Official Title: A Phase 2 Study Evaluating Futibatinib (TAS-120) Plus Pembrolizumab in the Treatment of Advanced or Metastatic Urothelial Carcinoma

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Clinical Study Protocol

A Phase 2 Study Evaluating Futibatinib (TAS-120) Plus Pembrolizumab in the Treatment of Advanced or Metastatic Urothelial Carcinoma

Futibatinib (TAS-120)

Protocol TAS-120-203

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Sponsor

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

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SUMMARY OF PROTOCOL AMENDMENTS

The original protocol for Study TAS-120-203 was approved on 10 March 2020; this document is Amendment 1, issued 10 June 2020. The table below summarizes substantive changes made in this amendment; all of these changes were made at the request of the US Food and Drug Administration. In addition, minor editorial changes were made throughout, including updating of headers and footers, adjustment of formatting, and correction of typographical errors.

Change Location[a]	Description of Change
Section 1.2 Pembrolizumab	The last paragraph of this section was amended as shown: Finally, FGFR inhibition may also modulate the tumor microenvironment in non-*FGFR3*-mutated tumors through the blockade of paracrine fibroblast growth factors (FGF) signaling, targeting immune evasion and angiogenesis and lead to enhanced efficacy when combined with pembrolizumab in both wild-type (WT) and *FGFR3*-mutated tumors (Ichikawa et al. 2020; Liu et al. 2014; Siefker-Radtke et al. 2018).
Section 4.1 Inclusion Criterion	The following text was added to inclusion criterion #1: For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval >12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment-naïve in the metastatic setting. Inclusion criterion #2, elaborating on the definition of "unfit for or intolerant to standard platinum-based chemotherapy," was added. All remaining inclusion criteria were renumbered accordingly.
Section 5.2 Definition of Dose-Limiting Toxicity	Two aspects of the DLT definition were amended as follows; the remainder of the definition was not changed: • Grade 4 ~~hematologic toxicity~~ neutropenia lasting ~~7~~ >5 days~~, except thrombocytopenia~~ • [Any Grade 3 or Grade 4 nonhematologic laboratory value if] the abnormality ~~persists for >1 week~~ does not recover to Grade ≤1 within 48 hours despite best supportive care.
Section 6.1 Ophthalmological Examination	The following text was added: In cases of retinal pigment epithelial detachment, events should be monitored at 2- to 3-week intervals.

a. All changes were also incorporated into the study synopsis as appropriate.

PROTOCOL SYNOPSIS

Protocol Title:

A Phase 2 Study Evaluating Futibatinib (TAS-120) Plus Pembrolizumab in the Treatment of Advanced or Metastatic Urothelial Carcinoma

Rationale:

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma.

The programmed death-ligand 1 (PD-1) receptor-ligand interaction is a major pathway that is hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab is indicated for the treatment of patients across a number of indications, and is associated with an acceptable preclinical and clinical safety profile as an intravenous (I.V.) immunotherapy.

Prior studies have demonstrated that fibroblast growth factor receptor 3 (FGFR3)-mutant urothelial carcinomas (UCs) are associated with decreased T-cell infiltration. As *FGFR3* mutations are enriched in luminal-like UC, and luminal-like UC has been shown to be relatively less responsive to PD-1/PD-L1 inhibition (checkpoint inhibition [CPI]), these data have led to the speculation that *FGFR3* mutations may be causally related to poor T-cell infiltration and that UC patients harboring *FGFR3* mutations may be suboptimal candidates for CPI such as pembrolizumab.

However, Wang et al. (2018) determined that while *FGFR3*-mutant UC is associated with a similar tumor mutational burden and lower T-cell infiltration, it is also associated with lower stromal transforming growth factor beta (TGF-b) immune suppressive signals. These findings suggest that *FGFR3* mutation status may not in fact be a biomarker of resistance to CPI, and provides a rationale for the combination of FGFR-targeted treatment with CPI treatment.

Moreover, recently published data (Palakurthi et al. 2019) show that FGFR inhibition and anti-PD-1 combination induced significant tumor regression and improved survival. For both erdafitinib monotherapy and combination treatments, tumor control was accompanied by tumor-intrinsic FGFR pathway inhibition, increased T-cell infiltration, decreased regulatory T cells, and downregulation of PD-L1 expression on tumor cells. Finally, FGFR inhibition may also modulate the tumor

microenvironment in non-*FGFR3*-mutated tumors through the blockade of paracrine fibroblast growth factors (FGF) signaling, targeting immune evasion and angiogenesis and lead to enhanced efficacy when combined with pembrolizumab in both wild-type (WT) and *FGFR3*-mutated tumors (Ichikawa et al. 2020; Liu et al. 2014; Siefker-Radtke et al. 2018).

Study Objectives:

Primary

- To evaluate the objective response rate (ORR) of futibatinib in combination with pembrolizumab in patients with advanced or metastatic UC who are not candidates to receive a platinum-based treatment regimen.

Secondary

- To assess the safety of futibatinib in combination with pembrolizumab.
- To evaluate the disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Exploratory

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

Study Endpoints:

All variables based on tumor response (ORR, DCR, DOR, PFS) will be calculated based on both Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and iRECIST criteria. The primary evaluation of efficacy will be based on RECIST 1.1. All evaluations of tumor response will be per local Investigator assessment.

Primary

- Objective response rate (ORR), defined as the proportion of patients experiencing a best overall response of complete response (CR) or partial response (PR).

Secondary

- Disease control rate (DCR), defined as the proportion of patients experiencing a best overall response of stable disease (SD), PR, or CR.
- Duration of response (DOR), defined as the time from the first documentation of response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first.
- Progression-free survival (PFS), defined as the time from the first dose of study therapy to the date of death (any cause) or disease progression, whichever occurs first.
- Overall survival (OS), defined as the time from the date of the first dose to the death date.

- Safety and tolerability, based on reported adverse events (AEs) and on-study laboratory parameters, graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0.

Exploratory

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

Overall Design:

Study TAS-120-203 is an open-label, non-randomized, multicenter Phase 2 study evaluating the combination of futibatinib and pembrolizumab in patients with advanced or metastatic UC who are not candidates to receive a platinum-based treatment regimen.

A treatment cycle is defined as 21 days. All enrolled patients will receive the same treatment regimen:

- Futibatinib at an oral (PO) dose of 20 mg daily (QD); and
- Pembrolizumab at an I.V. dose of 200 mg every 3 weeks (Q3W).

Treatment will continue until disease progression, unacceptable toxicity, or any other of the criteria for treatment discontinuation is met; of note, pembrolizumab may be administered for a maximum of 35 doses or a maximum duration of 2 years, whichever is earlier.

The study will begin with a safety lead-in period. During this period, a total of 6 patients with advanced or metastatic UC will be enrolled and treated for at least one 21-day cycle. Patients will be enrolled into this initial safety lead-in period without regard for *FGFR* alteration status.

After the first 6 patients have completed one cycle of treatment, a safety analysis will occur. After confirmation of the safety of the combination, a total of 20 additional patients will be enrolled into each of the following 2 cohorts:

- Cohort A: Patients with UC and *FGFR3* mutation or *FGFR1-4* fusion/rearrangement. Patients will be enrolled based on local results, but tissue samples will be archived for retrospective confirmation at a central lab using next-generation sequencing (NGS).
- Cohort B: All other patients with UC (including patients with other *FGFR* or non-*FGFR* genetic aberrations and patients with WT [non-mutated] tumors)

A second safety analysis will occur after enrollment of a total of 10 patients (including the 6 patients from the safety lead-in), in order to confirm the safety profile of the combination before proceeding to the enrollment of the remaining patients in Cohorts A and B.

Please note: At each safety analysis, the combination of futibatinib and pembrolizumab will be considered intolerable if the incidence of unacceptable toxicity including dose-limiting toxicity (as defined in the protocol) is ≥33%. If the combination is determined to be intolerable, the study may continue with a reduced dose of futibatinib (16 mg QD) if medically appropriate in the opinion of the Investigators and Sponsor.

The 6 patients initially enrolled in the safety lead-in will also be assigned to the respective cohort based on *FGFR* alteration, such that each cohort will contain a minimum of 20 and a maximum of 26 patients.

Number of Patients:

The study will enroll approximately 46 patients with advanced or metastatic UC: 6 patients in the safety lead-in, 20 patients with tumors positive for any *FGFR3* mutation or *FGFR* fusion alterations (Cohort A) and 20 patients with other FGFR aberrations or wild-type (WT) tumors (Cohort B).

Entry Criteria:

Inclusion Criteria

1. Histologically confirmed advanced or metastatic UC for patients who have not received systemic treatment for advanced metastatic disease. For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval >12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment-naïve in the metastatic setting.
    a. In safety lead-in: enrollment regardless of FGFR status
    b. Cohort A: must have an *FGFR3* mutation or *FGFR1-4* fusion/rearrangement
    c. Cohort B: all other patients with UC (including patients with other FGFR or non-FGFR genetic aberrations and patients with WT [nonmutated] tumors)
2. Unfit for or intolerant to standard platinum-based chemotherapy as defined by any one of the following criteria:
    a. Chronic kidney disease characterized by the estimated creatinine clearance rate (eCCr) per Cockcroft-Gault formula of <60 mL/min or estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, corresponding to NCI-CTCAE v.5.0 Grade ≥2
    b. Impaired hearing (measured by audiometry) of >25 dB at two contiguous test frequencies in at least one ear, corresponding to NCI-CTCAE v.5.0 Grade ≥2
    c. Peripheral sensory neuropathy Grade ≥ 2 by NCI-CTCAE v.5.0
    d. Patient refusal
    e. In the opinion of the Investigator, the patient is considered ineligible to receive any platinum-based chemotherapy
3. Be willing and able to provide written informed consent for the trial.
4. Be ≥18 years of age.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1.
6. Adequate organ function as defined by the following criteria:
    a. Absolute neutrophil count (ANC) ≥1.5×10^9/L
    b. Platelet count ≥100,000/mm^3

c. Hemoglobin ≥9.0 g/dL

d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤5.0 × ULN

e. Total bilirubin ≤1.5 × ULN, or ≤3.0 × ULN for patients with Gilbert's syndrome

f. Creatinine clearance (Ccr) (calculated or measured value): ≥30 mL/min. For calculated Ccr, use the Cockcroft-Gault formula

g. International normalized ratio (INR) OR prothrombin time ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as prothrombin time or activated partial thromboplastin time (aPTT) is within therapeutic range of intended use of anticoagulants

h. Phosphorus <1.5 ULN

7. Adequate recovery from the side effects of any prior therapy for nonmetastatic disease (generally defined as recovery of all AEs due to ≤ Grade 1 or baseline; however, patients with ≤ Grade 2 neuropathy, anemia, alopecia, and skin pigmentation may be eligible).
8. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.
9. Have a measurable disease per RECIST 1.1, as assessed by the local site Investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
10. A male patient must agree to use contraception during the treatment period and for at least 6 months following the last dose of study treatment.
11. A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP).
    b. A WOCBP who agrees to follow contraceptive guidance during the treatment period and for at least 6 months after the last dose of study treatment.
    c. A WOCBP who has a negative serum pregnancy test within 7 days prior to treatment.
12. Ability to take medications orally (feeding tube is not permitted)
13. Willing and able to comply with scheduled visits and study procedures.

<u>Exclusion Criteria</u>

1. Have received prior therapy with anti-PD-1, anti-PD-L1/L2 agent.
2. Have received prior FGFR inhibitor treatment including futibatinib
3. 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.

4. Corrected QT interval using Fridericia's formula (QTcF) >470 msec. Patients with an atrioventricular pacemaker or other condition (for example, right bundle branch block) that renders the QT measurement invalid are an exception and the criterion does not apply.
5. Has received major surgery within the previous 4 weeks.
6. Has received any non-investigational anticancer therapy within the previous 3 weeks (mitomycin within the previous 5 weeks).
7. Is currently participating in a study of an investigational agent/device, or has participated in a study of an investigational agent or used an investigational device within 4 weeks prior to the first dose of study treatment.
8. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
9. A serious illness or medical condition(s) including, but not limited to, the following:
    a. Has an active infection requiring systemic therapy.
    b. Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months
    c. History or current evidence of uncontrolled ventricular arrhythmia
    d. Chronic diarrhea diseases considered to be clinically significant in the opinion of the Investigator
    e. Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death
    f. Have an active autoimmune disease that has required systemic treatment in the past 2 years (that is, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (for example, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
    g. Have a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
    h. Have had an allogenic tissue/ organ transplant.

10. Has known human immunodeficiency virus (HIV) and/or history of Hepatitis B or C infections, or known to be positive for Hepatitis B antigen (HBsAg)/ Hepatitis B virus (HBV) DNA or Hepatitis C Antibody or RNA. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating Investigator.
12. Have known active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are radiologically stable, that is, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, and without steroid treatment requirement for at least 1 month prior to the first dose of study treatment.
13. The patient is pregnant or breastfeeding.
14. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.
15. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
16. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
17. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Evaluation Criteria:

Efficacy

Efficacy parameters will be assessed based on on-site tumor assessments (including computed tomography [CT] or magnetic resonance imaging [MRI] if CT scan is not feasible) performed by the Investigator/local radiologist according to RECIST 1.1 guidelines [Eisenhauer et al. 2009]). The primary endpoint will be ORR, defined as the proportion of patients experiencing a best overall response of CR or PR.

In addition to RECIST 1.1, iRECIST will be used. iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression, and make decisions regarding the continuation of study treatment.

When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in the protocol. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some

participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Safety

The assessment of safety will be based on the incidence of treatment-emergent adverse events (TEAEs) and on-study laboratory parameters. Grading of TEAEs will be performed using the NCI-CTCAE, Version 5.0.

CCI

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- CCI

Statistical Methods:

Determination of Sample Size

Approximately 20 patients with UC and FGFR3 mutations or FGFR1-4 fusion/rearrangement will be enrolled in Cohort A. Sample size considerations are based on differentiating a historical control ORR per RECIST 1.1 of 35% or less, with a target ORR per RECIST 1.1 of 65%. Assuming the true ORR per RECIST 1.1 is 65%, the cohort has an approximate 80% power to reject the null hypothesis that the true ORR per RECIST 1.1 is ≤35%, considering a 2-sided alpha of 10%. With a sample size of 20, observing at least 12 responders will have a 90% confidence interval (CI) lower bound excluding 10% (ORR per RECIST 1.1 of 60% with 90% CI (39.4% - 78.3%)).

Approximately 20 patients with UC and without FGFR3 mutations or FGFR1-4 fusions will be enrolled in Cohort B. Sample size considerations are based on differentiating a historical control ORR per RECIST 1.1 of 25% or less, with a target ORR per RECIST 1.1 of 50%. Assuming the true ORR per RECIST 1.1 is 50%, the cohort has an approximate 80% power to reject the null hypothesis that the true ORR per RECIST 1.1 is ≤25%, considering a 2-sided alpha of 10%. With a sample size of 20, observing at least 9 responders will have a 90% CI lower bound excluding 10% (ORR per RECIST 1.1 of 45% with 90% CI (25.9% - 65.3%)).

Interim Analyses

The first interim analysis of safety will be performed after the 6-patient safety lead-in period; a second interim analysis of safety will be performed after a total of 10 patients have been enrolled (including the initial 6 patients enrolled in the safety lead-in period). At each interim analysis, the combination of futibatinib and pembrolizumab will be considered intolerable if the incidence of unacceptable toxicity (as defined in the protocol) is >33%.

Analysis Populations

The analysis study populations in this study are defined as below:

Analysis Population	**Definition**
All Enrolled Population	All patients enrolled in this study
All Treated Population/ Full Analysis Set	All patients in the All Enrolled Population who received at least one dose of study drug
CCI [redacted]	CCI [redacted]

Efficacy Analyses

The efficacy analyses will be performed for each cohort using the All Treated Population, unless otherwise specified.

Efficacy data for the primary and secondary endpoints will be summarized descriptively.

For the primary efficacy analysis, ORR per RECIST 1.1 will be estimated with the exact 2-sided 90% CI. Only the evaluations before disease progression or initiation of new anticancer treatment will be used for the estimation.

ORR and DCR per RECIST 1.1 and iRECIST will be estimated with the exact 2-sided 95% CI. Only the evaluations before disease progression or initiation of new anticancer treatment will be used for the estimation.

DOR per RECIST 1.1 and iRECIST will be estimated only in patients with an objective response of CR or PR. Patients who are alive and progression-free as of the analysis cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy.

PFS per RECIST 1.1 and iRECIST will be estimated using the Kaplan-Meier method. Patients who die without a reported disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last tumor assessment. Patients who did not have any on-study assessments and did not die will be censored on the first dosing date. Patients who started any subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anticancer therapy.

Overall survival will be estimated the same as PFS. In the absence of death confirmation or for patients alive as of the OS cut-off date, survival time will be censored at the date of the last known alive date.

Safety Analyses

The safety analyses will be performed by each cohort and study drug using the All Treated Population.

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

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

Hematological and chemistry laboratory parameters will be graded according to the NCI-CTCAE (Version 5.0) where applicable. The worst severity grade, time to maximum Grade 3 or 4 value, and time to resolution (return to baseline grade or below) will be summarized.

A list of 12-lead electrocardiogram (ECG) findings will be presented by patient.

CCI [redacted] Analyses

The CCI [redacted] analyses will be performed using the CCI [redacted] CCI [redacted] data will be summarized descriptively as described in a separate Statistical Analysis Plan (SAP).

Schedule of Events

Evaluations on Day 1 (D1) of a cycle should be performed within 24 hours prior to dosing, unless otherwise noted. Procedures already performed during the screening period within 72 hours prior to dosing do not need to be repeated on Cycle 1 (C1) C1D1. The End of Treatment (EOT) visit must be performed 0-7 days after a decision is made to discontinue study treatment (for patients who discontinue at a planned study visit, that visit may be considered the EOT visit if all assessments required at EOT are performed).

Table 1: Schedule of Events

		Treatment Period (1 cycle =21 days)					Safety Follow-up			
		Cycle 1			Cycle ≥2					
Evaluation	**Screening (Within 28 days of 1st dose)**	**D1 (-1 day)**	**D8 (-1 day)**	**D15 (-1 day)**	**D1 (-1 day)**	**End of Cycle (±7days)**	**End of Treatment (+0-7 days)**	**30, 60, and 90 days after last dose (±3 days)**	**Survival Follow-up Period (every 12±2 weeks)**	**Notes**
Written informed consent	X									Written informed consent will be obtained prior to any study-related assessments or procedures.
Review eligibility criteria	X									
Demographics/medical history	X									
Review of baseline signs and symptoms	X									
Prior & concomitant medications, AE assessments	→									Collect from the time main informed consent is signed through 90 days after administration of the last dose of study therapy or until the start of new anticancer therapy, whichever is earlier.
Physical examination	X	X			X		X	X		Within 24 hours prior to dosing.
Vital signs	X	X			X		X	X		Heart rate, blood pressure, body temperature, and respiration rate.
Height and Weight	X	X			X		X	X		Height at screening only.

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =21 days)					Safety Follow-up		Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1			Cycle ≥2					
		D1 (-1 day)	D8 (-1 day)	D15 (-1 day)	D1 (-1 day)	End of Cycle (±7days)	End of Treatment (+0-7 days)	30, 60, and 90 days after last dose (±3 days)		
ECOG performance status	X	X			X		X	X		Within 24 hours prior to dosing.
12-Lead electrocardiogram		X			X		X	X		
Hematology	X	X	X	X	X		X	X		Within 24 hours prior to dosing. More frequent assessments may be performed if clinically indicated
Coagulation	X	X			X		X	X		
Chemistry (serum or plasma)	X	X	X	X	X		X	X		
Thyroid Function Tests	X	X			X					Every 6 weeks until discontinuation of pembrolizumab.
Pregnancy test	X						X			Serum pregnancy test required within 7 days prior to first dose for WOCBP. Additional testing (urine or serum) as required per local practice.
Ophthalmological examination	X			See Note						Examination to be performed by an ophthalmologist or qualified delegate. At screening, 4-6 weeks after first dose, and as indicated if symptoms or signs of mineral deposits. In cases of retinal pigment epithelial detachment, events should be monitored at 2-3-week intervals.
CCI [redacted]				X						CCI [redacted]

Evaluation	Screening (Within 28 days of 1st dose)	Treatment Period (1 cycle =21 days)					Safety Follow-up		Survival Follow-up Period (every 12±2 weeks)	Notes
		Cycle 1			Cycle ≥2					
		D1 (-1 day)	D8 (-1 day)	D15 (-1 day)	D1 (-1 day)	End of Cycle (±7days)	End of Treatment (+0-7 days)	30, 60, and 90 days after last dose (±3 days)		
Blood sample for CCI assessment		X			X		X			CCI
Tumor tissue collection for CCI assessment	X				X					Mandatory tissue collection at baseline (archival or new tumor biopsy). Optional tumor biopsy to be performedat Day 1 of Cycle 2 only.
Tumor assessments (CT/MRI)	X					(X)	X	X	X	At baseline and the end of every 3 cycles (±7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever comes first). For patients who discontinue treatment for reasons other than radiographic disease progression, imaging will be performed at EOT, (if the prior scan was performed ≥9 weeks before EOT) and during Survival Follow-up until radiologic disease progression or initiation of new anticancer therapy (whichever occurs first).
Survival status									X	For all patients,unless patient withdraws consent or the study is terminated early by the Sponsor.

Table 2: Schedule of Events – Study Extension Phase

	Treatment Period (1 cycle = 21 days)		Safety Follow-Up	Notes
	Daily	At Least Every 3 Cycles	30, 60, and 90 (±3 days) After Last Dose	
Physical examination		X	X	Within 24 hours prior to dosing on D1 of the cycle.
Vital signs		X	X	Heart rate, blood pressure, body temperature, and respiration rate.
Weight		X	X	
Ophthalmological examination		(X)	X	As needed due to local requirements, physician judgment, and/or symptoms or signs of mineral deposits.
ECOG performance status		X	X	Within 24 hours prior to dosing on D1
12-Lead electrocardiogram		X	X	
Hematology and coagulation		X	X	Within 24 hours prior to dosing on D1 of the cycle.
Chemistry (serum or plasma)		X	X	Within 24 hours prior to dosing on D1 of the cycle.
Thyroid function tests		See note	See note	Every 6 weeks until discontinuation of pembrolizumab.
Pregnancy test			X	Additional testing (urine or serum) as required per local practice.
Prior & concomitant medications, AE assessments		X	X	Collect from the time main informed consent is signed through 90 days after administration of the last dose of study therapy or until the start of new anticancer therapy, whichever is earlier.
Tumor assessments (CT/MRI)		X		Tumor assessments may be performed as necessary to determine continued benefit from treatment, every 3 cycles (± 7 days), or as clinically indicated, until radiologic PD or initiation of new anticancer therapy (whichever occurs first).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
Ccr	Creatinine clearance
CI	Confidence interval
CPI	Checkpoint inhibition / inhibitor
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment/end of therapy
FGFR	Fibroblast growth factor receptor
GCP	Good Clinical Practice
iCCA	Intrahepatic cholangiocarcinoma
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements
IEC	Independent Ethics Committee

Abbreviation	Definition
IND	Investigational New Drug
ir	Immune-related
IRB	Institutional Review Board
I.V.	Intravenous
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
CCI	CCI
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-ligand 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression free survival
P-gp	P-glycoprotein
CCI	CCI
PO	Oral
PR	Partial response
PT	Preferred term
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, Version 1.1
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOP	Standard operating procedure
TEAE	Treatment-emergent adverse event
TOI	Taiho Oncology, Inc.

Abbreviation	Definition
UC	Urothelial carcinoma / cancer
ULN	Upper limit of normal
WOCBP	Women of childbearing potential
WT	Wild-type

1. INTRODUCTION

1.1. Urothelial Carcinoma

Cancers affecting the surface epithelium of the renal collecting tubules, calyces, pelvis, ureter, bladder, and urethra (collectively "urothelium") are broadly divided into two categories: upper tract urothelial carcinoma (UTUC), which accounts for approximately 5-10% of cases; and urinary bladder cancer (UBC), which accounts for the remainder (Miyazaki and Nishiyama 2017). UBC is more common in men than in women, with age-standardized incidence rates for more developed regions of around 16.3 per 100,000 for the former and 3.6 per 100,000 for the latter (Ferlay et al. 2010).

For patients with advanced disease, systemic platinum-based chemotherapy is the standard treatment, and may improve overall survival (OS) from 6 months or less with untreated disease to 12-15 months (von der Maase et al. 2000; van der Maase et al. 2005). However, long-term prognosis is poor; the 5-year survival of patients with advanced disease is approximately 15% (von der Maase et al. 2005). Moreover, platinum-based chemotherapy is associated with substantial toxicity, which may render it unsuitable for some patients. New therapeutic options are needed for patients with advanced urothelial carcinomas (UC) who progress on or are not candidates for standard therapy.

1.2. Pembrolizumab

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma.

The programmed death-ligand 1 (PD-1) receptor-ligand interaction is a major pathway that is hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab is indicated for the treatment of patients across a number of indications, and is associated with an acceptable preclinical and clinical safey profile as an intravenous (I.V.) immunotherapy for advanced malignancies.

Prior studies have demonstrated that fibroblast growth factor receptor 3 (*FGFR3*)-mutant UCs are associated with decreased T-cell infiltration. As *FGFR3* mutations are enriched in luminal-like UC, and luminal-like UC has been shown to be relatively less responsive to PD-1/PD-L1 inhibition (checkpoint inhibition [CPI]), these data have led to the speculation that *FGFR3*

mutations may be causally related to poor T-cell infiltration and that UC patients harboring *FGFR3* mutations may be suboptimal candidates for CPI such as pembrolizumab.

However, Wang et al. (2018) determined that while *FGFR3*-mutant UC is associated with a similar tumor mutational burden and lower T-cell infiltration, it is also associated with lower stromal/transforming growth factor beta (TGF-b) immune suppressive signals. These findings suggest that *FGFR3* mutation status may not in fact be a biomarker of resistance to CPI, and provides a rationale for the combination of FGFR-targeted treatment with CPI treatment.

Moreover, recently published data (Palakurthi et al. 2019) shows that FGFR inhibition and anti-PD-1 combination induced significant tumor regression and improved survival. For both erdafitinib monotherapy and combination treatments, tumor control was accompanied by tumor-intrinsic, FGFR pathway inhibition, increased T-cell infiltration, decreased regulatory T cells, and downregulation of PD-L1 expression on tumor cells. Finally, FGFR inhibition may also modulate the tumor microenvironment in non-*FGFR3*-mutated tumors through the blockade of paracrine fibroblast growth factors (FGF) signaling, targeting immune evasion and angiogenesis and lead to enhanced efficacy when combined with pembrolizumab in both wild-type (WT) and *FGFR3* mutated tumors (Ichikawa et al. 2020; Liu et al. 2014; Siefker-Radtke et al. 2018).

1.3. Futibatinib (TAS-120)

1.3.1. Background

The fibroblast growth factor/fibroblast growth factor receptor (FGF/FGFR) signaling axis has been well characterized for its role in proliferation, differentiation, migration, and survival of cells, and it is fundamental to embryonic development, regulation of angiogenesis, and wound healing in adults. Accordingly, dysregulation of this signaling pathway has been associated with many developmental disorders and cancer.

Futibatinib is a novel and selective small molecule FGFR inhibitor, which is the first irreversible, covalent inhibitor of FGFR1–4 being tested in humans. Futibatinib selectively and irreversibly binds to FGFR to exert an inhibitory effect on the FGF/FGFR pathway. Preclinical studies have shown that futibatinib selectively inhibits the cell growth of human cancer cell lines bearing FGFR gene abnormalities; strong antitumor efficacy has been observed with futibatinib in nude mouse or nude rat xenograft models bearing tumors with FGFR gene abnormalities.

1.3.2. Clinical Overview

As of 05 September 2019, a total of 460 subjects (41 healthy volunteers and 419 patients) have been treated with futibatinib across 4 clinical trials. To date, 2 clinical studies in healthy volunteers have been completed, and 2 Phase 1-2 studies assessing the safety, efficacy, and pharmacokinetics (PK) of futibatinib in advanced cancers are currently ongoing.

The recommended dose and schedule of futibatinib is 20 mg QD (continuous daily dosing), based on the results of a Phase 1 dose escalation study (TAS-120-101). Accordingly, the starting dose of futibatinib in this Phase 2 study is 20 mg QD.

In all, more than 460 patients and healthy volunteers have been treated with futibatinib across all trials. Collectively, safety data from these studies suggest that futibatinib is associated with manageable toxicity in multiple patient populations. The most frequently reported treatment-

related adverse event (AE) overall has been hyperphosphatemia (a mechanism-based event), mostly of Grades 1-2 and without clinical complications. Other frequently reported treatment-related AEs included the gastrointestinal system disorders of diarrhoea, dry mouth, nausea, and stomatitis. Skin toxicity and increased liver enzymes have also been reported, most of which have been mild to moderate in severity. Ocular toxicities, which have been reported with other FGFR inhibitors, were observed with low frequency in all trials.

Efficacy has been observed in different tumor types:

- Solid tumors harboring *FGFR1-4* rearrangements, including intrahepatic cholangiocarcinoma (iCCA), head and neck, unknown primary, and gastric cancer
- Gastric cancer with *FGFR2* amplification
- Myeloid/lymphoid neoplasm with *FGFR1* rearrangement
- Other solid tumors with different *FGFR* aberrations

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

1.4. Summary of Study Rationale

Advanced UC is associated with very poor long term prognosis; even with standard therapy, the majority of patients will progress and the 5-year survival rate remains only approximately 15%. Moreover, many patients are unable to tolerate standard chemotherapy; for such patients, therapeutic options are even more limited. There is evidence that the combination of a PD-1/PD-L1 inhibitor and an FGFR inhibitor may result in treatment benefit in this population. This Phase 2 study will assess the effect of pembrolizumab and futibatinib on patients with UC, including patients with *FGFR3* mutation / FGFR1-4 fusion/rearrangement.

2. OBJECTIVES AND ENDPOINTS

The objectives and endpoints of this study are shown in Table 3.

All variables based on tumor response will be calculated based on the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1), as well as iRECIST criteria. The primary evaluation of efficacy will be based on RECIST 1.1. All evaluations of tumor response will be per local Investigator/radiologist assessment.

Table 3: Objectives and Endpoints

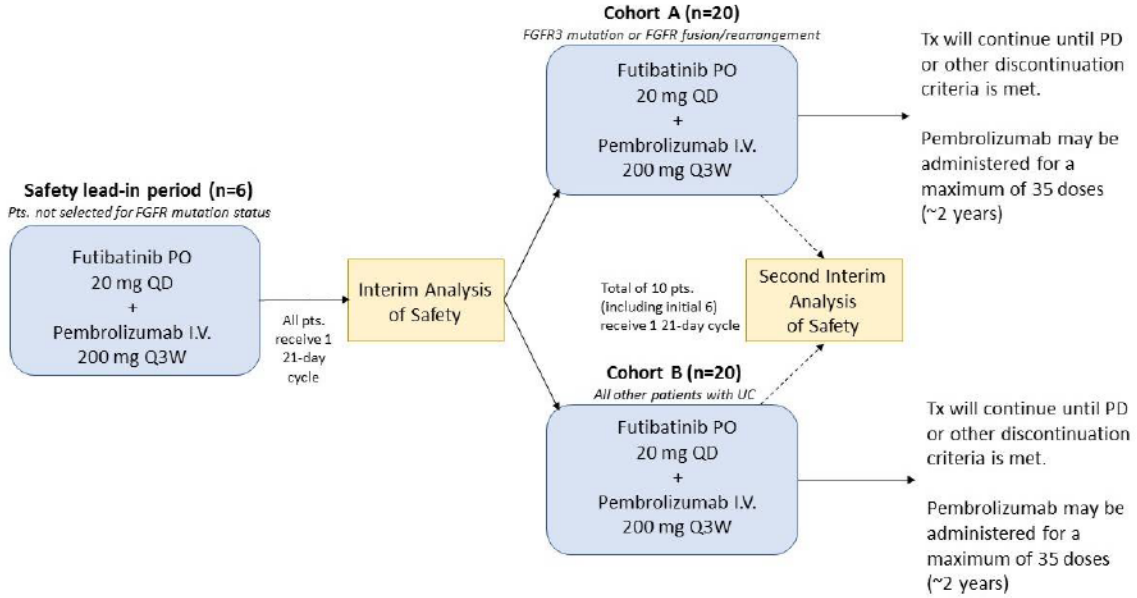
Primary	
Objective response rate (ORR)	• ORR, defined as the proportion of patients experiencing a best overall response of partial response (PR) or complete response (CR).
Secondary	
• Disease control rate (DCR) • Duration of response (DOR) • Progression-free survival (PFS) • Overall survival (OS) • Safety and tolerability	• DCR, defined as the proportion of patients experiencing a best overall response of stable disease (SD), PR, or CR. • DOR defined as the time from the first documentation of response (CR or PR) to the first documentation of objective tumor progression or death due to any cause, whichever occurs first. • PFS, defined as the time from first dose of study therapy to the date of death (any cause) or disease progression, whichever occurs first. • OS, defined as the time from the date of first dose to the death date. • Safety based on reported AEs and on-study laboratory parameters, graded according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0.
Exploratory Endpoints	
• CCI [redacted] • CCI [redacted] • CCI [redacted]	• CCI [redacted] • CCI [redacted] • CCI [redacted]

3. INVESTIGATIONAL PLAN

3.1. Overview of Study Design

Study TAS-120-203 is an open-label, nonrandomized, multicenter Phase 2 study evaluating the combination of futibatinib and pembrolizumab in patients with advanced or metastatic UC who are not candidates to receive a platinum-based treatement regimen.

The design is briefly summarized in Figure 1.



Abbreviations: FGFR=fibroblast growth factor receptor; I.V.=intravenous; mg=milligrams; PD=progressive disease; PO=oral; QD=daily; Q3W=every 3 weeks; Tx=treatment.

Figure 1: Study Schema

A treatment cycle is defined as 21 days. All enrolled patients will receive the same treatment regimen:

- Futibatinib at an oral (PO) dose of 20 mg daily (QD); and
- Pembrolizumab at an intravenous (I.V.) dose of 200 mg every 3 weeks (Q3W).

Treatment will continue until disease progression, unacceptable toxicity, or any other of the criteria for treatment discontinuation is met; of note, pembrolizumab may be administered for a maximum of 35 doses or a maximum duration of 2 years, whichever is earlier.

The study will begin with a safety lead-in period. During this period, a total of 6 patients with advanced or metastatic urothelial carcinoma will be enrolled and treated for at least one 21-day cycle. Patients will be enrolled into this initial safety lead-in period without regard for *FGFR* alteration status.

After the first 6 patients have completed one cycle of treatment, the first safety analysis will occur. After confirmation of the safety of the combination, a total of 20 additional patients will be enrolled into each of the following 2 cohorts:

- Cohort A: Patients with UC and *FGFR3* mutation or *FGFR* fusion/rearrangement. Patients will be enrolled based on local results but tissue samples will be archived for retrospective confirmation at a central lab using next generation sequencing (NGS).
- Cohort B: All other patients with UC (including patients with other *FGFR* or non-*FGFR* aberrations and patients with WT [non-mutated] tumors)

A second safety analysis will occur after enrollment of a total of 10 patients (including the 6 patients from the safety lead-in), in order to confirm the safety profile of the combination before proceeding to the enrollment of the remaining patients in Cohorts A and B.

Please note: at each safety analysis, the combination of futibatinib and pembrolizumab will be considered intolerable if the incidence of unacceptable toxicity including dose-limiting toxicity (as defined in Section 5.2) is ≥33%. If the combination is determined to be intolerable, the study may continue with a reduced dose of futibatinib (16 mg QD) if medically appropriate in the opinion of the Investigator and Sponsor.

Of note, the 6 patients initially enrolled in the safety lead-in period will also be assigned to the respective cohort based on *FGFR* alteration, such that each cohort will contain a minimum of 20 and a maximum of 26 patients.

3.2. Study Periods and Visits for Each Patient

The study periods / visits described in this section are defined for all patients. Please see Table 1 (Schedule of Events) for an outline of all assessments to be performed during each study period / visit.

For all patients, the Safety Assessment Period begins at the time the informed consent form (ICF) is signed and continues until at least 90 days after the last dose of study therapy. After the 30-day Safety Follow-Up Visit (see below), patients who have not started treatment with a new anti-cancer therapy will be assessed for study therapy-related serious adverse events (SAEs) only.

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

3.2.1. Screening Period

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

3.2.2. Treatment Period and End of Treatment Visit

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

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

The safety follow-up period is the time from the date of last dose of study therapy through the safety follow-up visits, which must be performed 30, 60 and 90 days (±3 days) following the last dose of study therapy. If the patient starts new anticancer therapy within 30 days of the last dose of study therapy, the 30-day safety follow-up visit should be performed before the start of new anticancer therapy. Every effort should be made to perform the assessments outlined in Table 1. If the patient is unable to return to the study site, a follow-up phone call can be made by the study site to collect any new safety information that occurred during the safety follow-up period.

3.2.3. Post-Discontinuation Considerations

Patients who discontinue without documented disease progression should continue to undergo tumor assessments according to the Schedule of Events (that is, every 9 weeks ±7 days) until progressive disease (PD) is documented, new anticancer therapy is initiated, the study is terminated, or the patient dies, withdraws consent, or is lost to follow-up).

3.2.4. Survival Follow-up

Once disease progression is confirmed or new anticancer therapy is initiated, whichever occurs first, the survival follow-up period begins. During this period, the patient or family should be contacted for survival follow-up every 12 weeks (±2 weeks) until patient withdraws consent or the study is terminated early by the Sponsor. In addition, all subsequent anticancer treatments will be recorded.

3.2.5. Study Completion and Study Extension

The study will be considered complete when:

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

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

During this period, all safety assessments are to continue according to the schedule in Table 2. However, electronic data collection will be reduced. Specifically, study extension data collection is to include, at a minimum:

- Study drug administration;
- Study drug accountability;
- SAEs;
- Non-serious AEs that are related to study treatment or result in treatment discontinuation; and
- Any cases of pregnancy, overdose, or medication error.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1. Inclusion Criteria

A patient must meet all of the following criteria to be eligible for participation in this study; waivers will not be granted for any of the elgibility criteria.

1. Histologically confirmed advanced or metastatic UC in patients who have not received systemic treatment for advanced metastatic disease. For patients who received prior adjuvant/neoadjuvant chemotherapy or chemo-radiation for urothelial carcinoma, a treatment-free interval >12 months between the last treatment administration and the date of recurrence is required in order to be considered treatment-naïve in the metastatic setting.
    a. In safety lead-in: enrollment regardless of FGFR status
    b. Cohort A: must have an *FGFR3* mutation or *FGFR1-4* fusion/rearrangement
    c. Cohort B: all other patients with UC (including patients with other FGFR or non-*FGFR* genetic aberrations and patients with WT [nonmutated] tumors)
2. Unfit for or intolerant to standard platinum-based chemotherapy as defined by any one of the following criteria:
    a. Chronic kidney disease characterized by the estimated creatinine clearance rate (eCCr) per Cockcroft-Gault formula of <60 mL/min or estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2, corresponding to NCI-CTCAE v.5.0 Grade ≥2
    b. Impaired hearing (measured by audiometry) of >25 dB at two contiguous test frequencies in at least one ear, corresponding to NCI-CTCAE v.5.0 Grade ≥2
    c. Peripheral sensory neuropathy Grade ≥2 by NCI-CTCAE v.5.0
    d. Patient refusal
    e. In the opinion of the Investigator, the patient is considered ineligible to receive any platinum-based chemotherapy
3. Be willing and able to provide written informed consent for the trial.
4. Be ≥18 years of age.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1.
6. Adequate organ function as defined by the following criteria:
    a. Absolute neutrophil count (ANC) ≥1.5 × 10^9/L
    b. Platelet count ≥100,000/mm^3
    c. Hemoglobin ≥9.0 g/dL
    d. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × upper limit of normal (ULN); if liver function abnormalities are due to underlying liver metastasis, AST and ALT ≤5.0 × ULN.

e. Total bilirubin ≤1.5 × ULN, or ≤3.0 × ULN for patients with Gilbert's syndrome.

f. Creatinine clearance (Ccr) (calculated or measured value): ≥30 mL/min. For calculated Ccr, use the Cockcroft-Gault formula.

g. International normalized ratio (INR) OR prothrombin time ≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as prothrombin time or aPTT is within therapeutic range of intended use of anticoagulants

h. Phosphorus <1.5 ULN

7. Adequate recovery from the side effects of any prior therapy for nonmetastatic disease (generally defined as recovery of all AEs due to ≤ Grade 1 or baseline; however, patients with ≤ Grade 2 neuropathy, anemia, alopecia, and skin pigmentation may be eligible).
8. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.
9. Have a measurable disease per RECIST 1.1, as assessed by the local site Investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
10. A male patient must agree to use contraception during the treatment period and for at least 6 months following the last dose of study treatment.
11. A female patient is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
    a. Not a woman of childbearing potential (WOCBP).
    b. A WOCBP who agrees to follow contraceptive guidance during the treatment period and for at least 6 months after the last dose of study treatment.
    c. A WOCBP who has a negative serum pregnancy test within 7 days prior to treatment.
12. Ability to take medications orally (feeding tube is not permitted).
13. Willing and able to comply with scheduled visits and study procedures.

4.2. Exclusion Criteria

A patient must not meet <u>any</u> of the following exclusion criteria to be eligible for participation in this study; waivers will not be granted for any of the elgibility criteria.

1. Have received prior therapy with anti-PD-1, anti-PD-L1/L2 agent.
2. Have received prior FGFR inhibitor treatment including futibatinib
3. 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.

4. Corrected QT interval using Fridericia's formula (QTcF) >470 msec. Patients with an atrioventricular pacemaker or other condition (for example, right bundle branch block) that renders the QT measurement invalid are an exception and the criterion does not apply.
5. Has received major surgery within the previous 4 weeks.
6. Has received any non-investigational anticancer therapy within the previous 3 weeks (mitomycin within the previous 5 weeks).
7. Is currently participating in a study of an investigational agent/device, or has participated in a study of an investigational agent or used an investigational device within 4 weeks prior to the first dose of study treatment.
8. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.
9. A serious illness or medical condition(s) including, but not limited to, the following:
   a. Has an active infection requiring systemic therapy.
   b. Myocardial infarction, severe/unstable angina, or symptomatic congestive heart failure within the previous 6 months
   c. History or current evidence of uncontrolled ventricular arrhythmia
   d. Chronic diarrhea diseases considered to be clinically significant in the opinion of the Investigator
   e. Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death
   f. Have an active autoimmune disease that has required systemic treatment in the past 2 years (that is, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (for example, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
   g. Have a history of (noninfectious) pneumonitis that required steroids or has current pneumonitis.
   h. Have had an allogenic tissue/ organ transplant.

10. Has known human immunodeficiency virus (HIV) and/or history of Hepatitis B or C infections, or known to be positive for Hepatitis B antigen (HBsAg)/ Hepatitis B virus (HBV) DNA or Hepatitis C Antibody or RNA. Active Hepatitis C is defined by a known positive Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
11. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating Investigator.
12. Have known active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are radiologically stable, that is, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable, and without steroid treatment requirement for at least 1 month prior to the first dose of study treatment.
13. The patient is pregnant or breastfeeding.
14. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of study drug.
15. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
16. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
17. Has a known psychiatric or substance abuse disorder that would interfere with the participant’s ability to cooperate with the requirements of the study.

4.3. Screen Failure

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

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

4.4. Discontinuation of Treatment

Pembrolizumab may be administered for a maximum of 35 doses or a maximum duration of 2 years, whichever is earlier. There is no maximum duration of futibatinib therapy. A patient will be discontinued from any or all study therapy for any of the following reasons:

1. Disease progression
2. Unacceptable AEs, or change in underlying condition such that the patient can no longer tolerate therapy, as evidenced by a dose delay > 21 days from the scheduled start date of the next cycle or need for more than 2 dose reductions outlined in this protocol. If such toxicity is associated with only 1 of the treatment components (futibatinib or pembrolizumab), the patient may discontinue that component and continue receiving the other if medically appropriate in the opinion of the Investigator.
3. Physician's decision, including need for other anticancer therapy not specified in the protocol or surgery or radiotherapy to the only site(s) of disease being followed in the study
4. Pregnancy
5. Termination of the study by the Sponsor, or
6. At the patient's request at any time irrespective of the reason.

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

4.5. Withdrawal from the Study

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

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

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

5. STUDY TREATMENT

5.1. Study Drug Administration

Please note: at any timepoint where futibatinib and pembrolizumab are administered on the same day, pembrolizumab should be administered prior to futibatinib if possible. A study cycle is defined as 21 days.

5.1.1. Futibatinib

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

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

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

5.1.2. Pembrolizumab

Pembrolizumab is administered as an I.V. infusion of 200 mg on Day 1 of each cycle (that is, every 3 weeks). Treatment continues for a maximum of 35 doses or a maximum duration of 2 years (whichever is earlier), or until the patient meets any of the administration discontinuation criteria (see Section 4.4).

Pembrolizumab should be administered according to the instructions on the approved product label.

5.2. Definition of Dose-Limiting Toxicity

For this study, unacceptable toxicity will include any event meeting the criteria for dose-limiting toxicity (DLT), as outlined below. An adverse event not meeting the criteria for a DLT may also be considered an unacceptable toxicity, if it is not tolerable in the long-term and necessitates discontinuation of one or more elements of the combination therapy.

DLT Definition

All toxicities will be graded using the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0, based on Investigator assessment. The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if assessed by the Investigator to be related to study treatment administration.

- Grade 4 nonhematologic toxicity (not laboratory)
- Grade 4 neutropenia lasting >5 days
- Grade 4 thrombocytopenia of any duration

- Grade 3 thrombocytopenia associated with clinically significant bleeding
- Any nonhematologic AE ≥Grade 3 in severity, with the following exceptions:
  - Grade 3 fatigue lasting ≤3 days;
  - Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheals per standard of care;
  - Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
- Any Grade 3 or Grade 4 nonhematologic laboratory value if:
  - Clinically significant medical intervention is required to treat the patient, or
  - The abnormality leads to hospitalization, or
  - The abnormality does not recover to Grade ≤1 within 48 hours despite best supportive care, or
  - The abnormality results in a drug induced liver injury
  - Exceptions: clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, hyperphosphatemia, etc.
- Febrile neutropenia Grade 3 or Grade 4:
  - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour
  - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Grade 3 or higher visual impairment
- Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity
- Any treatment-related toxicity that causes the participant to discontinue treatment during Cycle 1
- Missing >20% of futibatinib doses as a result of drug-related AE(s) during Cycle 1
- Grade 5 toxicity

5.3. Dose and Schedule Modifications

5.3.1. Dose Modifications for Futibatinib

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

Following a dose reduction, if a benefit/risk assessment favors an increase of futibatinib dose up to the initial starting dose (20 mg QD, or 16 mg QD if this is determined as the recommended dose), an agreement with the Sponsor's medical monitor is required prior to the dose increase.

If toxicities related to the dose reduction do not recover based on the criteria defined in the following sections within 21 days after the last dose of futibatinib, the patient will be discontinued permanently from treatment (Section 4.4). If resumption criteria are met within 21 days of the last dose of futibatinib, the patient may resume futibatinib treatment at the appropriate dose level.

5.3.1.1. Futibatinib Dose Modifications for Nonhematologic Toxicities

Dosing modification guidelines for nonhematologic and eye toxicities are provided in Table 4 and Table 5, respectively.

Table 4: Dose Modifications for Related Nonhematologic Toxicities

Grade	Dose Interruption/Resumption	Dose Adjustment
Grade 1 or 2	Maintain treatment at the same dose level	None
Grade 3	Withhold treatment until return to baseline or Grade ≤1	Reduce by 1 dose level from the previous level, except for Grade 3 nausea and/or vomiting controlled by aggressive antiemetic therapy or Grade 3 diarrhea responsive to antidiarrheal medication which does not require a dose hold or reduction.
Grade 4	Discontinue treatment	Permanent discontinuation of futibatinib.
Grade 4 (lab abnormality AE)	Withhold treatment until return to baseline or Grade ≤1	Futibatinib will be permanently discontinued if assessed by the Investigator as life threatening. If it is in the best interest of the patient to continue treatment in the opinion of the Investigator and after discussion with the Sponsor, the patient can continue treatment at a reduced dose level. However, futibatinib should first be held until toxicity returns to baseline or Grade ≤1.

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

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

Table 5: Dose Modifications for Related Eye Toxicities

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

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

Recommendations for hyperphosphatemia management are provided in Table 6. These guidelines are based on emerging data from studies evaluating *FGFR* inhibitors, and from the experience of Investigators participating in ongoing studies of futibatinib. In addition, please see Appendix B for dietary guidelines for the treatment of hyperphosphatemia.

Table 6: Recommendations for Hyperphosphatemia Management

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

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

[a] Serum phosphorus will be tested 4 days (± 24 hours) after Day 1 of Cycle 1 to initiate early intervention for hyperphosphatemia if indicated.
[b] mmol/L=mg/dL x 0.3229 (conversion factor)
[c] This grading for the range of serum phosphorus levels will be used for the protocol.
[d] 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.
[e] Titrate the dose every 2-3 weeks until an acceptable serum phosphate level is reached.

5.3.1.2. Futibatinib Dose Modifications for Hematologic Toxicities

Criteria for dose interruption and resumption for hematologic toxicities are presented in Table 7.

Table 7: Futibatinib Dose Interruption and Modification Criteria for Related Hematologic Toxicities

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

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

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

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

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

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

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

5.3.3. Dose Modifications for Pembrolizumab

5.3.3.1. Dose Modification and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related (ir) response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

General instructions for the management of irAEs are as follows; please see Table 8 for detailed guidelines.

1. Severe and life-threatening irAEs should be treated with I.V. corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

Table 8: Guidelines for Management of Immune-Related Adverse Events Associated with Pembrolizumab

irAEs	Toxicity grade or conditions (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor patients for signs and symptoms of pneumonitis • Evaluate patients with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor patients for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Patients with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Patients with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via I.V. infusion.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity grade or conditions (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
AST or ALT elevation or Increased Bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold[d]	• Initiate insulin replacement therapy for patients with T1DM • Administer anti-hyperglycemic in patients with hyperglycemia	• Monitor patients for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyper-thyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypo-thyroidism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increase creatinine or	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity grade or conditions (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
acute kidney injury				
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

a. AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal
b. AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal
c. AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal
d. The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the Investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.
e. Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

5.3.3.2. Infusion-Related Reactions

Pembrolizumab may cause severe or life threatening infusion-reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 9.

Table 9: Guidelines for Management of Infusion-Related Reactions to Pembrolizumab

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator.	None

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
indicated; intervention not indicated		
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, I.V. fluids); prophylactic medications indicated for ≤24 hrs.	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the patient should be premedicated for the next scheduled dose. **Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Patient may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilator support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** I.V. fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Patient is permanently discontinued from further study drug treatment.**	

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov

5.3.3.3. Other Permitted Dose Interruption for Pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs, such as medical / surgical events or logistical reasons not related to study therapy. Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's source documents.

5.4. Treatment Compliance

Each patient will be instructed to comply with the dosing regimen of futibatinib. Pembrolizumab will be administered at the site by qualified site personnel according to the protocol.

Compliance should be documented in the patient's source documents.

5.5. Concomitant Medications and Therapies

5.5.1. Prohibited Medications and Therapies

The following therapies are not permitted during the study treatment period:

- Any other investigational therapy
- Any other anticancer therapy (including chemotherapy, immunotherapy, biological response modifiers, or antineoplastic endocrine therapy)
- Radiation therapy (NOTE: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Investigator's discretion. Extended-field radiation therapy or palliative radiation to a focal site of measurable disease is prohibited. If it is deemed in the best interest of the patient and after discussion between the Investigator and Sponsor, it can be administered, but the patient will be censored for the primary endpoint analysis).
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE that is suspected to have an immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor (for example, for the control of acute asthma symptoms and for patients with brain metastases).

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

5.5.2. Concomitant Medications and Therapies Requiring Precautions

The following therapies are permitted:

- Bisphosphonates
- Denosumab
- Steroids for patients with brain metastases

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

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

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

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

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

5.5.3. Drug Interactions

The following information is based on results from *in vitro* studies and preliminary results from clinical pharmacology studies of drug interactions. Caution is advised if these drugs are given concomitantly (see Appendix C).

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

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

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

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

5.6. Effective Contraception During Study

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

For WOCBP, including female study participants and partners of male participants, effective contraception is required during the study and for 6 months after the last dose of study medication, or longer if necessary based on local requirements. Effective contraception is defined as follows:

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

Male patients with partners who are WOCBP should use a male condom in combination with at least one of the effective contraception methods during the study and for 6 months or longer based on local requirements after the last dose of study medication. Donation of sperm or ova is not allowed during the study and for 6 months or longer based on local requirements following the last dose of study drug.

5.7. Study Drug Materials and Management

Futibatinib will be supplied by the Sponsor. Pembrolizumab will be supplied to the Sponsor by Merck Sharp & Dohme Corp, and supplied to each site by the Sponsor.

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

Please refer to the Investigator's Brochures for futibatinib and pembrolizumab, respectively, for additional information, including details on packaging, labeling, and storage recommendations.

5.7.1. Accountability

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

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

6. STUDY ASSESSMENTS

The Schedule of Events (Table 1 and Table 2) summarizes the frequency and timing of all applicable study assessments, including allowable windows for study visits and assessments / procedures. Written informed consent must be provided before any study-related procedures are performed. Any AEs directly associated with a screening procedure should be reported as described in Section 9.1.

Assessment	Details
Review of inclusion/exclusion criteria	See Sections 4.1 and 4.2. Eligibility must be confirmed prior to first dose of study therapy.
Demographics/medical history	Sex, age, clinical diagnosis, date and method of diagnosis, prior cancer therapy, relevant medical history (past and concurrent).
Baseline signs and symptoms	Signs and symptoms occurring after signing of ICF but before administration of first dose of futibatinib.
Physical examination, Height and body weight	Height is collected for the purpose of BMI calculations at baseline only.
Vital signs	Pulse rate, systolic and diastolic blood pressure, body temperature, and respiration rate. Any abnormal reading should be repeatedly immediately.
ECOG performance status	See Appendix A.
12-lead ECG	Single, resting, semirecumbent 12-lead electrocardiogram (ECG) will be performed locally. Data collection includes RR interval (heart rate), QT interval, QTcF interval and abnormal findings; the Investigator is responsible for interpreting and measuring ECG data.
Hematology	Red blood cell count, hemoglobin, hematocrit, platelets, white blood cell count with differential, neutrophils (ANC), lymphocytes, monocytes, eosinophils, basophils
Chemistry (serum or plasma)	AST, ALT, ALP, bicarbonate, total bilirubin, direct bilirubin, albumin, lactate dehydrogenase, inorganic phosphorus, triglyceride, total cholesterol, creatinine, urea or blood urea nitrogen, bicarbonate, sodium, potassium, chloride, calcium (corrected value), magnesium, blood glucose, uric acid For a calculated creatinine clearance (Ccr) value, use the Cockcroft-Gault formula: Male Ccr (mL/min) = Body wt (kg)×(140-age)[72×serum creatinine (mg/dL)] Female Ccr (mL/min) = male Ccr×0.85
Thyroid function tests	Triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH).
Coagulation	Prothrombin time-international normalized ratio, activated partial thromboplastin time, fibrinogen
Pregnancy test	Serum β-human chorionic gonadotrophin (human chorionic stimulating hormone) test required for WOCBP at screening and EOT; serum or urine at all other timepoints.
Ophthalmological examination	See Section 6.1
CCI [redacted]	See Section 7.
Efficacy assessments	See Section 8.

Assessment	Details
AE monitoring	All AEs will be collected from the time the ICF is signed through 30 days after the last dose of any study therapy (safety follow-up) or until the start of new antitumor therapy, whichever is earlier. See Section 9. SAEs will be collected through 90 days after the last dose of any study therapy.
CCI [redacted]	See Section 10
Concomitant medication/concomitant therapy	Including all medications / therapies administered from the time ICF is signed through 30 days after administration of the last dose of study therapy or until the start of new anticancer therapy.
Survival follow-up	Once disease progression per RECIST 1.1 is confirmed or the first subsequent new anticancer therapy is initiated, whichever occurs first, the survival follow-up period begins. During this period, the patient or family should be contacted for survival follow-up every 12 weeks (±2 weeks) until withdrawal of consent, death, or lost to follow up, until study completion.

6.1. Ophthalmological Examination

The cornea and conjunctiva are readily visible tissues, and therefore, abnormalities of the cornea and conjunctiva can usually be recognized via external ocular examination and routine slit lamp biomicroscopy. The retina is visible through fundoscopy after dilation of the pupil. Ophthalmologic examination will be performed by an opthalmologist or qualified delegate at screening and 4-6 weeks after first dose; additional on-study evaluation may be performed as needed based on physician judgment and/or symptoms or signs of mineral deposits. In cases of retinal pigment epithelial detachment, events should be monitored at 2- to 3-week intervals.

Each evaluation will encompass:

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

6.2. Laboratory Assessments

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

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

7. CCI [redacted]

CCI [redacted]

Table 10: CCI [redacted]

Day of Study (Time Window)	Collection Time Point (hours) in Relation to Futibatinib Administration (Time Window)
CCI [redacted]	

8. EFFICACY EVALUATIONS

Efficacy parameters will be assessed based on on-site tumor assessments (including computed tomography [CT] or magnetic resonance imaging [MRI] if CT scan is not feasible) performed by the Investigator/local radiologist according to RECIST 1.1 guidelines [Eisenhauer et al. 2009]).

In addition to RECIST 1.1, iRECIST will be used. iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression, and make decisions regarding the continuation of study treatment.

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

Patients who discontinue without documented PD per RECIST 1.1 should continue to undergo tumor assessments/scans according to the study schedule until PD is documented per RECIST 1.1, new anticancer therapy is initiated, the study is terminated, or consent is withdrawn.

8.1. Evaluation of Efficacy per RECIST 1.1

8.1.1. Method of Imaging

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

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

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

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

8.1.2. Tumor Definitions

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

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

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

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

Target Lesions:

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

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

Non-target Lesions:

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

8.1.3. Response Criteria

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

8.1.3.1. Target and Non-Target Response Assessments

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

Table 11: Target and Non-target Lesions

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

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

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

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

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

If a patient is discontinued from the study before PD occurs and receives local or regional palliative radiotherapy during the follow-up period, the irradiation site must be omitted from the

response assessment of the patient; however, if the site is observed to demonstrate disease progression, this case should be judged as PD.

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

8.1.4. Objective Response Assessment

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

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

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

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

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

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

The efficacy evaluation criteria described above will be used to derive the primary and secondary efficacy endpoints as defined in Section 2.

8.2. Use of iRECIST to Guide Treatment Decisions

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment. Upon documentation of PD per RECIST 1.1, patients who are clinically stable should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in Appendix D.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any patient deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the patient may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should continue to be sent in to the Sponsor.

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the patient continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, patients will be discontinued from study treatment.

If a patient has confirmed radiographic progression (iCPD) as defined in Appendix D, study treatment should be discontinued; however, if the patient is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed.

A description of the adaptations and iRECIST process is provided in Appendix D, with additional details in the iRECIST publication (Seymour et al. 2017). A summary of imaging and treatment requirements after first radiologic evidence of progression is illustrated in Figure 2.

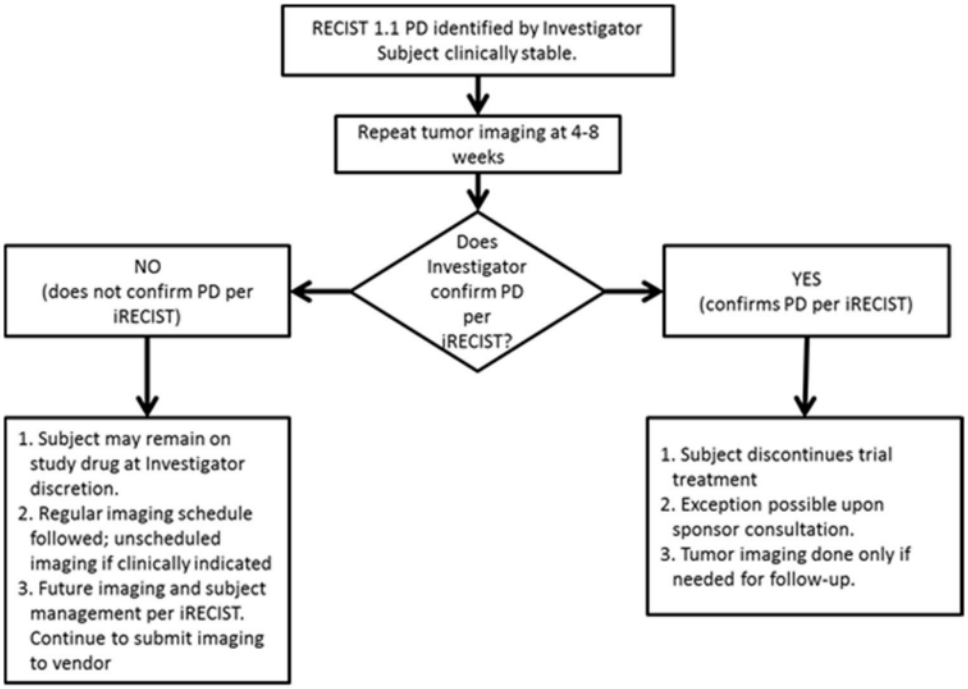


Figure 2: Imaging and treatment for clinically stable patients treated with pembrolizumab after the first radiologic evidence of progression per RECIST 1.1

9. SAFETY EVALUATIONS

9.1. Adverse Events

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

All AEs will be collected from the time the ICF is signed through 30 days after the last dose of any study therapy (safety follow-up) or until the start of new antitumor therapy, whichever is earlier; SAEs will be collected through 90 days after the last dose of any study therapy For all AEs that occur between signing ICF and first dose of study therapy, there is no need to record those that are unrelated unless it is mandatory by local regulations. All AEs will be documented in the eCRF. Any untoward medical event that occurs after the safety follow-up is not considered an AE, unless the Investigator considers that the AE is related to the study drug. Serious AEs related to study therapy will be collected through the survival follow-up.

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

For definitions and reporting of pregnancies, overdoses, and medication errors, refer to Section 9.5.

9.2. Reporting of Adverse Events

9.2.1. Terms of Reported Adverse Events

All AEs will be documented in the eCRF according to the eCRF Completion Guidelines. Documentation should include onset and resolution/stabilization dates, severity/grade, relationship to study drug, and outcome of the event. However, all SAEs must be reported on an SAE form as per the SAE form completion guidelines, as well as in the eCRF.

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

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

9.2.2. Severity of Adverse Events

The NCI-CTCAE Version 5.0 will be used to grade the severity of AEs.

9.2.3. Causal Relationship with Study Drug

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

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

9.2.4. Outcome of Adverse Events

Record the outcome of AEs as follows:

- Resolved
- Not resolved
- Fatal

9.2.5. Follow-up of Adverse Events

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

- The AE has resolved or stabilized
- Completion of safety follow-up visit
- Start of new antitumor therapy
- Withdrawal of consent

- Death
- Other (eg, transfer to another hospital)

9.3. Laboratory Assessments

9.3.1. Reporting and Evaluation of Laboratory Test Results

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

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

The NCI-CTCAE Version 5.0 will be used to grade the severity of laboratory data.

9.3.2. Repeat Testing

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

9.4. Serious Adverse Events

9.4.1. Definitions of Serious Adverse Events

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

- Results in death
  - Death due to disease progression or relapse is not considered an SAE unless the investigator deems it possibly related to the study drug.
- Is life-threatening
  - The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization to treat the AE.
- The following are not considered hospitalizations for the purposes of assessing seriousness (however, one of the other serious criteria may apply):
  - Emergency room visits < 24 hours;
  - Hospitalizations for preplanned procedures;
  - Hospitalization for study-related treatment and procedures.

- Results in persistent or significant disability/incapacity, where disability is defined as a substantial disruption of a person's ability to conduct normal life functions, either reported or defined as per clinical judgment.
- Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child).
- Is any other important medical event that based upon appropriate medical judgement may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definitions above. (eg, may not result in death, be life-threatening, or require hospitalization).

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

All SAEs occurring from the time the ICF is signed through the Safety Follow-up Period (90 days after the last dose of study drug or discontinuation of the Safety Follow-up Period, whichever is earlier) must be reported to Sponsor's Pharmacovigilance group or its designee **within 24 hours** from the time the Investigator first becomes aware of the SAE.

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

After the initial SAE notification to the Sponsor's Pharmacovigilance group or its designee, all follow-up SAE information will be submitted each time they become available (for example, clinical diagnosis, outcome, causality assessment, results of specific investigations) on a follow up SAE form. The Investigator also must submit further information if it is required by the Sponsor or the director of the study site or an institutional review board (IRB)/independent ethics committee (IEC). Every SAE should be followed until it has resolved, stabilized, or returned to baseline.

9.4.3. Reporting of Deaths (within 24 hours)

All deaths (except disease progression) occurring from the time the ICF is signed through the Safety Follow-up Period (90 days after the last dose of study drug or discontinuation, whichever is earlier) must be reported within 24 hours from the time the Investigator first becomes aware of the death. The primary cause of the death should be reported as the SAE term, if available, and entered on the death page of the eCRF.

9.5. Other Safety Information

9.5.1. Pregnancy

If a patient inadvertently becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information in a female patient (or for the female partner of a male patient) should be reported **as soon as possible** from the time the Investigator first becomes aware of a pregnancy or its outcome. This should be performed by completing a Pregnancy Form and faxing or e-mailing it to Sponsor's Pharmacovigilance or designee.

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

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

9.5.2. Overdose

For this study, an overdose of futibatinib is defined as the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose of pembrolizumab will be defined as any dose of 1000 mg or ≥5 times the indicated dose. 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 via faxing or emailing to Sponsor's Pharmacovigilance or designee within 24 hours from the time the Investigator first becomes aware of its occurrence.

No specific information is available on the treatment of overdose of pembrolizumab or futibatinib; there is no known antidote in the case of futibatinib overdose. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

9.5.3. Pembrolizumab Events of Clinical Interest

Selected non-serious and SAEs are also known as Events of Clinical Interest (ECI) for pembrolizumab, and must be reported to the Sponsor.

Events of clinical interest for this trial include:

1. an overdose of pembrolizumab, as defined in Section 9.5.2, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the ULN and an elevated total bilirubin lab value that is greater than or equal to 2X the ULN and, at the same time, an ALP lab value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and ALP that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study Investigators and the Sponsor Medical Monitor. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

For dose modification and other guidelines related to events of interest for both pembrolizumab and futibatinib, please see Section 5.3 of this protocol.

10. CCI EVALUATION

10.1. CCI Assessments

Patients will be enrolled based on local assessment of FGFR mutation status; however, tissue samples (if available from fresh biopsy [preferred] or archived tissue collected after termination of the last therapeutic regimen) will be archived for central retrospective confirmation.

On-study collection of tumor tissue and blood/plasma will be performed from patients who consent, according to the schedule in Table 1.

CCI

11. STATISTICAL CONSIDERATIONS

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

11.1. Estimation of Sample Size

Approximately 20 patients will be enrolled in Cohort A. Sample size considerations are based on differentiating a historical control ORR per RECIST 1.1 of 35% or less, with a target ORR per RECIST 1.1 of 65%. Assuming the true ORR per RECIST 1.1 is 65%, the cohort has an approximate 80% power to reject the null hypothesis that the true ORR per RECIST 1.1 is ≤35%, considering a 2-sided alpha of 10%. With a sample size of 20, observing at least 12 responders will have a 90% CI lower bound excluding 10% (ORR per RECIST 1.1 of 60% with 90% CI (39.4% - 78.3%)).

Approximately 20 patients will be enrolled in Cohort B. Sample size considerations are based on differentiating a historical control ORR per RECIST 1.1 of 25% or less, with a target ORR per RECIST 1.1 of 50%. Assuming the true ORR per RECIST 1.1 is 50%, the cohort has an approximate 80% power to reject the null hypothesis that the true ORR per RECIST 1.1 is ≤25%, considering a 2-sided alpha of 10%. With a sample size of 20, observing at least 9 responders will have a 90% CI lower bound excluding 10% (ORR per RECIST 1.1 of 45% with 90% CI (25.9% - 65.3%)).

11.2. Planned Interim Analyses

The first interim analysis of safety will be performed after the 6-patient safety lead-in period; a second interim analysis of safety will be performed after a total of 10 patients have been enrolled (including the initial 6 patients enrolled in the safety lead-in period).

11.3. Analysis Populations

The analysis populations in the study are defined in Table 14.

Table 14: Definitions of Analysis Populations

Analysis Population	Definition
All Enrolled Population	All patients enrolled in this study
All Treated Population/Full Analysis Set	All enrolled patients in the All Enrolled Population who received at least one dose of study drug
CCI [redacted]	CCI [redacted]

11.4. Criteria for Handling of Patient Data

The criteria for handling of patient data are provided in the Statistical Analysis Plan (SAP).

11.5. Statistical Analyses

11.5.1. Demographic and Baseline Characteristics

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

11.5.2. Study Drug Administration

In the All-Treated Population, the following data will be presented separately for futibatinib and pembrolizumab by each cohort and study drug:

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

11.5.3. Efficacy Analyses

The efficacy analyses will be performed for each cohort using the All Treated Population, unless otherwise specified.

11.5.3.1. Primary Efficacy Analysis

ORR per RECIST 1.1 will be estimated with the exact 2-sided 90% confidence interval (CI). Only the evaluations before disease progression or initiation of new anticancer treatment will be used for the estimation.

11.5.3.2. Secondary Efficacy Analyses

ORR and DCR per RECIST 1.1 and iRECIST will be estimated with the exact 2-sided 95% CI. Only the evaluations before disease progression or initiation of new anticancer treatment will be used for the estimation.

DOR per RECIST 1.1 and iRECIST will be estimated only in patients with an objective response of CR or PR. Patients who are alive and progression-free as of the analysis cut-off date will be censored at their last evaluable tumor response assessment prior to initiation of any new anticancer treatment. Patients who start subsequent anticancer therapy without a prior reported

progression will be censored at the last tumor assessments prior to initiation of the subsequent anticancer therapy.

PFS per RECIST 1.1 and iRECIST will be estimated using the Kaplan-Meier method. Patients who die without a reported disease progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last tumor assessment. Patients who did not have any on-study assessments and did not die will be censored on the first dosing date. Patients who started any subsequent anticancer therapy without a prior reported progression will be censored at the last tumor assessment prior to initiation of the subsequent anticancer therapy.

Overall survival will be estimated the same as PFS. In the absence of death confirmation or for patients alive as of the OS cut-off date, survival time will be censored at the date of the last known alive date.

11.5.4. Safety Analyses

The safety analyses will be performed by each cohort and study drug using the All Treated Population.

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

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

Hematological and chemistry laboratory parameters will be graded according to the NCI-CTCAE (Version 5.0) where applicable. The worst severity grade, time to maximum Grade 3 or 4 value, and time to resolution (return to baseline grade or below) will be summarized.

A list of 12-lead ECG findings will be presented by patient.

11.5.5. CCI [redacted] Analysis

CCI [redacted] data will be listed by cohort using the All Treated Population.

11.5.6. CCI [redacted] Analysis

The CCI [redacted] analyses will be performed using the CCI [redacted] CCI [redacted]. CCI [redacted] data will be summarized descriptively as described in a separate SAP.

12. ADMINISTRATIVE CONSIDERATIONS

12.1. Protocol Compliance

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

12.2. Protocol Deviations

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

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

12.3. Protocol Amendments

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

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

12.4. Study Termination

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

12.5. Case Report Forms

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

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

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

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

12.6. Access to Source Data/Documents

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

12.6.1. Source Data/Documents

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

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

12.6.2. Access to Source Data

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

12.7. Data Handling

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

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

12.8. Responsibilities of Recordkeeping

12.8.1. Investigator and Study Site

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

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

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

12.8.2. Sponsor

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

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

12.9. Monitoring

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

12.10. Financial Disclosure

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

12.11. Compensation for Health Injury

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

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

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

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

12.12. Study Administrative Structure

The study organization details will be maintained in a supplement.

13. QUALITY CONTROL AND QUALITY ASSURANCE

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

13.1. Quality Control

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

13.2. Quality Assurance

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

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

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

14. ETHICS

14.1. Ethical Conduct of the Study

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

14.2. Written Informed Consent

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

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

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

14.3. Institutional Review Board/Independent Ethics Committee

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

15. PUBLICATION POLICY

15.1. Publication Policy

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

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

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

15.2. Secondary Use of Data

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

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

16. REFERENCES

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APPENDIX A. 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, eg, light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

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

APPENDIX B. DIETARY GUIDELINES FOR TREATMENT OF HYPERPHOSPHATEMIA

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

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

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

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

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

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

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

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

Example of CYP3A Inhibitors

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

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

Example of CYP3A Inducers

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

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

Example of Inhibitors for P-gp and BCRP

Transporters	Gene	Inhibitor

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

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

Example of Substrates for P-gp and BCRP

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

a. P-gp: (1) AUC fold-increase ≥2 with verapamil or quinidine co-administration and (2) in vitro transport by P-gp expression systems, but not extensively metabolized.
b. BCRP: (1) AUC fold-increase ≥2 with pharmacogenetic alteration of ABCG2 (421C>A) and (2) in vitro transport by BCRP expression systems.

APPENDIX D. SUMMARY OF THE IRECIST PROCESS

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For patients who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a patient on study treatment until repeat imaging is obtained (using iRECIST for patient management). This decision by the Investigator should be based on the patient's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any patient deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the patient may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir

  Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5

lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the patient will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of unconfirmed progressive disease [iUPD]), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
- An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
- Visible growth of new non-target lesions
- The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND

- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the patient continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, patients will be discontinued from study treatment.

NOTE: If a patient has confirmed radiographic progression (iCPD) as defined above, but the patient is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in the protocol and submitted to the central imaging vendor.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥ 5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication (Seymour et al. 2017).