
2. Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
3. Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
4. Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
5. Death due to progressive disease that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 "Disease progression"** under the system organ class (SOC) of General disorders and administration site conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.53 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND will be reported. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.54 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.

10.55 Pregnancy and Lactation, Paternal Drug Exposure, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.
Include this form:

[redacted]

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Fetal loss at any gestational age should be reported expeditiously, as **Grade 4 "Pregnancy loss" under the SOC of "Pregnancy,**

puerperium and perinatal conditions”" under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as “Newborn death occurring during the first 28 days after birth” that is felt by the investigator to be at least possibly due to the investigational agent/intervention.

A neonatal death should be reported expeditiously as **Grade 4 “Death neonatal” under the SOC of General disorders and administration site conditions**.

10.56 Overdose

An overdose is defined as the accidental or intentional use of the 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 using the Mayo Expedited Event Report form [redacted] and to Taiho Pharmacovigilance or designee within 24 hours from the time the Investigator first becomes aware of its occurrence.

There is no known antidote available in case of futibatinib overdose. Overdose should be managed with close monitoring and administration of prophylactic and symptomatic therapies to prevent or correct potential side effects.

10.6 Required Routine Reporting

10.61 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation.
Grading is per CTCAE v5.0 **unless** alternate grading is indicated in the table below:

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Eye disorders	Dry eye	X	X
	Blurred vision	X	X
	Eye disorders – Other, specify (retinal pigment epithelial detachment RPED)	X	X
Gastrointestinal disorders	# of stools at baseline	X	
	Diarrhea		X
	Mucositis oral	X	X
General disorders and administration site conditions	Fatigue	X	X
Investigations	Alanine aminotransferase increased (ALT)	X	X
	Aspartate aminotransferase increased (AST)	X	X
	Blood bilirubin increased	X	X
	Hyperphosphatemia	X	X

CTCAE System/Organ/Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Skin and subcutaneous tissue disorders	Nail changes	X	X
	Palmar-plantar erythrodysesthesia syndrome	X	X
	Rash maculopapular	X	X

10.62 All other AEs

Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.624 Outcome of Adverse Events

Record the outcome of AEs as follows:

- Resolved
- Not resolved/ Ongoing
- Fatal/ Death

10.625 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)

10.7 Late Occurring Adverse Events

Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation/Measurement of Effect

NOTE: This study uses protocol RECIST v1.1 template dated 2/16/2011. See the footnote for the table regarding measureable disease in Section 11.44, as it pertains to data collection and analysis.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)[27]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated every 9 weeks.
In addition to a baseline scan, confirmatory scans should also be obtained 4-6 weeks following initial documentation of objective response.

11.2 Definitions of Measurable and Non-Measurable Disease

11.21 Measurable Disease

11.211 A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

11.212 A superficial non-nodal lesion is measurable if its longest diameter is ≥1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

11.213 A malignant lymph node is considered measurable if its short axis is >1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

NOTE: Tumor lesions in a previously irradiated area are not considered measurable disease.

11.22 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥1.0 to <1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/ pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis <1.0 cm are considered non- pathological (i.e., normal) and should not be recorded or followed.

[27] Eisenhauer EA, Therasse P, Bogaert J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 45(2): 228-247, 2009.

11.3 Guidelines for Evaluation of Measurable Disease

11.31 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.32 Acceptable Modalities for Measurable Disease:

- Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- PET-CT: If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.
- Physical Examination: For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- FDG-PET: FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A ‘positive’ FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered ‘negative.’ New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
    a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
   i. If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
   ii. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
   iii If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.33 Measurement at Follow-up Evaluation:

- A subsequent scan must be obtained not less than 4 weeks following initial documentation of an objective status of either complete response (CR) or partial response (PR).
- In the case of stable disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of not less than 6 weeks (see Section 11.44).
- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Effect

11.41 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.21) up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.21), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- **Baseline Sum of Dimensions (BSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will

be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.

- **Post-Baseline Sum of the Dimensions (PBSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- The **minimum sum of the dimensions** (MSD) is the minimum of the BSD and the PBSD.

11.42 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.22) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with Section 11.433.

11.43 Response Criteria

11.431 Measurement

All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Note: Pseudoprogression is a term describing an initial increase in tumor burden caused by immune-cell infiltration in the setting of T cell response. This phenomenon is observed in many solid malignancies. This study will allow all patients to continue their assigned therapy after apparent radiographic progression per RECIST v1.1, with close observation (e.g., 4 to 8 week intervals), provided the benefit is judged to be favorable by the investigator and repeat scans in 6 weeks do not show progression per RECIST v1.1. If subsequent imaging studies and/or clinical observations demonstrate that progression in fact has occurred, the date of confirmed progression should be noted as the scan at which the potential progression was first identified.

11.432 Evaluation of Target Lesions

- Complete Response (CR):All of the following must be true:
  a. Disappearance of all target lesions.

b. Each target lymph node must have reduction in short axis to <1.0 cm.

c. Normalization of tumor biomarkers.

- Partial Response (PR): At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (*see* Section 11.41).
- Progression (PD): At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.41). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.433 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

Complete Response (CR):	All of the following must be true: a. Disappearance of all non-target lesions. b. Each non-target lymph node must have a reduction in short axis to <1.0 cm. c. Normalization of tumor biomarkers
Non-CR/Non-PD:	Persistence of one or more non-target lesions or non-target lymph nodes, and/or maintenance of tumor marker level above the normal limits.
Progression (PD):	At least one of the following must be true: a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (<1.0 cm short axis) and increased to ≥1.0 cm short axis during follow-up. b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)

c. See Section 11.32 for details in regards to the requirements for PD via FDG-PET imaging.

11.44 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

11.441 Objective Status Table for Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

*See Section 11.431

** NOTE: This study uses the protocol RECIST v1.1 template dated 2/16/2011. For data collection and analysis purposes the objective status changed from SD to PR in the MCCC protocol RECIST v1.1 template as of 2/16/2011 and to match RECIST v1.1 requirements.

11.45 Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration. A patient is classified as having PD due to "symptomatic deterioration" if any of the following occur that are not either related to study treatment or other medical conditions:

- Weight loss >10% of body weight.
- Worsening of tumor-related symptoms.
- Decline in performance status of >1 level on ECOG scale.

12.0 Descriptive Factors

12.1 Prior lines of treatment: 0 vs. 1 vs. 2 vs. 3+

12.2 Extrahepatic spread of disease: Yes vs. No

12.3 Macrovascular invasion: Yes vs. No

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation of treatment

Patients who are CR, PR, or SD will continue treatment per protocol.

13.2 Progressive disease (PD)

Patients who develop PD while receiving therapy will go to the survival follow-up phase.

13.3 Off protocol treatment

Patients who go off protocol treatment for reasons other than PD will go to the clinical follow-up/observation phase per Section 4.0. Participants will be required to return to the consenting site for follow-up until disease progression, new anti-cancer therapy, death, withdrawal of consent for clinical followup, or a maximum of 18 months from Registration.

13.4 Duration of therapy for CR

Patients who achieve a CR will receive a maximum total of 35 cycles (i.e., 2 years). After 35 cycles, they will go to survival follow-up/event monitoring. Subsequent treatment is at the discretion of their attending physician.

13.5 Duration of therapy for PR or SD

Patients who are in PR or SD will continue on therapy for a total of 35cycles (i.e., 2 years). After 35 cycles, they will go to survival follow-up/event monitoring. Subsequent treatment is at the discretion of their attending physician.

13.6 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, per Section 4.0 of the protocol.

- If the patient never received treatment, on-study material must be submitted. Survival follow-up/event monitoring will be required per Section 4.0 of the protocol.

13.7 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in Cycle 1 of the initial therapy are severely violated that evaluability for primary endpoint is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, per Section 4.0 of the protocol.

13.8 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.9a Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up/event monitoring per Section 4.0.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to Be Collected for this Protocol

Research (Section for more information)	Specimen Purpose (check all that apply)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Baseline prior to Cycle 1, Day 1	Prior to Cycle 4 Day 1	End of treatment	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
cfDNA based studies (Section 14.2 and 14.3)	☒ Correlative	Mandatory	Whole blood for platelet poor plasma	Streck cfDNA BCT	10 mL (2)	X	X	X	Yes	Frozen
Immune profiling	☒ Correlative	Mandatory	Whole blood	EDTA tube (purple top)	10 mL (1)	X	X	X	No	Ambient - Send immediately to [redacted]
Banking	☒ Banking	Mandatory	Whole blood for DNA, buffy coat and plasma	EDTA tube (purple top)	10 mL (1)	X	X	X	Yes	Frozen
Banking	☒ Banking	Mandatory	Whole blood for DNA	EDTA tube (purple top)	4 mL (1)	X			Yes	Frozen

14.2 Collection and Processing

14.21 Sample collection should be restricted to Monday – Thursday. However, if the subject can only be seen on a Friday, please contact the laboratory of [redacted] and the Biospecimen Accessioning and Processing (BAP) Service Center for additional instructions (see protocol resource pages for contact information).

14.22 Specimen tube(s) must be labeled with the protocol number, study patient ID number, and the time and date of the blood draw.

14.23 Blood/blood products must be collected and shipped according to specific instructions provided in the kit and the table above.

14.3 Shipping (AZ/FL only)

14.31 Verify that ALL sections of the Blood Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly. Enter information from the Blood Specimen Submission Form into the remote data entry system within 7 days after specimen collection (see Forms Packet).

14.32 Specimens collected in the Streck cfDNA BCT and AccuCyte tubes should be shipped at ambient temperature on the same day they are drawn.

14.33 Specimens collected in EDTA tubes should be processed for DNA from whole blood, a buffy coat back up and plasma aliquots then stored frozen.
NOTE: DNA extraction may be done at site where it's collected.

14.34 Samples should be shipped to BAP Freezer Mondays – Thursdays according to kit instructions. Samples should not be sent on weekends or just prior to federal holidays. (If samples can only be shipped on Fridays, please contact the Biospecimen Resource Manager for additional instructions.)

14.4 Processing

NOTE: BAP Shared Resource will process the specimens.

14.41 Double spun, platelet poor plasma will be derived from the Streck cfDNA BCT tubes using established laboratory processes, and stored at ≤-65ºC by BAP.

14.42 DNA will be extracted from whole blood, and white blood cells and plasma will be derived from remaining blood from the EDTA tubes, divided into aliquots, and stored at ≤-65ºC by BAP according to patient consent information.

14.43 One EDTA should be delivered immediately to [redacted] Immunology, Guggenheim 4-06.

14.44 As part of ongoing research at the Mayo Clinic, we will retain residual whole blood, white blood cells, DNA, and plasma for future research studies, according to patient consent information. Samples will be stored until specific analyses are identified and may be used for exploratory biomarker analyses, validation

studies, or potential diagnostic development. As protocols are developed, they will be presented for IRB review and approval.

14.5 Methodology

14.51 cfDNA

10 mL whole blood samples will be collected in Streck cfDNA BCT tubes. These specimens will be shipped immediately at ambient temperature to Mayo Clinic Rochester and then processed to aliquots of platelet poor plasma within 7 days of collection using standard protocols. Samples will be stored until we are ready for DNA extraction and mutational analysis. Mutation analysis will be performed on the baseline cfDNA samples. Selected mutations identified at baseline will be verified and quantified in all cfDNA samples using ultrasensitive digital droplet PCR based assays.

15.0 Drug Information

15.1 Futibatinib (TAS-120)

15.11 Background

Futibatinib is a novel and selective small molecule irreversible, covalent kinase inhibitor of fibroblast growth factor receptor (*FGFR*) 1–4. Futibatinib equally inhibited all 4 subtypes of FGFR and showed high selectivity for FGFR when tested against a panel of 296 kinases. Futibatinib was highly active against cancer cell lines with FGFR gene abnormalities including cancer cell lines that acquired resistance to other adenosine triphosphate (ATP) competitive FGFR tyrosine kinase inhibitors (TKIs).

15.12 Formulation

Futibatinib (TAS-120) is available as 4 mg tablets in dose pak blister cards containing 28 tablets/card. The 4 mg tablet is a round, white or light yellow, film coated tablet.

15.13 Preparation and storage

Store at room temperature between 15-30° Celsius.

15.14 Administration

Futibatinib is taken orally at a starting dose of 20 mg daily at the same time each day. Futibatinib may be taken with or without food.

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.

15.15 Pharmacokinetic information

PK parameters of futibatinib at a dose of 20 mg daily (Study TAS-120-101):
C_{max} (CV%): 50%
T_{max}: 2 hours
AUC_{last}: 790 ng*hr/mL
$T_{1/2}$: 3hours
Protein Binding: 95%
Metabolism: The primary cytochrome P450 enzyme is CYP3A
(minor: glutathione S-transferase [GST])

15.16 Potential drug interactions

To date, three clinical drug-drug interaction studies and one PK model analysis have been conducted in humans. These studies have shown that strong inhibitors or inducers of CYP3A and dual P-gp have potential clinical drug-drug interactions with futibatinib. Such inihibitors may increase futibatinib exposure and thus increase the incidence and severity of AEs associated with futibatinib. And such inducers may decrease futibatinib exposure and thus reduce the efficacy of futibatinib.

Effect of Other Drugs on Futibatinib
Futibatinib is a substrate of CYP3A and P-gp.

Dual P-gp and Strong CYP3A Inhibitors: Avoid concomitant use of drugs that are dual P-gp and strong CYP3A inhibitors with futibatinib. Concomitant use of drugs that are dual P-gp and strong CYP3A inhibitors with futibatinib may

increase futibatinib exposure, which may increase the incidence and severity of adverse reactions.

Dual P-gp and Strong CYP3A Inducers:
Avoid concomitant use of dual P-gp and strong CYP3A inducers with futibatinib. Concomitant use of drugs that are dual P-gp and strongCYP3A inducers may decrease futibatinib exposure, which may reduce the efficacy of futibatinib.

Effect of Futibatinib on Other Drugs
Futibatinib is an inhibitor of P-gp and BCRP.

P-gp or BCRP Substrates:
Consider more frequent monitoringfor adverse reactions associated with concomitantly administered drugs that are sensitivesubstrates of P-gp or BCRP and reduce the dose of these drugs per their Prescribing Information.
Futibatinib may increase exposure of drugs that are substrates of P-gp or BCRP.

15.17 Known potential adverse events

Reported from daily dosing schedule (Study 10059010)
Most common adverse events (≥15%):
Hyperphosphatemia, decreased appetite, constipation, diarrhea, nausea, vomiting, ALT and AST increased, anemia, stomatitis

Reported from daily dosing schedule (Study TPU-TAS-120-101)
Most common adverse events (≥15%):
Hyperphosphatemia, diarrhea, constipation, nausea, dry mouth, ALT and AST increased, fatigue, vomiting, alopecia, decreased appetite, anemia, stomatitis, abdominal pain, dry skin, palmar-plantar erythrodysesthesia syndrome, blood creatinine increased, hypercalcemia, back pain, dry eye, pyrexia, arthralgia, dysgeusia, urinary tract infection, weight decreased, nail disorder, hyponatremia, onycholysis, onychomadesis

Reported from daily dosing schedule (Study TAS-120-201)
Most common adverse events (≥15%):
Hyperphosphatemia, constipation, ALT and AST increased, decreased appetite, diarrhea, dry mouth, nausea, alopecia, fatigue, anemia, asthenia, rash, vomiting

15.18 Drug procurement:

Futibatinib will be supplied by the Taiho Oncology, Inc.

Outdated or remaining drug is to be destroyed on-site per procedures in place at each institution.

15.19 Nursing guidelines

15.191 Assess patient's concomitant medications as there are many drug-drug interactions.

15.192 Gastrointestinal side effects are common, including diarrhea, constipation, nausea, vomiting and abdominal pain. Treat symptomatically and monitor for effectiveness.

15.193 Monitor LFTs.

15.194 Patients may experience dermatologic side effects including, dry skin, and palmar-plantar erythrodysesthesia (PPE aka hand-foot syndrome). Instruct patients to report any skin changes to the study team. For PPE, encourage frequent moisturizing of the hands and feet, with a urea based cream if possible.

15.195 Patients may experience pyrexia. Instruct patients to report fever to the study team.

15.196 Instruct patients to report all side effects to the study team.

15.197 Eye problems are common. Instruct patient to report any changes in their eyes or vision to the study team.

15.2 **Pembrolizumab** (MK-3475, SCH 900475, Keytruda®)

15.21 Background

Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

15.22 Formulation

Pembrolizumab is available as a liquid 25 mg/mL, 100 mg/vial.

15.23 Preparation and storage

Vials should be stored in the refrigerator at temperatures between 2-8°C.

Drug concentrate is further diluted with normal saline (or 5% dextrose in the concentration range of 1 to 10 mg/mL) in IV containers made of polyvinyl chloride (PVC) or non-PVC material. The infusion solution in the IV bag should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative period of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags may be stored at 2-8°C for up to a cumulative time of 20 hours. This 24-hour total hold time from dilution may include up to 6 hours at room temperature

15.24 Administration

Pembrolizumab is administered by intravenous infusion over 30 minutes via a 0.22 micron in-line filter. The final infusion volume must be between 1 and 10 mg/mL. Maximum rate of infusion should not exceed 6.7 mL/minute through a peripheral or indwelling catheter. Flush the line with 0.9% NaCL following the completion of the infusion.

15.25 Pharmacokinetic information

a) Absorption – Because pembrolizumab is administered intravenously, it is immediately and completely bioavailable. Steady-state concentrations of pembrolizumab are reached by16 weeks of repeated dosing with a Q3W regimen, and the systemic accumulation is 2.1-fold. The peak concentration, trough concentration, and area under the plasma concentration versus time curve at steady state of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg Q3W.
b) Distribution – Pembrolizumab has a limited volume of distribution.
c) Excretion – CL is approximately 23% lower after achieving maximal change at steady state compared with the first dose. The terminal elimination half-life (t½) is estimated to be 22 days at steady state.
d) Metabolism - Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its CL.

15.26 **Potential Drug Interactions**: There are no known significant drug interactions.

15.27 Known potential adverse events:

Very common known potential adverse events, ≥10%:
Skin and subcutaneous tissue disorders: Pruritus, skin rash
Gastrointestinal disorders: Diarrhea, nausea, abdominal pain
General disorders and administration site conditions: fatigue

Common known potential adverse events, >10%:
Blood and lymphatic system disorders: anemia
Immune system disorders: infusion related reaction
Endocrine disorders: hyperthyroidism, hypothyroidism
Metabolism and nutrition disorders: decreased appetite
Nervous system disorders: headache, dizziness, dysgeusia
Respiratory, thoracic, and mediastinal disorders: pneumonitis, dyspnea, cough
Gastrointestinal disorders: colitis, vomiting, constipation, dry mouth
Skin and subcutaneous tissue disorders: severe skin reactions, vitiligo, dry skin, erythema
Musculoskeletal and connective tissue disorders: arthralgia, myositis, musculoskeletal pain, arthritis, pain in extremity
General disorders and administration site conditions: asthenia, edema, pyrexia, influenza like illness, chills
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased

Uncommon known potential adverse events, 1% - 10%:
Infusion related reactions
Blood and lymphatic system disorders: neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia
Endocrine disorders: hypophysitis, adrenal insufficiency, thyroiditis, hypopituitarism
Metabolism and nutrition disorders: type I diabetes mellitus, hyponatremia, hypokalemia, hypocalcemia
Psychiatric disorders: insomnia, confusional state
Nervous system disorders: epilepsy, lethargy, peripheral neuropathy
Eye disorders: uveitis, dry eye
Cardiac disorders: myocarditis, atrial fibrillation
Vascular disorders: hypertension
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Skin and subcutaneous tissue disorders: lichenoid keratosis, psoriasis, alopecia, dermatitis, dermatitis acneiform, eczema, hair color changes, papule
Musculoskeletal and connective tissue disorders: tenosynovitis
Renal and urinary disorders: nephritis, acute kidney injury
Investigations: blood bilirubin increased, amylase increased, hypercalcemia

Rare known potential adverse events, <1% (Limited to important or life-threatening):
Blood and lymphatic system disorders: immune thrombocytopenic purpura, hemolytic anemia
Immune system disorders: sarcoidosis
Nervous system disorders: Guillain-Barre syndrome, myasthenic syndrome
Gastrointestinal disorders: small intestinal perforation

Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum

The risk profile for pembrolizumab also includes two important potential risks: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and veno-occlusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

15.28 Drug procurement

Commercial supply.

15.29 Nursing Guidelines

15.291 Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.292 Diarrhea can be seen, however is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.293 Rash/pruritis/dermatitis is seen. Patients should report any rash to the study team. Treat per Section 9.0 and monitor for effectiveness.

15.294 Monitor LFTs closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.295 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.296 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysitis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and “not feeling well.” Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.297 Patients who are started on steroid therapy for any side effects of pembrolizumab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.298 Fatigue is common and may or may not be associated with immune related side effects. Assess patient’s fatigue level prior to each cycle of therapy and report any changes to the study team.

15.299a Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.

15.299b Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and veno-occlusive disease, if they have previously been treated with pembrolizumab

15.299c Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.

15.299d Autoimmune hematologic disorders including ITP and hemolytic anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.

15.299e Rare neurologic disorders including Guillain-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, paresthesias or numbness, tingling to the study team immediately.

16.0 Statistical Considerations and Methodology

16.1 Primary Endpoint

The primary endpoint is progression-free survival (PFS) at 6 months (PFS6) after registration. Six months is defined as 27 weeks.

16.2 Secondary Endpoints

Secondary endpoints include: overall response rate (ORR), overall survival (OS), incidence of adverse events, and quality of life.

16.3 Sample Size

We plan to accrue 22 evaluable patients. Evaluable patient is defined as those who are eligible, consented, are positive for FGF19, received any protocol treatment, and are without major violation. With 22 evaluable patients, we have 80% power to detect PFS6 from 25% (historical control) to 47%, assuming a 1-sided significance level of 0.1 and an accrual rate of 2 patients per month.

The trial has a single interim analysis for futility and the overall type I error rate is controlled. The interim analysis will be considered non-binding. The accrual will not be halted for the interim analysis.

We anticipate accruing an additional 3 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, maximum accrual is projected to be 25 patients. Sample size calculation was based on simulation using R.

16.4 Statistical Analysis

Interim analysis will be conducted around 6 months after the 11^{th} evaluable patient has been enrolled and the data from the third re-staging scan, if available, has been entered into the electronic database. The PFS6 rate will be calculated using the Kaplan-Meir method. The study may temporarily close to accrual if the PFS6 rate is $\leq$ 30% at the interim analysis.

Final analysis will be conducted around 6 months after the 22^{nd} evaluable patient has been enrolled and the data from the third re-staging scan, if available, has been entered into the electronic database. The PFS6 rate will be calculated using the Kaplan-Meir method and 80% confidence interval will be calculated using Greenwood's formula with logit transformation. The combination therapy will be declared as promising for future study if the lower bound of the 80% confidence interval is greater than 25%.

16.5 Operation Characteristics

The probability of declaring that this regimen warrants further studies (i.e., statistical power) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is:	*25%*	*47%*
then the probability of stopping early is:	0.4597	0.0037
and the probability of declaring that the regimen warrants further studies is:	0.0651	0.7923

The operation characteristics were calculated using simulation with 10,000 replications. PFS6 of 25% is generated using Weilbul distribution (scale=0.3, shape=0.6667) PFS6 of 47% is generated using Weilbul distribution (scale=0.73, shape=0.8850)

16.6 Analysis Plan for Secondary Outcome and Translational Endpoints

The below analyses will be done on FGF19 positive patients. The analyses will also be performed on FGF19 negative patients as exploratory analyses.

16.61 Objective Response

Objective response by RECIST v1.1 criteria will be estimated using objective response rate (ORR) where ORR is defined as the number of evaluable patients achieving a response (PR or CR per RECIST v1.1) during treatment with study therapy divided by the total number of evaluable patients. Point estimates will be generated for objective response rates along with 95% binomial confidence intervals[28].

16.62 Overall Survival

Overall survival time is defined as the time from registration to death due to any cause. Patients who are alive will be censored at last follow-up for overall survival. The distribution of survival time will be estimated using the method of Kaplan-Meier[29]. OS medians will be estimated along with 95% confidence intervals.

16.63 Incidence of Adverse Events (AEs)

Adverse events will be evaluated, per CTCAE v5.0, for each patient. Grade 3+ AEs, at least possibility related, which occur more than 10% of patients will be reported by grade.

16.64 Quality of Life (QoL) Outcomes

To assess overall health-related quality of life, as measured by the global health domain of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30). The raw score will be calculated per scoring manual[30] and transformed to scores raning from 0 to 100. Change in score between baseline and first re-staging will be calculated for each individual. The median QOL change from baseline along with a 95% CI will be estimated using the Hodges-Lehmann method.[31]

16.65 Prognostic effect of baseline cfDNA

Cox proportional hazard model will be used to evaluate the prognostic effect of baseline cfDNA.

16.66 The association between change in cfDNA and PFS/OS

Patients will be categorized as increase vs. other in cfDNA. Cox proportional hazard model will be used to evaluate the prognostic effect of change in cfDNA (increase vs. other).

[28] Clopper, C.J. and E.S. Pearson, *The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial.* Biometrika, 1934. **26**(4): p. 404-413.
[29] Kaplan, E.L. and P. Meier, *Nonparametric Estimation from Incomplete Observations.* Journal of the American Statistical Association, 1958. **53**(282): p. 457-481.
[30] Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A on behalf of the EORTC Quality of Life Group. EORTC QLQ-C30 Scoring Manual (3rd edition). Brussels: EORTC, 2001.
[31] Hodges, J. L.; Lehmann, E. L. (1963). "Estimation of location based on ranks". Annals of Mathematical Statistics. 34 (2): 598–611.

16.67 Correlation of drug response in patient derived organoid with clinical response

The correlation of drug response in patient derived organoid with clinical response will be tested using Chi-square test.

16.7 Data & Safety Monitoring

16.71 Safety review

The principal investigator(s) and the study statistician will review the study monthly to identify accrual, adverse events, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least biannually, based on reports provided by the MCCC Statistical Office.

16.72 Adverse Event Stopping Rules

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time, we observe events considered to be at least possibly related to study treatment (i.e., an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy the following:

- If at any time, 4 of the initial 10 treated patients or 40% or more of all patients (i.e., when accrual is greater than 10 patients) have experienced a Grade 4+ adverse event at least possibly related to study treatment. per NCI Common Terminology Criteria for Adverse Events v.5.0, excluding the following:
    - Grade 4 white blood cell decreased lasting ≤3 days
    - Grade 4 platelet count decreased lasting ≤3 days
    - Grade 4 electrolyte alteration* lasting ≤3 days

    *Electrolyte alterations include the following events in SOC “Metabolism and nutrition disorders”
        - Hyperglycemia or Hypoglycemia
        - Hyperkalemia or Hypokalemia

We note that we will review Grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.8 Subset Analyses for Minorities

16.81 Study availability

This study will be available to all eligible patients, regardless of gender, race or ethnic origin.

16.82 Statistical analysis by subset

There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analyses will look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.83 Regional population

The geographical region served by MCCC has a population which includes approximately 3% minorities. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Targets			
	Sex/Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	11	12	23
Ethnic Category: Total of all subjects	**12**	**13**	**25**
Racial Category			
American Indian or Alaskan Native	1	0	1
Asian	0	1	1
Black or African American	1	0	1
Native Hawaiian or other Pacific Islander	0	1	1
White	10	11	21
Racial Category: Total of all subjects	**12**	**13**	**25**

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa.

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

17.1 Summary Table of Research Tissue Specimens to be Collected for this Protocol

Research Study (Section for more information)	Specimen Purpose (check all that apply)	Mandatory or Optional	Type of Tissue to Collect	Block, Slides, Core, etc. (# of each to submit)	At any time after Reg*	At time of disease progression	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
FGF-19 Testing, and correlative studies including Immunohistochemistry (Section 17.2 and 17.3)	☒ Eligibility ☒ Correlative	Mandatory	Formalin Fixed Paraffin Embedded	2 cores (or archived 5 unstained slides)*	X		No	Ambient
Patient-derived tumor organoid culture and studies (Section 17.2 and 17.3) Rochester ONLY	☒ Correlative	Mandatory	Fresh Tissue	4-6 cores or pieces of tissue	X		No	Cold, ice pack
Tumor tissue at disease progression**	☒ Banking	Optional	Formalin Fixed Paraffin Embedded	3 cores or 10 unstained slides		X	No	Ambient

*All patients should have baseline biopsy for FGF-19 testing and correlative studies. If archived tissue is available and used for FGF-19 testing, then eligible patients will still need a baseline biopsy to collect correlative tissue unless already collected under IRB 17-003174. If baseline biopsy cannot be done (e.g., because not medically feasible or lack of lab capacity), and PI agrees, patient is still eligible if archived tissue is available for FGF-19 screening.

**If biopsy or surgery is done at time of disease progression for clinical reasons, a sample of tumor tissue is requested for comparison with baseline sample

17.2 Tissue Collection

17.21 Tissue Kits will not be provided for this protocol.

All patients should have baseline biopsy for FGF-19 testing and correlative studies after Preregistration.

If archived tissue is available and used for FGF-19 testing, then eligible patients will still need a baseline biopsy to collect correlative tissue prior to starting treatment unless already collected under IRB 17-003174.

If baseline biopsy cannot be done (e.g., because not medically feasible or lack of lab capacity), and PI agrees, patient is still eligible if archived tissue is available for FGF-19 screening.

17.23 Fresh Tissue

17.231 Six cores of fresh tumor tissue will be collected after registration and prior to Cycle 1 Day 1 of treatment.

17.232 Tissue must be labeled with the protocol number, study patient ID number, and the time and date of the biopsy.

17.233 Fresh tissue must be collected according to the table above.

17.234 A portion of the fresh tissue should be routed and made into formalin-fixed, paraffin-embedded (FFPE) blocks

17.234 Fresh tissue must be stored in tissue media on cold ice pack (~0ºC) until delivery to the lab

17.24 Paraffin Embedded Tissue

17.241 One block of HCC tumor tissue from research biopsy will be submitted after registration and prior to Cycle 1 Day 1 of treatment.

17.242 Paraffin embedded tissue must be labeled with the protocol number, study patient ID number, and the time and date of the biopsy.

17.243 Paraffin embedded tissue must be collected and shipped according to specific instructions provided in the table above.

17.244 Paraffin embedded tissue can be stored at ambient temperature.

17.25 Submission/Shipping

17.251 Verify that ALL sections of the Tissue Specimen Submission Form (see Forms Packet), BAP Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly. Enter information from the Tissue Specimen Submission Form into the remote data entry system within 7 days after specimen collection (see Forms Packet).

17.252 Rochester ONLY: Fresh tissue specimens collected in tissue media should be placed on cold ice pack (~0ºC) and immediately delivered to the following laboratories at Mayo Clinic in Rochester, MN:

[redacted]

17.26 Processing

17.261 Paraffin embedded tissue block

DLMP or BAP/PRC Shared Resource will process the paraffin embedded tissue specimens according to routine protocols.

Study Coordinator will route blocks to [redacted] that sample is on the way by email [redacted]

Rochester internal address:
[redacted]

From outside of Rochester ship ambient and include room temperature cool pack if needed, to:

[redacted]

17.262 Fresh tissue cores – Rochester ONLY

17.2621 The laboratory of [redacted] will process half of the fresh tissue specimens.

Email [redacted] and copy [redacted] when you have a potential patient for the study (include patient name, MCN, diagnosis, biopsy location, and date/time of procedure, as well as study coordinator contact info) and then send a second email to confirm once the patient has consented.

On the day of the procedure, study coordinator will display/digital page the lab at [redacted] (do not priority page) when the procedure is about to start so the lab can send staff to collect tissue. Also contact lab directly at [redacted] to make sure the page is not missed.

17.2622 The laboratory of [redacted] will process half of the fresh tissue specimens.

Email [redacted] when you have a potential patient for the study (include patient name, MCN, diagnosis, biopsy location, and date/time of procedure, as well as study coordinator contact info) and then send a second email to confirm once the patient has consented.

On the day of the procedure, study coordinator will display/digital page [redacted] (do not priority page) when the procedure is about to start so the lab can send staff to collect tissue. Also contact lab directly [redacted] to make sure the page is not missed.

17.3 Background and Methodology

17.31 Patient-derived tumor organoid

Preclinical tumor models are important tools to study cancer biology, develop novel therapeutics, and provide information for treatment decisions. However currently available tumor models such as cell lines, transgenic mice and patient-derived xenograft (PDX) model have inherent limitations that can adversely affect the translation of preclinical findings to the clinic. Patient-derived tumor organoid is a 3-D cell culture which enables the establishment of *ex vivo* tumor model from scant core-needle biopsy specimen in a timely manner. These tumor organoids recapitulate both phenotypes and genotypes of the donor tumor. (Vlachogiannis et al. 2018) The laboratory of [redacted] at our institution has successfully established such tumor organoids from core-biopsy tumor specimens donated by patients with metastatic cholangiocarcinoma.

The established tumor organoids were ready for drug screening and related molecular studies within 4-6 weeks of the biopsy. Though the concordance between treatment effect in tumor organoids and the clinical benefit observed in the donor patients have been reported, the role of tumor organoids has not been prospectively evaluated in clinical trials of patients with advanced HCC. Here, we aim to 1) determine if drug response from a parallel *ex vivo* trial using patient-derived tumor organoid correlates with clinical response to futibatinib plus pembrolizumab and 2) to evaluate the role of thymidine kinase 1 in predicting the clinical response to treatment and discover potential mechanisms of resistance and sensitivity.

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up/Event Monitoring

See Section 4.

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

18.4 Site responsibilities

Each site will be responsible for ensuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation

This study requires supporting documentation for evidence of response to study therapy and progression after study therapy. These documents should be submitted within 14 days after the visit at which response or progression is determined.

Results of genomic testing should be uploaded when they are available.

Imaging reports for PET/CT or PET/MRI as well as for standard imaging should be uploaded within 14 days after the visit.

18.6 Labeling of materials

Each site will be responsible for ensuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report is available on the Cancer Center Systems homepage.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

Routine clinical care costs will be the responsibility of the patient and/or the patient's insurance company, including pembrolizumab and its administration

19.2 Tests to be research funded:

- Futibatinib (TAS-120) will be provided by Taiho Oncology
- Correlative studies
- Collection, processing and storage of blood for research.

19.3 Other budget concerns:

Taiho Oncology will provide a grant through NCCN to Mayo Clinic to help with costs for the conduct of this study.

Mayo Clinic Cancer Center will provide Development funding to cover additional costs associated with the conduct of this study.

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Appendix I ECOG Performance Status

ECOG PERFORMANCE STATUS*	
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, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

*As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From [redacted]

Appendix II Child Pugh Scores

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.[1]

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dL	>3.5	2.8-3.5	<2.8
Prothrombin time (PT), INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild (or suppressed with medication)	Moderate to Severe (or refractory)
Hepatic encephalopathy	None	Grade I-II	Grade III-IV

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.[1]

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

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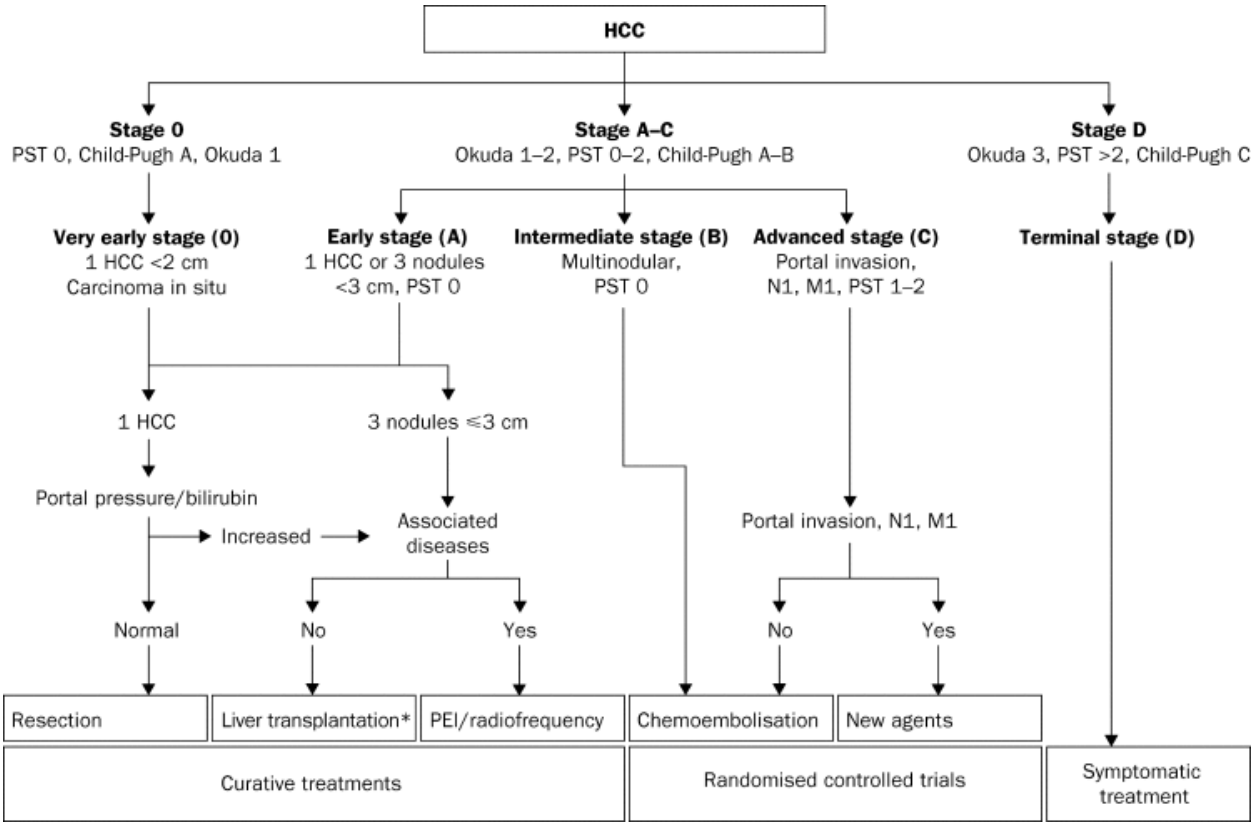
Appendix III Barcelona Clinic Liver Cancer (BCLC) Staging Classification & Treatment Schedule[32]



PST=performance status test. N=nodules. M=metastases. PEI=percutaneous ethanol injection. *Cadaveric liver transplantation or living donor liver transplantation. Modified from[33] [34] with permission from The American Association for the Study of Liver Disease.

[32] Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003,362:1907–1917.
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Appendix IV Guidelines for Contraception

Your study doctor will discuss prohibited and acceptable birth control methods for use during your participation in this study and for 120 days after the last dose of study drug. These guidelines apply to all persons capable of becoming pregnant or persons capable of fathering a child and their partners of child-bearing potential.

You should notify your study doctor if birth control methods other than those specified below are started during the course of this study or if you start any prescription drug or other medication (including herbal and over-the-counter medications) not prescribed by the study doctor.

One of the two forms of birth control must be highly effective and the second method may also be highly effective or selected from the list of other contraceptive methods.

<table>
<tr><td rowspan="6">Highly Effective Methods of Contraception</td><td colspan="2">Progestogen only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)</td></tr>
<tr><td colspan="2">Hormonal methods of contraception including
• combined oral contraceptive pills (that is, those that contain both estrogen and progestogen)
• intravaginal (e.g. vaginal ring)
• transdermal, injectables, implants and intrauterine devices (IUDs)
Sometimes, hormonal levels of birth control can be affected by the study drug. Your doctor will tell you whether hormonal forms of birth control are allowed for this study.</td></tr>
<tr><td colspan="2">Non-hormonal IUDs</td></tr>
<tr><td colspan="2">Bilateral tubal occlusion</td></tr>
<tr><td colspan="2">Vasectomized partner</td></tr>
<tr><td colspan="2">Complete abstinence</td></tr>
<tr><td rowspan="6">Less than Highly Effective Methods of Contraception</td><td colspan="2">Diaphragm with spermicide</td></tr>
<tr><td colspan="2">Cervical cap with spermicide</td></tr>
<tr><td colspan="2">Vaginal sponge with spermicide</td></tr>
<tr><td colspan="2">Progestin only pills</td></tr>
<tr><td>Male condoms with or without spermicide*</td><td rowspan="2">*A male and a female condom must not be used together</td></tr>
<tr><td>Female Condoms*</td></tr>
<tr><td rowspan="4">Unacceptable Methods of Contraception</td><td colspan="2">Periodic abstinence (calendar, symptothermal, post-ovulation methods)</td></tr>
<tr><td colspan="2">Withdrawal (coitus interruptus)</td></tr>
<tr><td colspan="2">Spermicide only</td></tr>
<tr><td colspan="2">Lactation/amenorrhea method (LAM)</td></tr>
</table>

If you choose abstinence as a method of contraception, your doctor will discuss other methods of contraception with you in the case you choose not to continue abstinence. Pregnancy testing remains mandatory even if you do choose abstinence as your method of contraception. If pregnancy occurs in you or your partner, you must report the pregnancy to the study investigator and agree to be followed for the entire course of pregnancy and birth.

Appendix V Patient Medication Diary

Patient Medication Diary is provided as a standalone document per Mayo Clinic IRB requirements.

Appendix VI Classification of Substrates, Inhibitors, & Inducers of CYP Enzymes & 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.

[redacted]

CYP3A inhibitors and inducers: CYP3A is involved in the metabolism of futibatinib. CYP3A inhibitors and inducers may alter the concentration and activity of futibatinib.

CYP3A substrates: Futibatinib is a potential time-dependent inhibitor of CYP3A. Futibatinib may increase the concentration and activity of CYP3A substrates.

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

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]**
CYP3Ac	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.		

Appendix VII Patient Questionnaire Booklet

Patient Information Sheet
Patient Completed Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your health as a patient receiving treatment for cancer. You answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains oneset of questions:
    - EORTC-QLQ-C30 Questionnaire (30 questions)

2. Please select one answer for each question.

3. Please complete the booklet during your scheduled clinical visit and return it to your nurse or your physician.

Thank you for taking the time to help us.

EORTC-QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____
Your birthdate (Day, Month, Year): _____
Today's date (Day, Month, Year): 31 _____

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent