

COMPOUNDS FOR TREATING SOLID TUMORS HAVING ACTIVATING FGFR2 GENE ALTERATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application Nos. 63/604,042, filed November 29, 2023, and 63/610,444, filed December 15, 2023, the entireties of which are incorporated herein.

TECHNICAL FIELD

[0002] The disclosure is directed to methods of treating cancer using an FGFR2 inhibitor.

BACKGROUND

[0003] The fibroblast growth factor (FGF) family of receptor tyrosine kinases is composed of four highly conserved membrane-associated proteins (FGFR1, FGFR2, FGFR3, and FGFR4) that function to regulate cellular growth, differentiation, and homeostasis. The molecular structures of the FGFRs contain an extracellular domain, transmembrane domain, and an intracellular tyrosine kinase domain. The activity of the intracellular kinase domain is modulated by interactions of the extracellular domain with members of the FGF family of ligands. Twenty-two FGF family members have been identified, eighteen of which are secreted and act as ligands for the FGFRs. Most of the FGF ligands act locally in a paracrine fashion affecting neighboring cells, while three of the FGFs (FGF19, FGF21, and FGF23) circulate in the blood and act in an endocrine fashion to regulate FGFRs in distant tissues. When activated, FGFRs stimulate multiple cellular pathways including proliferation. *See* Xie Y, Su N, Yang J, et al. FGF/FGFR signaling in health and disease. *Signal Transduct Target Ther.* 2020;5(1):181.

[0004] The four FGFRs are structurally homologous but have specific physiologic roles depending on their tissue expression and ligand interactions. The functions of these receptors are often redundant and overlapping, and include roles in embryogenesis, tissue homeostasis, tissue repair, apoptosis, and cellular migration. *See* Yue S, Li Y, Chen X, et al. FGFR-TKI resistance in cancer: current status and perspectives. *J Hematol Oncol.* 2021;14:23. Germline mutations in the receptors can be associated with genetic disorders (*e.g.*, a point mutation in FGFR3 can lead to achondroplasia, the most common form of dwarfism in humans).

[0005] In the FGFR family of receptors, oncogenic alterations can occur in the ligand-binding and transmembrane domains, acting as constitutive activators, as well as directly in the intracellular kinase domain. Likewise, in addition to mutations, oncogenesis can occur in the FGFRs through gene rearrangements and gene amplifications. Activating mutations, fusions, or amplifications trigger multiple intracellular pathways, such as the mitogen-activated protein kinase and phosphoinositide 3-kinase pathways, that are common with other oncogenes. *See* Facchinetti F, Hollebecque A, Bahleda R, et al. Facts and new hopes on selective FGFR inhibitors in solid tumors. *Clin Cancer Res.* 2020;26(4):764-74. Using next-generation sequencing (NGS) it has been shown that 7.1% of cancers have some form of FGFR alteration with gene amplification being the most common (66%), followed by activating mutations (26%). The most common cancers manifesting mutations appear to be urothelial (32%), breast (18%), endometrial (13%), lung (13%), and ovarian (9%). *See* Helsten T, Elkin S, Arthur E, Tomson BN, Carter J, Kurzrock R. The FGFR Landscape in Cancer: Analysis of 4,853 Tumors by Next-Generation Sequencing. *Clin Cancer Res.* 2016;22(1):259-67.

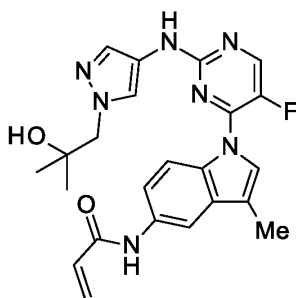
[0006] Cholangiocarcinoma is an aggressive epithelial tumor that is classified as intrahepatic, perihilar, and distal on the basis of its anatomic location in the biliary tree. *See* Rizvi S, Khan SA, Hallemeier CL, et al. Cholangiocarcinoma - evolving concepts and therapeutic strategies. *Nat Rev Clin Oncol.* 2018;15(2):95-111. Intrahepatic cholangiocarcinoma (ICC) is a rare tumor, accounting for only 3% of gastrointestinal malignancies worldwide. Diagnosis of ICC can be difficult as early-stage disease is often clinically silent and non-specific symptoms, such as dull abdominal pain, weight loss, and elevated liver enzymes, may not be present until later in the disease course. *See id.* The median overall survival for patients diagnosed with late-stage disease is less than 1 year. The incidence of ICC appears to have risen in the past several decades, although it is not clear whether this is simply due to improvements in the diagnosis of ICC, where previously some ICC may have been classified as a carcinoma of unknown primary. *See* Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol.* 2014;60(6):1268-1289.

[0007] Current approved and late-stage pan-FGFR inhibitors are susceptible to acquired resistance mutations in the gatekeeper and molecular brake of the FGFR2 kinase

domain. Resistance to FGFR2 inhibitors is often polyclonal, as detected by ctDNA in patients who progress on-treatment with current generation therapies.

[0008] Thus, a need exists for methods of treating cancers that have activating FGFR2 gene alterations using isoform-selective FGFR2 inhibitors.

[0009] The compound of Formula (I) is a highly selective inhibitor of FGFR2 that is in development for the treatment of FGFR2-driven cancers. The compound of Formula (I) has the following structure:



Formula (I).

[0010] A description of the synthesis of the compound of Formula (I) and its activity, as well as pharmaceutical compositions that may contain the compound of Formula (I) (and/or its salts), can be found in WO2022182972, which is incorporated by reference herein.

SUMMARY

[0011] The present disclosure meets the need for methods of treating cancers that have activating FGFR2 gene alterations using isoform-selective FGFR2 inhibitors by providing methods of treating cancer in a patient, wherein the methods comprise administering to the patient a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some embodiments, the cancer has an activating FGFR2 gene alteration.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Fig. 1 shows a schematic representation of the study design. Abbreviations: FGFR = fibroblast growth factor receptor; FGFR2 = fibroblast growth factor receptor 2; Dose B1 = Part B Dose 1; Dose B2 = Part B Dose 2; i3 + 3 = interval 3 + 3; ICC = intrahepatic cholangiocarcinoma.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0013] The disclosure may be more fully appreciated by reference to the following description, including the following definitions and examples. Certain features of the disclosed methods which are described herein in the context of separate aspects, may also be provided in combination in a single aspect. Alternatively, various features of the disclosed methods that are, for brevity, described in the context of a single aspect, may also be provided separately or in any subcombination.

[0014] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to the plural as is appropriate to the context and/or application. The various singular/plural permutations may be expressly set forth herein for sake of clarity. The indefinite article “a” or “an” does not exclude a plurality. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage. Any reference signs in the claims should not be construed as limiting the scope.

[0015] The term “pharmaceutically acceptable salt” refers to a salt of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compound. In several embodiments, the salt is an acid addition salt of the compound. Pharmaceutical salts can be obtained by reacting a compound with inorganic acids such as hydrohalic acid (e.g., hydrochloric acid or hydrobromic acid), sulfuric acid, nitric acid and phosphoric acid. Pharmaceutical salts can also be obtained by reacting a compound with an organic acid such as aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, benzenesulfonic, succinic, lactic, malic, tartaric, citric, ascorbic, nicotinic, methanesulfonic, ethanesulfonic, p-toluenesulfonic, salicylic or naphthalenesulfonic acid. Pharmaceutical salts can also be obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)ethylamine, C₁-C₇ alkylamine, cyclohexylamine, triethanolamine, ethylenediamine, and salts with amino acids such as arginine and lysine..

[0016] It is understood that, in any compound described herein having one or more chiral centers, if an absolute stereochemistry is not expressly indicated, then each center may

independently be of R-configuration or S-configuration or a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, enantiomerically enriched, racemic mixture, diastereomerically pure, diastereomerically enriched, or a stereoisomeric mixture. In addition, it is understood that, in any compound described herein having one or more double bond(s) generating geometrical isomers that can be defined as E or Z, each double bond may independently be E or Z a mixture thereof. It is understood that, in any compound described herein having one or more chiral centers, all possible diastereomers are also envisioned. It is understood that, in any compound described herein all tautomers are envisioned. It is also understood that, in any compound described herein, all isotopes of the included atoms are envisioned. For example, any instance of hydrogen, may include hydrogen-1 (protium), hydrogen-2 (deuterium), hydrogen-3 (tritium) or other isotopes; any instance of carbon may include carbon-12, carbon-13, carbon-14, or other isotopes; any instance of oxygen may include oxygen-16, oxygen-17, oxygen-18, or other isotopes; any instance of fluorine may include one or more of fluorine-18, fluorine-19, or other isotopes; any instance of sulfur may include one or more of sulfur-32, sulfur-34, sulfur-35, sulfur-36, or other isotopes.

[0017] A “pharmaceutically acceptable excipient” refers to a substance that is non-toxic, biologically tolerable, and otherwise biologically suitable for administration to a subject, such as an inert substance, added to a pharmacological composition or otherwise used as a vehicle, carrier, or diluent to facilitate administration of a compound of Formula (I) and that is compatible therewith.

[0018] As used herein, “subject,” “host,” “patient,” “participant,” and “individual” are used interchangeably and shall be given its ordinary meaning and shall also refer to an organism that has FGFR proteins. This includes mammals, e.g., a human, a non-human primate, ungulates, canines, felines, equines, mice, rats, and the like. The term “mammal” includes both human and non-human mammals.

[0019] The terms “treatment,” “treating,” “treat” and the like shall be given its ordinary meaning and shall also include herein to generally refer to obtaining a desired pharmacologic and/or physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of a partial or complete stabilization or cure for a disease and/or adverse effect attributable to the disease. “Treatment” as used herein shall be given its ordinary meaning

and shall also cover any treatment of a disease in a mammal, particularly a human, and includes: (a) preventing the disease or symptom from occurring in a subject which may be predisposed to the disease or symptom but has not yet been diagnosed as having it; (b) inhibiting the disease symptom, e.g., arresting its development; and/or (c) relieving the disease symptom, e.g., causing regression of the disease or symptom.

[0020] The term “administering,” when used in the context of administering a therapeutic agent to a patient, refers to introducing the therapeutic agent into the patient’s body. For example, therapeutic agents may be introduced into a patient’s body orally, nasally, subcutaneously, intravenously, intravesically, intramuscularly, transdermally, vaginally, rectally or in any combination thereof.

[0021] The terms “cancer,” “neoplasm,” and “tumor” are used interchangeably herein, shall be given its ordinary meaning and shall also refer to cells which exhibit relatively autonomous growth, so that they exhibit an aberrant growth phenotype characterized by a significant loss of control of cell proliferation. In general, cells of interest for detection or treatment in the present application include precursors, precancerous (*e.g.*, benign), malignant, pre-metastatic, metastatic, and non-metastatic cells.

[0022] As used herein, an “activating FGFR2 gene alteration” refers to a mutation, rearrangement, or amplification of the FGFR2 gene, relative to the wild-type FGFR2 gene, such that the FGFR2 gene having an activating FGFR2 gene alteration encodes an FGFR kinase that has greater FGFR2 kinase activity than the FGFR kinase that is encoded by the wild-type FGFR2 gene.

[0023] In some aspects, the disclosure is directed to methods of treating cancer in a patient, wherein the method comprises administering to the patient a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0024] In some aspects, the disclosure is directed to methods of treating cancer in a patient, wherein the method comprises administering to the patient a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and wherein the cancer has an activating FGFR2 gene alteration.

[0025] In some embodiments, the cancer is urothelial cancer, breast cancer, endometrial cancer, lung cancer, ovarian cancer, cholangiocarcinoma, or intrahepatic cholangiocarcinoma (ICC).

[0026] In other embodiments, the cancer is urothelial cancer, breast cancer, gastric cancer, endometrial cancer, lung cancer, ovarian cancer, cholangiocarcinoma, or intrahepatic cholangiocarcinoma (ICC).

[0027] In some embodiments, the cancer is gastric cancer.

[0028] In some embodiments, the cancer is urothelial cancer.

[0029] In other embodiments, the cancer is urothelial carcinoma.

[0030] In other embodiments, the cancer is breast cancer.

[0031] In other embodiments, the cancer is endometrial cancer.

[0032] In other embodiments, the cancer is lung cancer.

[0033] In other embodiments, the cancer is ovarian cancer.

[0034] In other embodiments, the cancer is cholangiocarcinoma.

[0035] In some embodiments, the cancer is intrahepatic cholangiocarcinoma (ICC).

[0036] In other embodiments, the cancer is a locally advanced solid tumor.

[0037] In other embodiments, the cancer is a metastatic solid tumor.

[0038] In some aspects of the disclosed methods, the cancer has an activating FGFR2 gene alteration.

[0039] In some embodiments, the activating FGFR2 gene alteration is a mutation. As used in this context, the term “mutation” refers to a change in the FGFR2 gene that results in the encoded FGFR2 kinase having a different amino acid sequence than the wild-type FGFR2 kinase. Methods of identifying FGFR2 mutations are known in the art.

[0040] In some embodiments, the mutation is any one or more of the following (FGFR2 numbering based on reference sequence NM_000141.5):

FGFR2 p.M537I;

FGFR2 p.V564F;

FGFR2 p.L617V;

FGFR2 p.N549D;

FGFR2 p.V564I;

FGFR2 p.K659E;

FGFR2 p.N549H;

FGFR2 p.V564L;

FGFR2 p.K659N;

FGFR2 p.N549K;
FGFR2 p.E565A;
FGFR2 p.K659M;
FGFR2 p.N549T; or
FGFR2 p.L617F.

[0041] In some embodiments, the mutation is an extracellular domain in-frame deletion.

[0042] In other embodiments, the activating FGFR2 gene alteration is a rearrangement of the FGFR2 gene.

[0043] In some embodiments, the rearrangement of the FGFR2 gene is a fusion. As used in this context, a “fusion” is a gene that results from the joining of two previously independent genes.

[0044] In other embodiments, the rearrangement of the FGFR2 gene is a C-terminal deletion.

[0045] In other embodiments, the activating FGFR2 gene alteration is a gene amplification.

[0046] In some aspects of the methods of the disclosure, the patient is administered a compound of Formula (I).

[0047] In other aspects of the methods of the disclosure, the patient is administered a pharmaceutically acceptable salt of a compound of Formula (I).

[0048] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 5 mg – 90 mg per day, such as, for example, one of 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, 25 mg/day, 30 mg/day, 35 mg/day, 40 mg/day, 45 mg/day, 50 mg/day, 55 mg/day, 60 mg/day, 65 mg/day, 70 mg/day, 75 mg/day, 80 mg/day, 85 mg/day, or 90 mg/day. In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 5 mg – 120 mg per day, such as, for example, one of 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, 25 mg/day, 30 mg/day, 35 mg/day, 40 mg/day, 45 mg/day, 50 mg/day, 55 mg/day, 60 mg/day, 65 mg/day, 70 mg/day, 75 mg/day, 80 mg/day, 85 mg/day, 90 mg/day, 95 mg/day, 100 mg/day, 105 mg/day, 110 mg/day, 115 mg/day, or 120 mg/day. In some embodiments of

the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 5 mg – 200 mg per day, such as, for example, one of 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, 25 mg/day, 30 mg/day, 35 mg/day, 40 mg/day, 45 mg/day, 50 mg/day, 55 mg/day, 60 mg/day, 65 mg/day, 70 mg/day, 75 mg/day, 80 mg/day, 85 mg/day, 90 mg/day, 95 mg/day, 100 mg/day, 105 mg/day, 110 mg/day, 115 mg/day, 120 mg/day, 125 mg/day, 130 mg/day, 135 mg/day, 140 mg/day, 145 mg/day, 150 mg/day, 155 mg/day, 160 mg/day, 165 mg/day, 170 mg/day, 175 mg/day, 180 mg/day, 185 mg/day, 190 mg/day, 195 mg/day, or 200 mg/day.

[0049] In other embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 10 mg – 200 mg per day, such as, for example, one of 10 mg/day, 15 mg/day, 20 mg/day, 25 mg/day, 30 mg/day, 35 mg/day, 40 mg/day, 45 mg/day, 50 mg/day, 55 mg/day, 60 mg/day, 65 mg/day, 70 mg/day, 75 mg/day, 80 mg/day, 85 mg/day, 90 mg/day, 95 mg/day, 100 mg/day, 105 mg/day, 110 mg/day, 115 mg/day, 120 mg/day, 125 mg/day, 130 mg/day, 135 mg/day, 140 mg/day, 145 mg/day, 150 mg/day, 155 mg/day, 160 mg/day, 165 mg/day, 170 mg/day, 175 mg/day, 180 mg/day, 185 mg/day, 190 mg/day, 195 mg/day, or 200 mg/day. When the compound of Formula (I) is administered as a pharmaceutically acceptable salt, the amount of the salt that is administered is based on the compound of Formula (I). That is, the amount of the salt that is administered is an amount that contains the specified amount of Formula (I) free base.

[0050] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 5 mg per day.

[0051] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 10 mg per day.

[0052] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 20 mg per day.

[0053] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 40 mg per day.

[0054] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 60 mg per day.

[0055] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 90 mg per day.

[0056] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 100 mg per day.

[0057] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 110 mg per day.

[0058] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 120 mg per day.

[0059] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 130 mg per day.

[0060] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 140 mg per day.

[0061] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 150 mg per day.

[0062] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 160 mg per day.

[0063] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 170 mg per day.

[0064] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 180 mg per day.

[0065] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 190 mg per day.

[0066] In some embodiments of the disclosed methods, the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 200 mg per day.

[0067] In some embodiments of the methods of the disclosure, the daily amount of the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), is administered in a single dose.

[0068] In some embodiments of the methods of the disclosure, the daily amount of the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), is given in a multiple doses, wherein each of the multiple doses contains a portion of the daily amount.

[0069] In some embodiments, the daily amount of the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), is given in two doses, wherein each of the two doses contains a portion of the daily amount.

[0070] In some embodiments, the daily amount of the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), is given in two doses, wherein each of the two doses contains one half of the daily amount.

[0071] In the methods of the disclosure, the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), may be administered by any suitable route of administration, such as, for example, orally, nasally, subcutaneously, intravenously, intravesically, intramuscularly, transdermally, vaginally, rectally or in any combination thereof.

[0072] In some embodiments, the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), is administered orally.

[0073] In the methods of the disclosure, the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), may be administered in any suitable pharmaceutical dosage form. Suitable dosage forms include, but are not limited to capsules, tablets, powders, suspensions, solutions, and the like. The pharmaceutical dosage form is typically formulated to provide a therapeutically effective amount of a compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), as the active ingredient. In some embodiments, the pharmaceutical dosage form also contains one or more pharmaceutically acceptable excipients.

[0074] In some embodiments of the disclosure, the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), is administered for at least 28 days. In some aspects, the administration is at least once daily. In some aspects, the administration is once daily.

[0075] In other embodiments of the disclosure, the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), is administered for 28 days. In some aspects, the administration is at least once daily. In some aspects, the administration is once daily.

[0076] In some aspects, the disclosed methods comprise administering the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), together with additional therapy.

[0077] In some embodiments, the additional therapy includes one or more of radiation therapy, chemotherapy, surgery (e.g., at least partial resection of the tumor).

[0078] In some embodiments, the additional therapy is chemotherapy, *i.e.*, administering one or more additional therapeutic agents.

[0079] In some embodiments, the additional therapeutic agent is a checkpoint inhibitor.

[0080] In some embodiments, the checkpoint inhibitor is a PD-1/PD-L1 inhibitor, such as, for example, one or more of pembrolizumab, nivolumab, avelumab, durvalumab, atezolizumab, cemiplimab, dostarlimab, JTX-4014, spartalizumab, camrelizumab, sintilimab, tislelizumab, toripalimab, INCMGA00012 (MGA012), AMP-224, or AMP-514 (MEDI0680).

[0081] In other embodiments, the checkpoint inhibitor is a CTLA-4 inhibitor, such as, for example, one or more of ipilimumab, tremelimumab, or AGEN-1884.

[0082] In some embodiments, the additional therapeutic agent is an antibody-drug conjugate, such as, for example, enfortumab vendotin, sacituzumab govitecan, disitamab vedotin, or Vic-trastuzumab duocarmazine (SYD985).

[0083] In other embodiments, the additional therapeutic agent is cisplatin, carboplatin, gemcitabine, docetaxel, paclitaxel, vinflunine, methotrexate, vinblastine, mitomycin, valrubicin, or doxorubicin.

[0084] In some embodiments, the additional therapeutic agent is an MEK inhibitor, such as, for example, trametinib, cobimetinib, or binimetinib.

[0085] In some embodiments, the additional therapeutic agent is a PARP inhibitor, such as, for example, olaparib, veliparib, niraparib, rucaparib, or talazoparib.

[0086] In some embodiments, the additional therapeutic agent is an HER2 inhibitor, such as, for example, lapatinib, afatinib, AZD8931, AST-1306, AEE-788, canertinib (CI-1033), CP724, CP714, CUDC-101, TAK-285, AC-480 (BMS-599626), dacomitinib (PF299804 PF299) (Dacomitinib), or pelitinib (EKB-569).

[0087] In some embodiments, the additional therapeutic agent is an SHP2 inhibitor, such as, for example, TNO-155, or RMC-4630.

[0088] In some embodiments, the additional therapeutic agent is an antibody.

[0089] In some embodiments, the antibody is an HER2 antibody such as one or more of trastuzumab or pertuzumab.

[0090] In some embodiments, the antibody is a bispecific antibodies such as one or more of MM-111 or ertumaxomab.

[0091] In some embodiments, the additional therapy is a biologic immunotherapy such as, for example, intravesicle BCG (*Bacillus Calmette-Guerin*).

[0092] In embodiments of the disclosed methods that comprise administering the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), together with additional therapy, the compound of Formula (I) (or salt thereof) is administered before, during, or after the administration or application of the additional therapy.

[0093] In embodiments of the disclosed methods wherein the additional therapy is a chemotherapy, the chemotherapeutic agent may be administered by any suitable route of administration, such as, for example, orally, nasally, subcutaneously, intravenously,

intravescically, intramuscularly, transdermally, vaginally, rectally, or in any combination thereof.

[0094] In some embodiments, the compound of Formula (I) (or salt thereof) is administered before administration or application of the additional therapy.

[0095] In some embodiments, the compound of Formula (I) (or salt thereof) is administered during administration or application of the additional therapy.

[0096] In some embodiments, the compound of Formula (I) (or salt thereof) is administered after administration or application of the additional therapy.

[0097] In some aspects of the methods of the disclosure, the cancer exhibits a complete response (CR) or a partial response (PR), as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, to the administration of the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I).

[0098] In some embodiments, the cancer exhibits a complete response (CR), as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, to the administration of the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I).

[0099] In other embodiments, the cancer exhibits a partial response (PR), as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, to the administration of the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I).

[00100] The Example provided below further illustrates and exemplifies the disclosed methods. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following Example.

Example

Abbreviation	Definition
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count

AST	aspartate aminotransferase
AUC	area under the curve
AUC _{0-last}	area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration
AUC _{0-∞}	area under the concentration-time curves from time zero to infinity
AUC _{Tau}	area under the plasma concentration-time curve for a dosing interval
BCRP	breast cancer resistance protein
BID	twice daily
BMI	body mass index
BOR	best overall response
BSA	body surface area
CDx	companion diagnostic
CI	confidence interval
CKD-EPI _{cr}	Chronic Kidney Disease Epidemiology Collaboration creatinine
CL/F	oral clearance
C _{max}	maximum concentration
COVID-19	coronavirus disease 2019
CR	complete response
CSR	central serous retinopathy
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CV	coefficient of variation

Abbreviation	Definition
CYP	cytochrome p450
DCR	disease control rate
DILI	drug-induced liver injury
DL	dose level
DLT	Dose Limiting Toxicity
DNA	deoxyribonucleic acid
DOR	duration of response

EAS	Efficacy-evaluable Analysis Set
EC	endometrial carcinoma
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
eGFR _{cr}	estimated glomerular filtration rate - creatinine
EIDs	extracellular domain in-frame deletions
EIU	exposure in utero
EOT	end of treatment
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HED	human equivalent dose
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HRT	hormone replacement therapy
HTD	highest tolerated dose

Abbreviation	Definition
i3 + 3	interval 3 + 3
IB	Investigator's Brochure
ICC	intrahepatic cholangiocarcinoma
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification number

INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IV	Intravenous
LBW	lean body weight
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NGS	next-generation sequencing
OAT	organic ion transporter
OATP1B1	organic ion transporting polypeptide 1B1
OCT	optical coherence tomography
ORR	overall response rate
OTC	over-the-counter
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
PR	partial response
PRN	as needed
Q12W	every 12 weeks
QD	once daily

Abbreviation	Definition
QOD	every other day
QTcF	QT interval corrected by Fridericia's formula
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RNA	ribonucleic acid
RPED	retinal pigment epithelial detachment

SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SoA	schedule of assessments
SOC	system organ class
SOP	standard operating procedure
SRC	Safety Review Committee
STD	severely toxic dose
$t_{1/2}$	apparent terminal half-life
TBil	total bilirubin
TBW	total body weight
TdP	torsades de pointes
TID	3 times daily
TKI	tyrosine kinase inhibitor
Tmax	time to reach Cmax
TRAE	treatment-related adverse event
TTR	time to response
ULN	upper limit of normal
US	United States
USM	urgent safety measure
Vd/F	volume of distribution

Study Title: A Multicenter, Open-label, First-in-Human Study of Formula (I) in Advanced Intrahepatic Cholangiocarcinoma and Other Solid Tumors with Activating FGFR2 Gene Alterations

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To characterize the safety and tolerability of Formula (I) in participants with advanced solid tumors with FGFR/FGF pathway alterations	- Incidence of DLT events during the DLT evaluation period (Cycle 1 [28 days]) - Incidence of AEs characterized by study part, cohort, seriousness, relationship to study drug, timing, and severity - Changes in clinical laboratory parameters, vital signs, ECG parameters, and physical examination status
Secondary	
To conduct a preliminary characterization of the PK in participants treated with Formula (I)	Single-dose and steady-state PK parameters, including but not limited to accumulation ratio, C_{max}, T_{max}, AUC_{0-last}, AUC_{Tau}, AUC_{0-∞} (after first dose only), V_d/F, CL/F, and t_{1/2}
To evaluate the preliminary antitumor activity of Formula (I) in participants with intrahepatic cholangiocarcinoma previously treated with an FGFR inhibitor who now have known kinase domain resistance mutations to FGFR inhibitors	Investigator-assessed ORR, defined as either a confirmed CR or confirmed PR by RECIST v1.1
To characterize DOR	DOR
To characterize DCR >12 weeks	DCR, defined as CR, PR, or SD for >12 weeks
To characterize TTR	TTR
Exploratory	
To identify additional biomarkers of FGFR engagement/inhibition, toxicity, tumor response, and resistance to Formula (I) in blood	Assessment of FGFR target engagement and/or inhibition using known pharmacodynamic biomarkers (serum phosphorous, calcium, FGF23, FGF19, calcitriol, and PTH), tumor response, and changes in ctDNA

Objectives	Endpoints
To evaluate concordance between tissue and ctDNA-based results for the detection of FGFR2 gene alterations	Evaluate concordance between tissue-based NGS results and central ctDNA assay for detection of FGFR2 gene alterations in participants enrolled in Parts A and B
To estimate PFS in Part B	PFS

Abbreviations: AEs = adverse events; $AUC_{0-\infty}$ = area under the concentration-time curves from time zero to infinity; AUC_{0-last} = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; AUC_{Tau} = area under the plasma concentration-time curve for a dosing interval; CL/F = oral clearance; C_{max} = maximum concentration; CR = complete response; ctDNA = circulating tumor deoxyribonucleic acid; DCR = disease control rate; DLT = Dose Limiting Toxicity; DOR = duration of response; ECG = electrocardiogram; FGF = fibroblast growth factor; FGFR = fibroblast growth factor receptor; NGS = next generation sequencing; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; PTH = parathyroid hormone; RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; SD = stable disease; $t_{1/2}$ = apparent terminal half-life; T_{max} = time to reach C_{max} ; TTR = time to response; Vd/F = volume of distribution.

Study Design:

[00101] This open-label, first-in-human study is designed to evaluate Formula (I) in participants with advanced intrahepatic cholangiocarcinoma (ICC) and other solid tumors with gene alterations of the fibroblast growth factor receptor (FGFR)/fibroblast growth factor (FGF) pathway. This is a dose-escalation/dose-expansion study to be conducted in 2 parts.

[00102] The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of Formula (I) in cancers with *FGFR2* activating gene alterations, including unresectable locally advanced/metastatic intrahepatic cholangiocarcinoma and other advanced solid tumors.

[00103] This is a single arm, multi-part, phase 1 clinical trial studying Formula (I), a novel, potent fibroblast growth factor receptor (FGFR) 1/2/3 tyrosine kinase inhibitor, in unresectable locally advanced/metastatic intrahepatic cholangiocarcinoma and other advanced solid tumors with activating alterations in *FGFR2*. Part A is a dose escalation study in participants with any advanced solid tumor with FGFR/FGF pathway alterations who have exhausted approved standard therapies. Part A evaluates the safety,

tolerability, and PK of Formula (I) to determine the optimal and maximum tolerated dose (MTD). Part B evaluates the preliminary antitumor activity of Formula (I) in participants with unresectable locally advanced/metastatic intrahepatic cholangiocarcinoma who have previously received an FGFR inhibitor and have *FGFR2* kinase-domain mutations resistant to other FGFR inhibitors.

Phase 1, Part A: Dose Escalation

[00104] Participants with any advanced solid tumor with FGFR/FGF pathway alterations (including FGFR gene mutations, fusions, and amplifications, as well as FGFR ligand amplifications) who have exhausted or refused approved standard therapies are eligible to be enrolled in Part A. Formula (I) is taken once daily by mouth in 28-day cycles starting at 5 mg daily. The Formula (I) starting dose in Part A will be 5 mg daily dose level (DL; DL1), with an anticipated dose-escalation schema as follows:

- DL1: 5 mg daily
- DL2: 10 mg daily
- DL3: 20 mg daily
- DL4: 40 mg daily
- DL5: 60 mg daily
- DL6: 90 mg daily
- In some aspects, dose escalation may increase beyond 90 mg daily, with additional doses including DL7: 100 mg daily, DL8: 110 mg daily, DL9: 120 mg/daily, DL10: 130 mg/daily, DL11: 140 mg/daily, DL12: 150 mg/daily, DL13: 160 mg/daily, DL14: 170 mg/daily, DL15: 180 mg/daily, DL16: 190 mg/daily, DL17: 200 mg/daily.

[00105] The study uses an $i3 + 3$ design with a target toxicity rate of the highest DL tested of 0.3 (0.25 to 0.33). Each DL is assessed through the DLT evaluation period (Cycle 1 [28 days]) before the next DL can be enrolled. Depending on the number of participants and the number of DLTs observed, the decision is to escalate to a higher dose or continue enrollment in the highest dose (E), stay at the same dose (S), de-escalate to the previous lower dose (D), or de-escalate to the previous lower dose and never repeat the current dose (DU).

[00106] Initial DLs proceed in an accelerated fashion, monitoring toxicity in 1 participant during the DLT evaluation period. Any $\geq$ Grade 2 AE, irrespective of relatedness to study treatment (unless there is a clear alternative cause), constitutes a DLT in these single-participant cohorts. If a DLT occurs, the dose escalation converts to $i3 + 3$ and further DLTs are determined using the standard DLT definitions in the protocol (Section 3.1.7). If no $\geq$ Grade 2 AE occurs, the next participant is enrolled to the next higher DL. Incremental escalation in single-participant cohorts is up to 100% of the previous dose until a $\geq$ Grade 2 AE is encountered, or until DL3 is completed. If DL3 is completed as a single-participant cohort, DL4 begins enrollment as $i3 + 3$.

[00107] After completion of accelerated dose escalation, all subsequent DLs use $i3 + 3$ criteria and enroll a minimum of 3 participants per DL using the standard study DLT definitions. Subsequent dose escalation increments are no more than 30 to 50% of the previous dose. Intermediate DLs also are explored. Dose escalation continues until the $i3 + 3$ criteria indicate that further dose escalation should not continue based on the incidence of DLTs at the highest DL tested.

Phase 1, Part B: Dose Expansion

[00108] Part B begins once dose escalation in Part A is completed. Dose expansion is conducted in participants with FGFR2-mutated ICC with secondary FGFR resistance mutations arising from treatment with a prior FGFR inhibitor. The purpose of Part B is to obtain additional safety data at the defined dose(s), explore pharmacodynamics and biomarkers in depth, and evaluate the preliminary anti-tumor activity of Formula (I) in participants who have benefited from, but then experienced disease progression, with a prior FGFR inhibitor due to kinase domain resistance mutations. Formula (I) is taken once daily by mouth in 28-day cycles.

[00109] Eligible FGFR2 gene mutations are listed in the table below.

Eligible On-Target Acquired Resistance Mutations for Participants in Part B

Gene Mutation		
FGFR2 p.M537I	FGFR2 p.V564F	FGFR2 p.L617V
FGFR2 p.N549D	FGFR2 p.V564I	FGFR2 p.K659E
FGFR2 p.N549H	FGFR2 p.V564L	FGFR2 p.K659N

FGFR2 p.N549K	FGFR2 p.E565A	FGFR2 p.K659M
FGFR2 p.N549T	FGFR2 p.L617F	
FGFR2 numbering based on reference sequence NM_000141.5		

[00110] Two doses are selected to be evaluated in Part B. Dose B1 is not higher than the highest tolerated dose (HTD) in Part A. Dose B2 is a lower dose, but may be an intermediate dose between 2 tolerated doses in Part A. Participants are alternatively assigned to 1 of the 2 DLs as they are enrolled. Up to 10 participants are evaluated at each DL for biomarker analysis and preliminary anti-tumor activity. Participants who receive Dose B2 with stable disease at the end of 6 cycles may be escalated to Dose B1 with medical monitor approval if they meet all other criteria for intraparticipant dose escalation as outlined in the Intra-participant Dose Escalation Decisions section below.

Intra-participant Dose Escalation Decisions

[00111] In Part A, intra-participant dose escalation is allowed for participants in lower dose cohorts under the following circumstances:

- The participant must have completed at least 2 cycles of Formula (I) and have at least 1 postbaseline tumor imaging assessment.
- A higher dose has been cleared in dose escalation and was deemed to be tolerated.
- The participant has not had a $\geq$ Grade 2 treatment-related adverse event (TRAE) on any previous cycle of Formula (I).
- A $\geq$ Grade 3 TRAE has not occurred in any participant in the DL to which the participant is to be escalated.
- In the opinion of the investigator, and with approval from the medical monitor, a higher dose under study in an enrolling or completed DL may be safe and potentially more effective in treating the participant’s tumor than the current dose.

[00112] Participants with a partial tumor response at a lower dose should remain on the lower dose. If disease progression occurs due to a newly acquired resistance mutation, the

participant may be allowed to increase to a higher dose if data suggest that the resistance mutation may respond at a higher dose of Formula (I), with medical monitor approval and they meet the criteria described in the Treatment Beyond Disease Progression section below.

Treatment Beyond Disease Progression

[00113] In both Parts A and B, participants with evidence of progressive disease (PD), as defined by RECIST v1.1, continue to receive Formula (I) if, in the opinion of the investigator and with approval from the medical monitor, the participant is deriving benefit from continuing Formula (I). The following criteria must be met in order to provide assurance that the participant is not exposed to an unreasonable risk:

- Absence of signs and symptoms indicating clinically significant progression of disease.
- No decline in Eastern Cooperative Oncology Group performance (ECOG PS).
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (eg, symptomatic pleural effusion, spinal cord compression, etc).

[00114] At the time of radiographic progression, participants are also reconsented and provided with details of all approved therapies, and potential clinical benefits that the participant may be foregoing in order to continue receiving Formula (I).

Doses are increased no more than 30 to 50% of the previous dose after accelerated dosing; intermediate doses may be explored. The SRC will oversee participant safety and determine whether the i3 + 3 criteria indicate that higher DLs should no longer be evaluated. A participant may be replaced if they do not receive at least 75% of the planned dose during the DLT evaluation period for reasons other than a TRAE or if they discontinue the study for non-DLT reasons during the DLT evaluation period.

Dose Escalation Decisions – Phase 1, Part A and B

[00115] In general, dose escalation and expansion proceed according to the i3 + 3.

[00116] If any of the study stopping criteria are met within a DL, further enrollment into that level does not proceed until all safety data from participants at that dose are reviewed. If the decision is made not to initiate a new DL before all planned prior levels are completed, it is not considered as premature study termination. Following the review of safety data, 1 of the following recommendations are made:

- To continue with the study as planned (i.e., there are no significant safety concerns) or with appropriate study amendments to address emerging safety risks.
- To continue with the study but at a dose between the current dose and the next planned dose, or at a dose between the current dose and the previous lower dose.
- To continue with the study but expand either the current DL, or a higher/lower dose, by an appropriate number of participants for a more detailed safety evaluation.
- To terminate the study.

Definition of Dose-limiting Toxicities

[00117] For an AE to qualify as a DLT it must be causally related to Formula (I) (not all causally related AEs are regarded as a DLT). A DLT is defined as any of the following occurring during Cycle 1 of a DL and regarded by the investigators and/or sponsor to be related to Formula (I). The Common Terminology Criteria for Adverse Events (CTCAE) v5.0 will be used to assess toxicities/AEs.

Hematological Dose Limiting Toxicities

- Any Grade 4 toxicity
- Absolute neutrophil count (ANC) $<500/\text{mm}^3$ for more than 7 days
- Febrile neutropenia (a disorder characterized by an ANC $<1,000/\text{mm}^3$ and a single temperature $>38.3^\circ\text{C}$ or a sustained temperature of $>38.0^\circ\text{C}$ for more than 1 hour); or Grade 3 neutropenia that lasts for more than 7 days with or without drug intervention
- Platelets $<25,000/\text{mm}^3$
- Grade 3 thrombocytopenia with any clinically significant bleeding (ie, need for medical intervention)

Nonhematologic Dose Limiting Toxicities

- Any Grade 4 toxicity, regardless of response to treatment
- Any Grade 3 toxicity, **except** the following:
 - Grade 3 nausea, vomiting, or diarrhea of <72 hours duration
 - Grade 3 fatigue for <1 week

- $\geq$ Grade 3 electrolyte abnormality (excluding hyperphosphatemia) that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions
- $\geq$ Grade 3 amylase or lipase that is not associated with symptoms or clinical or radiographic manifestations of pancreatitis
- Grade 3 hyperphosphatemia (severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated) regardless of resolution with phosphate binders will be considered a DLT
- Hy's law
 - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $>3 \times$ upper limit of normal (ULN) and
 - Total bilirubin (TBil) $>2 \times$ ULN and
 - Alkaline phosphatase $<2 \times$ ULN and
 - No other reason for liver injury
- Any AST or ALT elevation $>8 \times$ ULN regardless of duration and AST or ALT evaluation 5 to $8 \times$ ULN that persists for greater than 2 weeks – all regardless of the presence or absence of liver metastasis
- Dose delay of >14 days for the study drug due to an AE
- Any death not clearly due to the underlying disease or extraneous causes

Miscellaneous Dose Limiting Toxicities

[00118] In case an unexpected drug-related toxicity is seen more frequently, this toxicity may be declared a DLT for the remainder of the study after thorough consultation between the investigator, the sponsor, and the SRC.

[00119] Any toxicity thought to be related to Formula (I) that, at the discretion of the investigator, or their designated associate(s), is thought to warrant withholding the drug for >7 days during the DLT evaluation period. Such toxicities might be Grade 1 or Grade 2 toxicities which interfere with the activities of daily life (eg, long-lasting fatigue or anorexia), making a dose interruption/reduction necessary in order to ensure the participant's compliance. Examples may include Grade 2 nail loss or Grade 3 paronychia that does not improve after 4 weeks of supportive treatment.

[00120] In single-participant cohorts, any $\geq$ Grade 2 AE, irrespective of relatedness to study treatment (unless there is a clear alternative cause), will constitute a DLT. Following conversion to an i3 + 3 design, all subsequent dose escalation decisions use the standard study DLT definitions described above.

[00121] Results from the dose escalation and dose expansion cohorts are analyzed for safety, as well as potential relationships between dose, PK, biomarkers of target engagement, and preliminary antitumor activity of Formula (I).

Study Stopping Criteria

[00122] The study is terminated at any time if the incidence and severity of AEs in this study suggest that the risk-benefit to participants is no longer appropriate to continue the study. Examples include, but are not limited to, cases of severe liver toxicity without an underlying cause or unexplained participant deaths not due to disease progression or extraneous causes.

Study Duration

[00123] All enrolled participants receive Formula (I) until disease progression, death, unacceptable toxicity, withdrawal of participant's consent for treatment, withdrawal from the study at the discretion of the investigator, or study termination, whichever occurs first.

Planned Sample Size and Treatment Group(s):	The total number of participants enrolled depends on the number of escalation cohorts and the number of dose expansion cohorts evaluated. It is estimated that up to 20 participants could be enrolled in Part A and up to 20 participants in Part B. No formal sample size calculation was performed. The sample size in Part A is dictated by the i3 + 3 design. Expansion in Part B enrolls up to 10 participants per dose tested.
Target Population:	<i>Part A:</i> Participants with any advanced solid tumor with an FGFR/FGF pathway alteration, including FGFR gene mutations, fusions, and amplifications, as well as FGFR ligand amplifications. <i>Part B:</i> Participants with locally advanced/metastatic ICC with an oncogenic/likely oncogenic FGFR2 gene alteration previously treated with an FGFR inhibitor(s) who have defined resistance mutations in the FGFR2 kinase domain.
Eligibility Criteria:	General Study Inclusion Criteria 1. Male and female participants who are 18 years of age or older on the day of signing the informed consent form (ICF).

2. Life expectancy >12 weeks.
3. Ability to understand and willingness to sign the ICF.
4. Ability to swallow oral formulations.
5. Adequate organ and bone marrow function as demonstrated by the following:
 - a. Absolute neutrophil count $\geq 1500/\text{mm}^3$.
 - b. Platelet count $\geq 75,000/\text{mm}^3$.
 - c. International normalized ratio (INR) $\leq 1.5 \times$ upper limit of normal (ULN).
 - i. Participants treated with anticoagulants (eg, warfarin or heparin) will be allowed to participate provided no prior evidence of an underlying abnormality in these parameters exists. Close monitoring of at least weekly evaluations will be performed until INR is stable based on a predose measurement as defined by the local standard of care.
 - d. Total bilirubin (TBil) $\leq 1.5 \times$ ULN. Documented Gilbert syndrome is allowed if TBil is mildly elevated ($<6 \text{ mg/dL}$).
 - e. Alanine aminotransferase and aspartate aminotransferase $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN for participants with liver involvement of their cancer).
 - f. Serum albumin $>2 \text{ g/dL}$.
 - g. Estimated glomerular filtration rate – creatinine (eGFR_{Cr}) $\geq 60 \text{ mL/min}$ calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine (CKD-EPI_{Cr}) formula or creatinine clearance $\geq 60 \text{ mL/min}$ measured directly via 24- hour urine collection.
6. Participants and their partners should practice contraception prior to study entry and up to 180 days after the last dose of study treatment.
 - a. Women of childbearing potential must have a negative pregnancy test result within 7 days of starting Formula (I).

Specific Inclusion Criteria for Part A

7. Participants with any histologically confirmed advanced solid tumor with FGFR/FGF pathway alterations including FGFR gene mutations, fusions, and amplifications, as well as gene amplifications of FGFR ligands, who have exhausted or refused approved standard therapies.
8. Disease evaluable by RECIST v1.1.
9. ECOG PS $\leq$ 1

Specific Inclusion Criteria for Part B

10. Participants must have histologically confirmed locally advanced/metastatic intrahepatic cholangiocarcinoma with a previously identified FGFR2 gene mutation or rearrangement.
11. Participants must have received a prior FGFR inhibitor. Participants may have received more than 1 prior FGFR inhibitor.
12. Participants must also have an FGFR2 kinase domain mutation that confers resistance to previous/other FGFR inhibitors; resistance mutations should be identified by a US Food and Drug Administration authorized/approved companion diagnostic or a Clinical Laboratory Improvement Amendments validated local test performed in a certified laboratory.

Note: Participants must submit a blood sample for concordance testing using the sponsor-designated ctDNA assay. These results of the sponsor's ctDNA test do not need to be available before dosing.

13. At least 1 measurable lesion by RECIST v1.1.
14. ECOG PS $\leq$ 1.

General Study Exclusion Criteria

1. Participant has received chemotherapy, targeted therapy, immunotherapy, or an investigational therapy within 4 weeks (within 6 weeks for nitrosoureas and mitomycin) or 5 half-lives, whichever is shorter, before the first dose of study treatment.
2. Participant has not recovered from reversible toxicity of prior anticancer therapy to $<$ Grade 1 or baseline (except toxicities that are not clinically significant, including but not limited to, alopecia, skin discoloration, or Grade 1 neuropathy).

3. Participant discontinued a prior anti-FGFR therapy due to significant toxicity, defined as hepatotoxicity $\geq$ Grade 3 or any Grade 4 toxicity according to Common Terminology Criteria for Adverse Events v5.0.
4. Had major surgery within 4 weeks prior to enrollment.
5. Any reason that, in the view of investigator, would substantially impair the ability of the participant to comply with study procedures and increase the risk to the participant. Examples include poorly controlled diabetes (glycated hemoglobin $>8\%$) and ongoing active infection requiring intravenous antibiotics.
6. Females who are pregnant, breastfeeding, or planning to become pregnant within 180 days after the last dose of Formula (I) and males who plan to father a child while enrolled in this study or within 180 days after the last dose of Formula (I).
7. Has impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions.
8. Has persistent serum phosphorous level $>$ ULN during screening (within 14 days of treatment and prior to Cycle 1, Day 1) that remains $>$ ULN despite medical management with phosphate binders.
9. Any ocular condition which, in the opinion of the investigator, is likely to increase the risk of eye toxicity. Examples include:
 - a. History of or current evidence of central serous retinopathy (CSR; including $\geq$ Grade 2 CSR while receiving a prior FGFR inhibitor) or retinal vascular occlusion.
 - b. Active wet, age-related macular degeneration.
 - c. Diabetic retinopathy with macular edema.
 - d. Uncontrolled glaucoma (per local standard of care).
10. History of or current uncontrolled cardiovascular disease including:
 - a. Unstable angina, myocardial infarction, or known congestive heart failure Class II to IV within the preceding 12 months.
 - b. Cerebrovascular accident or transient ischemic attack within the preceding 3 months.

c. Pulmonary embolism within the preceding 3 months.

11. Risk factors associated with QT interval prolongation and torsades de pointes (TdP):

a. Repeated demonstration of baseline QT interval corrected by Fridericia's formula (QTcF) >470 msec.

Note: If the screening electrocardiogram (ECG) demonstrates QTcF >470 msec, ECGs may be repeated in triplicate. If the average QTcF of the triplicate ECGs is <470 msec, the participant may be enrolled.

b. Family history of prolonged QT syndrome.

c. Conditions that increase the risk of TdP, such as hypokalemia, hypomagnesemia, and heart failure.

Note: hypokalemia and/or hypomagnesemia may be corrected and repeated and, if potassium and magnesium levels are within normal limits, the participant may be enrolled.

12. Active, symptomatic, or untreated brain metastases.

a. Prior brain metastases treated at least 4 weeks prior to signing the full-study ICF or that are clinically and radiographically stable for at least 1 month prior to Cycle 1, Day 1 and do not require chronic corticosteroid treatment are allowed.

13. Gastrointestinal disorders that will affect oral administration or absorption of Formula (I).

14. Known human immunodeficiency virus (HIV) infection, or active hepatitis B or C infection.

a. Participants with a history of HIV on antiviral therapy with undetectable viral load by polymerase chain reaction (PCR) are allowed.

b. Participants with a history of hepatitis B virus infection with positive hepatitis B surface antibody, or positive hepatitis B core antibody with a negative PCR test, or active hepatitis B virus infection receiving active antiviral therapy with adequate viral suppression per institutional standards, are allowed.

c. Participants with hepatitis C infection previously treated with antiviral therapy and negative for hepatitis C virus by PCR are allowed.

15. History of a second primary malignancy within 3 years of signing the ICF (except definitively treated early-stage cancer such as resected skin cancers and/or completely resected prostate cancer, cervical intraepithelial neoplasia, differentiated thyroid cancer, ductal carcinoma in situ, or other cancer of no clinical significance in the opinion of the investigator).
16. Does not meet local COVID-19 vaccination and testing requirements (if any).
17. Known allergy to Formula (I) or any excipients of the formulated product.
18. Concomitant use of the following medications:
 - a. Strong and moderate cytochrome p450 (CYP)3A4 inhibitors;
 - b. Strong and moderate inducers of CYP3A;
 - c. Inhibitors and inducers of P-glycoprotein and breast cancer resistance protein;
 - d. Gastric acid reducing agents.

Specific Exclusion Criteria for Part B

19. Participants with ICC who had primary progression on a prior FGFR inhibitor therapy, defined as disease progression within <6 months of starting a prior FGFR inhibitor with no tumor response and no evidence of an FGFR2 resistance mutation in ctDNA or tumor biopsy.

Note: Participants who had an initial response to an FGFR inhibitor, defined as a partial response (PR), or stable disease (SD) for >6 months, may be enrolled with medical monitor approval if they had primary progression on a second and/or third FGFR inhibitor due to a known FGFR2 resistance mutation.

**Study
Drug(s):**

Formula (I) as a solution at 1 mg/mL concentration and filled into 60 cc high density polyethylene bottles. The participants are provided with a press-in-bottle adapter and an oral dosing syringe to withdraw the required amount of solution, based on the dose, from the bottle for dosing.

Participants are instructed to take Formula (I) at the same time of day each day. Formula (I) should be administered in the fasted state, at

least 1 hour before and 2 hours after ingesting food. On Cycle 1, Day 1 and Cycle 1, Day 15, Formula (I) should be administered after a ≥ 2 -hour fast and participants should remain fasted for ≥ 2 hours after administration.

	Screening	Cycle 1 ^a			Cycle 2 ^a		Cycles 3 to 12 ^a	Cycle 13 Onward ^a	EOT ^a	Safety Follow-up ^b	Survival Follow-up ^c
	Day -28 to -1	C1D1	C1D8	C1D15	C2D1	C2D15	CXD1	CXD1	Final Visit	28 Days After Last Dose	Every 3 Months
Time window	-	-	± 1 day	± 2 days	± 3 days	± 3 days	± 3 days	± 3 days	± 7 days	+7 days	± 15 days
Administrative											
Informed consent	X	-	-	-	-	-	-	-	-	-	-
Contact IRT	X	X	-	-	X	-	X	X	X	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-
Medical history and oncology history	X	-	-	-	-	-	-	-	-	-	-
Prior and concomitant medication review	X	X ^d	-	X	X	X	X	X	X	-	-
Dispense Formula (I) and distribute reminder cards ^e	-	X	-	-	X	-	X	X	-	-	-
Assess compliance	-	-	-	-	X	-	X	X	-	-	-
Safety follow-up	-	-	-	-	-	-	-	-	-	X	-
Survival status	-	-	-	-	-	-	-	-	-	-	X
Subsequent anticancer therapy	-	-	-	-	-	-	-	-	-	X	X

Safety assessments											
Height	X	-	-	-	-	-	-	-	-	-	-
Weight	X	X ^d	-	X	X	X	X	X	X	-	-
Physical examination and vital signs ^f	X	X ^d	X	X	X	X	X	X	X	-	-
ECOG PS	X	X	-	-	X	-	X	X	X	-	-

	Screening	Cycle 1 ^a			Cycle 2 ^a		Cycles 3 to 12 ^a	Cycle 13 Onward ^a	EOT ^a	Safety Follow-up ^b	Survival Follow-up ^c
	Day -28 to -1	C1D1	C1D8	C1D15	C2D1	C2D15	CXD1	CXD1	Final Visit	28 Days After Last Dose	Every 3 Months
Time window	-	-	±1 day	±2 days	±3 days	±3 days	±3 days	±3 days	±7 days	+7 days	±15 days
ECG (and as indicated) ^g	X	X ^h	-	X ^h	X ^h	-	X ^h (C3 D1, C4 D1, C5 D1)	-	X ^h	-	-
Ophthalmologic examination (and as indicated) ⁱ	X	-	-	-	-	-	X ^j	X ^j	-	-	-
Amsler grid	-	X ^d	-	-	X	-	X ^k	X ^k	-	-	-
Adverse event review and evaluation	X	X	X	X	X	X	X	X	X	X	-
Local laboratory tests											
Hematology ^l	X	X ^d	-	X	X	-	X	X	X	-	-
Serum chemistry ^m	X	X ^d	X	X	X	X	X	X	X	-	-

Pregnancy testing (female participants of childbearing potential only) ⁿ	X	Xd	-	-	X	-	X	X	X	-	-
Viral hepatitis serology ^o	X	-	-	-	-	-	-	-	-	-	-
Efficacy assessments											
Radiologic/imaging assessment ^p	Xq	-	-	-	-	-	Xr	Xs	Xt	-	-
Sample collection (for central processing)											
PK sampling ^a	-	Xv	-	Xv	Xv	-	Xu (C3 D1, C4 D1, C5 D1)	-	-	-	-
Pharmacodynamic sampling (blood) ^v	-	Xd	-	X	X	-	-	-	-	-	-
ctDNA sampling (blood) ^w	Xw	Xw	-	Xw	Xw	-	Xw	Xw	Xw	-	-
Archived tumor tissue ^x	X	-	-	-	-	-	-	-	-	-	-

1 cycle = 4 weeks (28 days).

- ^a Unscheduled visits are held at any time, at the investigator's discretion, and appropriate clinical assessments and laboratory measurements are performed based on adverse events or other findings. Data and results should be entered in the electronic case report form. A PK blood sample is to be collected at any unscheduled visit due to an adverse event. The last study drug administration date and time, and the PK sampling time (24-hour clock time) should be accurately recorded.

- b Participants are followed up for safety (via telephone or video contact) 28 days (+7 days) after the last dose of study drug. Subsequent anticancer therapy is also collected.
- c Participants are followed up for survival every 3 months (± 15 days) until the participant withdraws consent for further participation, is lost to follow-up, has died, or study closure. Contact may be performed via telephone, video, email, or certified mail. Subsequent anticancer therapy is also collected.
- d The following assessments and local laboratory samples required at C1D1 may be performed within 2 days prior to C1D1: concomitant medicine review; physical exam including weight; Amsler grid; laboratory samples (hematology, serum chemistry, pregnancy testing); and pharmacodynamic blood sampling.
- e Distribution of reminder cards should be documented in the source.
- f A full physical examination is performed at screening only. Targeted physical examinations are performed from C1D1 onwards. Vital signs include body temperature, respiratory rate, sitting radial pulse rate, and sitting systolic and diastolic blood pressures.
- g ECGs are transmitted from the site electronically to the sponsor-designated central vendor for "collect and hold." In the event of Formula (I) dose reduction for the management of QT interval prolongation, repeat triplicate ECGs should be performed at 1, 4, and 8 weeks after resuming Formula (I).
- h Scheduled triplicate 12-lead ECGs are performed within 10 minutes prior to PK blood draws on C1D1 (predose, 15 and 30 minutes and 1, 2, 4, 8, and 24 hours postdose; C1D15 (predose, 15 and 30 minutes and 1, 2, 4, 8, and 24 hours postdose; C2D1 (predose), C3D1 (predose), C4D1 (predose), and C5D1 (predose).
- i Evaluation includes noncontact intraocular pressure, slit lamps, fundus examinations, and optical coherence tomography. Changes in vision during treatment should be referred for ophthalmologic examination.
- j Ophthalmologic examination are performed at screening, C3D1 (± 7 days), on Day 1 (± 7 days) of every 3 cycles thereafter (ie, C6D1, C9D1, C12D1, etc), and as clinically indicated.
- k Amsler grid are performed on all CxD1 visits without a scheduled ophthalmology examination (ie, C1D1, C2D1, C4D1, C5D1, C7D1, C8D1, etc).
- l Complete blood count with platelets and international normalized ratio (international normalized ratio only at screening and for monitoring, as needed, for anticoagulation).

- m Albumin, alanine aminotransferase, alkaline phosphatase, amylase, aspartate aminotransferase, bicarbonate, bilirubin (direct, indirect, and total), blood urea nitrogen/urea nitrogen, calcium, chloride, creatinine, gamma-glutamyl transpeptidase, glucose, lactate dehydrogenase, lipase, phosphorus, potassium, total protein, and sodium.
- n Urine pregnancy testing, for female participants of childbearing potential only, is performed at Screening and on Day 1 of each cycle, as per local requirements. A positive urine pregnancy test result at screening is confirmed by serum testing.
- o Hepatitis B virus and hepatitis C virus testing required at screening. Hepatitis B virus testing includes hepatitis B surface antigen, hepatitis B core antibody total, and hepatitis B DNA PCR if either hepatitis B surface antigen or hepatitis B core antibody test results are positive. Hepatitis C virus testing includes hepatitis C antibody, and hepatitis C RNA PCR if the hepatitis C antibody test result is positive.
- p The preferred tumor imaging assessment modality is computed tomography with intravenous contrast; however, noncontrast computed tomography of the chest and magnetic resonance imaging of the abdomen and pelvis are permitted if intravenous contrast is clinically contraindicated. Screening and postbaseline efficacy assessments are performed using the same imaging method.
- q Baseline tumor assessment is completed within 28 days prior to the first dose of study drug. It is recommended to perform computed tomography of the chest, abdomen, pelvic cavity, and any other location where disease is present at baseline; additional tumor imaging evaluation must be performed if clinically indicated or if suspicious lesions are identified in other areas. Baseline brain magnetic resonance imaging is not required unless there is a prior history of brain metastases or neurologic symptoms suggestive of new brain metastases.
- r Every 8 weeks (C3D1, C5D1, C7D1, C9D1, C11D1, and C13D1) with a window of ± 7 days.
- s Every 12 weeks, starting at C13D1 (C16D1, C19D1, etc) with a window of ± 7 days.
- t If study drug is discontinued due to reasons other than documented disease progression (eg, toxicity), radiologic/imaging assessments should continue as planned until initiation of subsequent treatment or withdrawal from the study.
- u PK blood sample collection on C1D1 (predose, 15 and 30 minutes and 1, 2, 4, 8, and 24 hours postdose), C1D15 (predose, 15 and 30 minutes and 1, 2, 4, 8, and 24 hours postdose), and C2D1 (predose). PK blood samples on C1D1 and C1D15 collected predose and 15 and 30 minutes and 1 and 2 hours postdose are to be collected in a fasted state (≥ 2 -hour fast) and the date and time of the last meal prior to predose PK blood samples are to be recorded. For all PK samples, the actual study drug administration time and PK sampling time (24-hour clock time) should be accurately

recorded. Additional sparse PK collection will continue with predose triplicate ECGs on C3D1, C4D1, and C5D1.

- v Blood samples for circulating biomarkers are collected predose at C1D1, C1D15, and C2D1. Blood biomarkers include, but are not limited to, FGF23, parathyroid hormone, calcitriol, FGF19, matrix metalloproteinase-1, matrix metalloproteinase-10, and fibroblast growth factor binding protein 1.
- w ctDNA sample collection at screening (anytime), C1D1 (anytime), C1D15 (anytime), C2D1 (anytime), C3D1 (anytime), C5D1 (anytime), C7D1 (anytime), C9D1 (anytime), C11D1 (anytime), C13D1 (anytime), C16D1 (anytime), C19D1 (anytime), and Q12W thereafter, and at EOT (anytime). Note: A new C1D1 sample does not have to be collected if the screening sample was collected within 3 days of C1D1.
- x Archival tumor biopsy for participants in Part A with FGFR2 gene alterations only and all participants in Part B. An archival tumor biopsy sample must be provided, if available; however, no new biopsy is required if an archival sample is not available. Alternatively, a redacted report documenting the FGFR2 gene alteration from a US Food and Drug Administration approved test or Clinical Laboratory Improvement Amendments validated assay may be submitted.

Abbreviations: COVID-19 = Coronavirus Disease 2019, ctDNA = circulating tumor deoxyribonucleic acid, CxDx = Cycle x, Day x, DNA = deoxyribonucleic acid;

ECG = electrocardiogram, ECOG PS = Eastern Cooperative Oncology Group Performance Status, EOT = end of treatment, FGF = fibroblast growth factor, FGFR = fibroblast growth factor receptor, IRT = interactive response technology, PCR = polymerase chain reaction, PK = pharmacokinetic; Q12W = every 12 weeks; RNA = ribonucleic acid.

Screening is the interval between signing the ICF and the day the participant is enrolled in the study (Cycle 1, Day 1). The screening visit is to occur within 28 calendar days prior to the start of study drug administration.

For each participant, the treatment period continues in 4-week cycles (ie, 28 days) until disease progression, unless the participant fulfills 1 of the discontinuation of treatment criteria.

The safety follow-up period is the interval between the EOT visit and the scheduled follow-up visit, which should occur 28 to 35 days after the EOT visit (or after the last dose of study drug if the EOT visit was not performed).

Once a participant has completed the safety follow-up visit and/or starts a new anticancer therapy, the participant will move into the survival follow-up period and should be contacted

by telephone, video call, email, or visit at least every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

Primary Endpoint(s):	• Phase 1 Part A: To determine the maximum tolerated dose (MTD) of Formula (I). [Time Frame: Initiation of study treatment through 28 Days] • Phase 1 Part B: To determine the optimal dose of Formula (I) in participants with unresectable locally advanced or metastatic intrahepatic cholangiocarcinoma who have previously received an FGFR inhibitor and have FGFR2 kinase-domain mutations resistant to other FGFR inhibitors. [Time frame: Initiation of study treatment through 28 days (up to approximately 18 months)] • Incidence of DLT events during the DLT evaluation period (Cycle 1 [28 days]) • Incidence of AEs characterized by study part, cohort, seriousness, relationship to study drug, timing, and severity • Changes in clinical laboratory parameters, vitalsigns, ECG parameters, and physical examination status
Secondary Endpoint(s):	1. Number of participants with adverse events (AEs) and serious adverse events (SAEs) as a measure of safety and tolerability. [Time Frame: From day 1 treatment through 28-days post treatment (up to 2 years).] 2. Frequency in changes in laboratory parameters and physical signs of toxicity. [Time Frame: From day 1 treatment through 28-days post treatment (up to 2 years).] 3. Pharmacokinetics: maximum plasma concentration (C_{max}) [Timeframe: From Day 1 through Cycle 3 Day 1 (each cycle is 28 days)] 4. Pharmacokinetics: time to reach maximum plasma concentration T_{max} [Timeframe: From Day 1 through Cycle 3 Day 1 (each cycle is 28 days)] 5. Pharmacokinetics: area under the plasma concentration-time curve (AUC)

[Timeframe: From Day 1 through Cycle 3 Day 1 (each cycle is 28 days)]

6. Pharmacokinetics: half-life of Formula (I) ($t_{1/2}$)
[Timeframe: From Day 1 through Cycle 3 Day 1 (each cycle is 28 days)]
7. ORR, defined as the proportion of participants with complete response (CR) or partial response (PR) as determined by the investigator using RECIST V1.1.
[Time Frame: From enrollment, every 8 or 12 weeks (up to 2 years).]
8. Duration of response, defined as the time from the initial CR or PR to the time of relapse or death, whichever occurs first among participant with an objective response.
[Time Frame: From enrollment, every 8 or 12 weeks (up to 5 years).]
9. Disease control rate, defined as the proportion of participants having a CR, PR or stable disease (SD) for >12 weeks. [Time Frame: From enrollment up to 5 years.]
10. Time to response, defined as time to first CR or PR that is subsequently confirmed according to RECIST v1.1.
[Time Frame: Up to 5 years]
11. Progression-free survival, defined as the time from the date of first study drug administration to the earliest date of documented disease progression or death.
[Time Frame: From the date of the first dose of study drug until disease progression or death as assessed up to the last efficacy assessment for disease progression (up to 5 years)].
- Single-dose and steady-state PK parameters, including but not limited to accumulation ratio, C_{max} , T_{max} , AUC_{0-last} , AUC_{Tau} , $AUC_{0-\infty}$ (after first dose only), V_d/F , CL/F , and $t_{1/2}$

Investigator-assessed ORR, defined as either a confirmed CR or confirmed PR by RECIST v1.1

DOR

DCR, defined as CR, PR, or SD for >12 weeks

TTR

Exploratory Endpoint(s):	To identify additional biomarkers of FGFR engagement/inhibition, toxicity, tumor response, and resistance to Formula (I) in blood. Assessment of FGFR target engagement and/or inhibition using known pharmacodynamic biomarkers (serum phosphorous, calcium, FGF23, FGF19, calcitriol, and PTH), tumor response, and changes in ctDNA
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[00124] Efficacy Assessments

[00125] Baseline tumor assessment are completed within 28 days prior to the first dose of study drug. It is recommended to perform CT of the chest, abdomen, pelvic cavity, and any other location where disease is present at baseline; additional tumor imaging evaluation must be performed if clinically indicated or if suspicious lesions are identified in other areas. Baseline brain MRI is not required unless there is a prior history of brain metastases or neurologic symptoms suggestive of new brain metastases. The preferred tumor imaging assessment modality is CT with IV contrast; however, noncontrast CT of the chest and MRI of the abdomen and pelvis are permitted if IV contrast is clinically contraindicated. Baseline and postbaseline efficacy assessments are performed using the same imaging method and, as far as possible, by the same investigator (RECIST v1.1).

[00126] Tumor imaging assessment should be performed every 8 weeks (± 7 days) until Cycle 13, Day 1, and then every 12 weeks (± 7 days) thereafter, regardless of study treatment status, until disease progression, death, unacceptable toxicity, withdrawal of participant's consent for treatment, or withdrawal from the study at the discretion of the investigator, whichever occurs first. The timing of tumor imaging assessments is calculated based on the date of the first dose of study drug (ie, Cycle 1, Day 1). Participants who discontinue study drug for reasons other than disease progression or death should continue imaging assessments per the protocol-defined schedule until disease progression, death, withdrawal of participant's consent for treatment, or withdrawal from the study at the discretion of the investigator. If an imaging result shows complete response (CR) or partial response (PR) for the first time, it is necessary to repeat the tumor imaging no earlier than 4 weeks later to confirm the response.

[00127] Efficacy assessments include ORR, DCR, DOR, and TTR (RECIST v1.1).

[00128] Response Evaluation Criteria in Solid Tumors Guidelines:

[00129] The RECIST v1.1 guideline is presented below. *See Eisenhauser EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.*

[00130] Definitions

[00131] At baseline, tumor lesions/lymph nodes are categorized measurable or nonmeasurable as follows:

Measurable

[00132] Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable).
- 20 mm by chest x-ray.

[00133] Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis is measured and followed.

Nonmeasurable

[00134] All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions:

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, which can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are nonmeasurable. Cystic lesions:
- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts.
- “Cystic lesions” thought to represent cystic metastases can be considered as measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

[00135] Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

- Method of Assessment

Measurement of Lesions

[00136] All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

[00137] The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- *Clinical lesions:* Clinical lesions are only considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by

both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

- *Chest x-ray*: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- *CT, MRI*: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).
- *Ultrasound*: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 1 assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- *Endoscopy, laparoscopy*: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in studies where recurrence following CR or surgical resection is an endpoint.
- *Tumor markers*: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a participant to be considered in CR. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate-specific antigen response (in recurrent prostate cancer) have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria that are to be integrated with objective tumor assessment for use in first-line studies in ovarian cancer.
- *Cytology, histology*: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (eg, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable

tumor has met criteria for response or SD in order to differentiate between response (or SD) and PD.

[00138] Response Criteria

Evaluation of Target Lesions

- *CR*: Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to <10 mm.
- *PR*: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- *PD*: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (note: the appearance of 1 or more new lesions is also considered progression).
- *SD*: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.
- *Lymph nodes*: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the “sum” of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. eCRFs or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
- *Target lesions that become “too small to measure”*: While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scans that the radiologist may not feel comfortable assigning an exact measure and may report them as being “too small to measure.” When this occurs it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: it is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present

and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially nonreproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

- *Lesions that split or coalesce on treatment:* When non-nodal lesions “fragment,” the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as 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.”

Evaluation of Nontarget Lesions

[00139] While some nontarget lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- *CR:* Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
- *Non-CR/Non-PD:* Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
- *PD:* Unequivocal progression (see comments below) of existing nontarget lesions (note: the appearance of 1 or more new lesions is also considered progression).
- *When the participant also has measurable disease:* In this setting, to achieve “unequivocal progression” on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see further details below). A modest “increase” in the size of 1 or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.
- *When the participant has only nonmeasurable disease:* This circumstance arises in some Phase 3 studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in nonmeasurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly nonmeasurable) a useful test that can be applied when assessing participants for unequivocal progression is to consider if the

increase in overall disease burden based on the change in nonmeasurable 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 diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large,” an increase in lymphangitic disease from localised to widespread, or may be described in protocols as “sufficient to require a change in therapy.” If “unequivocal progression” is seen, the participant should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to nonmeasurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions

[00140] The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (eg, some “new” bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the participant’s baseline lesions show partial or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not. A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the participant who has visceral disease at baseline and while on study has a CT or MRI brain ordered that reveals metastases. The participant’s brain metastases are considered to be evidence of PD even if they did not have brain imaging at baseline.

[00141] If a new lesion is equivocal, eg, because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

[00142] While fluorodeoxyglucose (FDG)-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible “new” disease).

New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion (a “positive” FDG-PET scan lesion means 1, which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image).
- b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
 - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
 - If the positive FDG-PET at follow-up corresponds to a preexisting site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

[00143] Evaluation of Best Overall Response (BOR)

[00144] The BOR is the best response recorded from the start of the study treatment until the EOT taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of BOR. Protocols must specify how any new therapy introduced before progression will affect best response designation. The participant’s BOR assignment will depend on the findings of both target and nontarget disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized studies where response is the primary endpoint, confirmation of PR or CR is needed to deem either 1 as the “BOR.”

[00145] The BOR is determined once all the data for the participant is known. Best response determination in studies where confirmation of complete or PR is not required: best response in these studies is defined as the best response across all time points (eg, a participant who has SD at first assessment, PR at second assessment, and PD on last assessment has a BOR of PR).

[00146] When SD is believed to be best response, it must also meet the protocol-specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best timepoint response, the participant’s best response depends on the subsequent assessments. For example, a participant who has SD at first assessment, PD at second and

does not meet minimum duration for SD, will have a best response of PD. The same participant lost to follow-up after the first SD assessment would be considered inevaluable.

[00147] Timepoint Response: Participants with Target ($\pm$ Nontarget) Disease

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

[00148] Timepoint Response: Participants with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PR ^a
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

^a “Non-CR/non-PD” is preferred over “SD” for nontarget disease since SD is increasingly used as endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.

Abbreviations: CR = complete response, NE = not evaluable, PD = progressive disease, SD = stable disease.

[00149] Best response determination in studies where confirmation of complete or PR is required: CR or PR may be claimed only if the criteria for each are met at a subsequent timepoint as specified in the protocol (generally 4 weeks later). In this circumstance, the BOR can be interpreted as in the table below.

[00150] Best Overall Response when Confirmation of CR and PR Required

Overall Response, First Timepoint	Overall Response, Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR ^a
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

^a If a CR is truly met at first timepoint, then any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes “CR” may be claimed when subsequent scans suggest small lesions were likely still present and in fact the participant had PR, not CR at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

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

[00151] When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of “zero” on the eCRF.

[00152] In studies where confirmation of response is required, repeated “NE” timepoint assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of

response and progression. For example, in most studies it is reasonable to consider a participant with timepoint responses of PR-NE-PR as a confirmed response.

[00153] Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study drug. The objective response status of such participants is to be determined by evaluation of target and nontarget disease as shown in the tables herein.

[00154] Conditions that define “early progression, early death and inevaluability” are study-specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

[00155] In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of CR. FDG-PET may be used to upgrade a response to CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

[00156] For equivocal findings of progression (e.g., 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.

[00157] Confirmatory Measurement and Duration of Response

Confirmation

[00158] In nonrandomized studies where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error.

[00159] This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such studies. However, in all other circumstances, ie, in randomized studies (Phase 2 or 3) or studies where SD or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of study results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies that are not blinded.

[00160] In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 to 8 weeks) that is defined in the study protocol.

Duration of Overall Response

[00161] The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study).

[00162] The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

[00163] SD is measured from the start of the treatment (in randomized studies, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

[00164] The clinical relevance of the duration of SD varies in different studies and diseases. If the proportion of participants achieving SD for a minimum period of time is an endpoint of importance in a particular study, the protocol should specify the minimal time interval required between 2 measurements for determination of SD.

[00165] Note: The DOR and SD as well as the PFS are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between studies are to be made.

[00166] Pharmacokinetic assessments

[00167] Blood samples are collected for the measurement of plasma concentrations of Formula (I). Samples may be collected at additional time points during the study, if warranted and agreed upon between the investigator and the sponsor. Samples collected for analyses of Formula (I) plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. The actual date and time (24-hour clock time) of each sample is recorded. The testing of PK samples is performed by a designated bioanalytical contract research organization with a validated method.

Pharmacokinetic Blood Sample and Triplicate Electrocardiogram Timing

Study Visit	PK Sample (2 mL) Collection Timepoint	Fasted State Required (Yes/No)	Triplicate ECG ^a
C1D1	• Predose ^b	• Yes ^b	• Yes
	• 15-min postdose (±5 min) ^b	• Yes ^b	• Yes
	• 30-min postdose (±10 min) ^b	• Yes ^b	• Yes
	• 1-hour postdose (±10 min) ^b	• Yes ^b	• Yes
	• 2-hours postdose (±10 min) ^b	• Yes ^b	• Yes
	• 4-hours postdose (±10 min)	• No	• Yes
	• 8-hours postdose (±10 min)	• No	• Yes
	• 24-hours postdose (±1 hour)	• No	• Yes
C1D15	• Predose ^a	• Yes ^b	• Yes
	• 15-min postdose (±5 min) ^b	• Yes ^b	• Yes
	• 30-min postdose (±10 min) ^b	• Yes ^b	• Yes
	• 1-hour postdose (±10 min) ^b	• Yes ^b	• Yes
	• 2-hours postdose (±10 min) ^b	• Yes ^b	• Yes
	• 4-hours postdose (±10 min)	• No	• Yes
	• 8-hours postdose (±10 min)	• No	• Yes
	• 24-hours postdose (±1 hour)	• No	• Yes
C2D1	• Predose	• No	• Yes
C3D1, C4D1, C5D1	• Predose	• No	• Yes

Unscheduled visit due to an AE ^c	• Anytime during visit	• No	-
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- ^a Triplicate ECGs are to be collected within 10 minutes **before** the corresponding timed PK blood draw
- ^b Blood sample is to be collected in a fasted state at least 2-hours predose to 2-hours postdose.
- ^c A PK blood sample is to be collected at any unscheduled visit due to an AE. The last study drug administration date and time, and the PK sampling time (24-hour clock time) should be accurately recorded.
- Abbreviations: AE = adverse event; ECG = electrocardiogram; min = minutes; PK = pharmacokinetics.

[00168] The predose, 15- and 30-minutes postdose, and 1- and 2-hour postdose PK samples collected on Cycle 1, Day 1 and Cycle 1, Day 15 are to be collected in a fasted state (≥ 2 -hour fast) and the date and time of the last meal prior to predose PK blood draws are to be recorded. For all PK samples, the actual study drug administration time and PK sampling time should be accurately recorded.

[00169] Sparse PK (predose) is collected at Cycle 3, Day 1; Cycle 4, Day 1; and Cycle 5, Day 1 for all participants. As PK data become available, the collection of PK sampling may be adjusted by the sponsor, but the frequency of PK sampling does not increase.

[00170] Pharmacodynamic assessments

[00171] Blood samples are collected for the measurement of circulating biomarkers, which may include but not be limited to FGF23, parathyroid hormone, calcitriol, FGF19, matrix metalloproteinase-1, matrix metalloproteinase-10, and FGF binding protein 1, as specified in the table below.

[00172] Assessments beyond those described below may be evaluated at the discretion of the sponsor using excess biomarker or PK samples. Analyses may be conducted by sponsor-designated central laboratory.

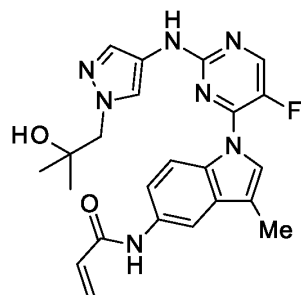
[00173]

Study Visit	Timing of Sample (2 × 10 mL)
Cycle 1, Day 1	• Predose
Cycle 1, Day 15	• Predose
Cycle 2, Day 1	• Predose

Safety Outcome Measures:	Safety is assessed by close monitoring and timely assessment of AEs, laboratory parameters (hematology, clinical chemistry), vital signs (blood pressure, heart rate), participant's medical condition (targeted physical examination including weight), ophthalmological examination, and general well-being and activities of daily life (ECOG PS).
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What is claimed:

1. A method of treating cancer in a patient in need thereof, comprising administering to the patient a compound of Formula (I),



Formula (I),

or a pharmaceutically acceptable salt thereof.

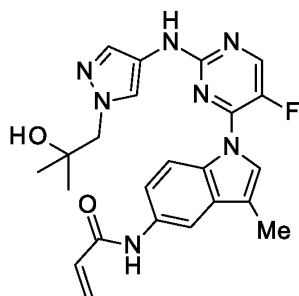
2. The method of claim 1, wherein the cancer has an activating FGFR2 gene alteration.
3. The method of claim 2, wherein the cancer is urothelial cancer, breast cancer, gastric cancer, endometrial cancer, lung cancer, ovarian cancer, cholangiocarcinoma, or intrahepatic cholangiocarcinoma (ICC).
4. The method of claim 3, wherein the cancer is urothelial cancer.
5. The method of claim 3, wherein the cancer is urothelial carcinoma.
6. The method of claim 3, wherein the cancer is breast cancer.
7. The method of claim 3, wherein the cancer is gastric cancer.
8. The method of claim 3, wherein the cancer is endometrial cancer.
9. The method of claim 3, wherein the cancer is lung cancer.
10. The method of claim 3, wherein the cancer is ovarian cancer.

11. The method of claim 3, wherein the cancer is cholangiocarcinoma.
12. The method of claim 3, wherein the cancer is ICC.
13. The method of any one of claims 1 to 12, wherein the cancer is a locally advanced solid tumor.
14. The method of any one of claims 1 to 12, wherein the cancer is a metastatic solid tumor.
15. The method of any one of claims 2 to 14, wherein the activating FGFR2 gene alteration is a mutation.
16. The method of claim 15, wherein the mutation is or comprises one or more of
FGFR2 p.M537I;
FGFR2 p.V564F;
FGFR2 p.L617V;
FGFR2 p.N549D;
FGFR2 p.V564I;
FGFR2 p.K659E;
FGFR2 p.N549H;
FGFR2 p.V564L;
FGFR2 p.K659N;
FGFR2 p.N549K;
FGFR2 p.E565A;
FGFR2 p.K659M;
FGFR2 p.N549T; or
FGFR2 p.L617F.
17. The method of claim 15, wherein the mutation is an extracellular domain in-frame deletion.

18. The method of any one of claims 2 to 14, wherein the activating FGFR2 gene alteration is a FGFR2 gene rearrangement.
19. The method of claim 18, wherein the FGFR2 gene rearrangement is a fusion.
20. The method of claim 18, wherein the FGFR2 gene rearrangement is a C-terminal deletion.
21. The method of any one of claims 2 to 14, wherein the activating FGFR2 gene alteration is a gene amplification.
22. The method of any one of claims 1 to 21, wherein the patient is administered a compound of Formula (I).
23. The method of any one of claims 1 to 21, wherein the patient is administered a pharmaceutically acceptable salt of a compound of Formula (I).
24. The method of any one of claims 1 to 23, wherein the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 5 mg – 90 mg per day.
25. The method of claim 24, wherein the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 5 mg per day.
26. The method of claim 24, wherein the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 10 mg per day.
27. The method of claim 24, wherein the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 20 mg per day.

28. The method of claim 24, wherein the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 40 mg per day.
29. The method of claim 24, wherein the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 60 mg per day.
30. The method of claim 24, wherein the patient is administered the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), in an amount of 90 mg per day.
31. The method of any one of claims 22-30, wherein the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), is administered orally.
32. The method of any one of claims 1 to 31, wherein the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), is administered for at least 28 days.
33. The method of claim 32, wherein the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), is administered for 28 days.
34. The method of any one of claims 1 to 33, wherein the cancer exhibits a complete response (CR) or a partial response (PR), as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, to the administration of the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I).
35. The method of claim 34, wherein the cancer exhibits a complete response (CR), as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, to the administration of the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I).

36. The method of claim 34, wherein the cancer exhibits a partial response (PR), as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, to the administration of the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I).
37. A compound of Formula (I), or a pharmaceutically acceptable salt thereof, for use in treating cancer in a patient in need thereof:



Formula (I).

38. The compound for use of claim 37, wherein the cancer has an activating FGFR2 gene alteration.
39. The compound for use of claim 38, wherein the cancer is urothelial cancer, breast cancer, gastric cancer, endometrial cancer, lung cancer, ovarian cancer, cholangiocarcinoma, or intrahepatic cholangiocarcinoma (ICC).
40. The compound for use of claim 39, wherein the cancer is urothelial cancer.
41. The compound for use of claim 39, wherein the cancer is urothelial carcinoma.
42. The compound for use of claim 39, wherein the cancer is breast cancer.
43. The compound for use of claim 39, wherein the cancer is gastric cancer.
44. The compound for use of claim 39, wherein the cancer is endometrial cancer.
45. The compound for use of claim 39, wherein the cancer is lung cancer.

46. The compound for use of claim 39, wherein the cancer is ovarian cancer.
47. The compound for use of claim 39, wherein the cancer is cholangiocarcinoma.
48. The compound for use of claim 39, wherein the cancer is ICC.
49. The compound for use of any one of claims 37 to 48, wherein the cancer is a locally advanced solid tumor.
50. The compound for use of any one of claims 37 to 48, wherein the cancer is a metastatic solid tumor.
51. The compound for use of any one of claims 37 to 50, wherein the activating FGFR2 gene alteration is a mutation.
52. The compound for use of claim 51, wherein the mutation is or comprises one or more of
 - FGFR2 p.M537I;
 - FGFR2 p.V564F;
 - FGFR2 p.L617V;
 - FGFR2 p.N549D;
 - FGFR2 p.V564I;
 - FGFR2 p.K659E;
 - FGFR2 p.N549H;
 - FGFR2 p.V564L;
 - FGFR2 p.K659N;
 - FGFR2 p.N549K;
 - FGFR2 p.E565A;
 - FGFR2 p.K659M;
 - FGFR2 p.N549T; or
 - FGFR2 p.L617F.

53. The compound for use of claim 51, wherein the mutation is an extracellular domain in-frame deletion.
54. The compound for use of any one of claims 37 to 50, wherein the activating FGFR2 gene alteration is a FGFR2 gene rearrangement.
55. The compound for use of claim 54, wherein the FGFR2 gene rearrangement is a fusion.
56. The compound for use of claim 54, wherein the FGFR2 gene rearrangement is a C-terminal deletion.
57. The compound for use of any one of claims 37 to 50, wherein the activating FGFR2 gene alteration is a gene amplification.
58. The compound for use of any one of claims 37 to 57, wherein the compound is a compound of Formula (I).
59. The compound for use of any one of claims 37 to 57, wherein the compound is a pharmaceutically acceptable salt of a compound of Formula (I).
60. The compound for use of any one of claims 37 to 59, wherein the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), is administered in an amount of 5 mg – 90 mg per day.
61. The compound for use of claim 60, wherein the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), is administered in an amount of 5 mg per day.
62. The compound for use of claim 60, wherein the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), is administered in an amount of 10 mg per day.

63. The compound for use of claim 60, wherein the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), is administered in an amount of 20 mg per day.
64. The compound for use of claim 60, wherein the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), is administered in an amount of 40 mg per day.
65. The compound for use of claim 60, wherein the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), is administered in an amount of 60 mg per day.
66. The compound for use of claim 60, wherein the compound of Formula (I), or a pharmaceutically acceptable salt of a compound of Formula (I) (on a Formula (I) basis), is administered in an amount of 90 mg per day.
67. The compound for use of any one of claims 58-66, wherein the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), is administered orally.
68. The compound for use of any one of claims 58 to 67, wherein the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), is administered for at least 28 days.
69. The compound for use of claim 68, wherein the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I), is administered for 28 days.
70. The compound for use of any one of claims 37 to 69, wherein the cancer exhibits a complete response (CR) or a partial response (PR), as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, to the administration of the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I).

71. The compound for use of claim 70, wherein the cancer exhibits a complete response (CR), as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, to the administration of the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I).
72. The compound for use of claim 70, wherein the cancer exhibits a partial response (PR), as evaluated by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria, to the administration of the compound of Formula (I), or pharmaceutically acceptable salt of a compound of Formula (I).