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Protocol Title

A Phase II Study of Futibatinib and Pembrolizumab in Metastatic Microsatellite Stable Endometrial Carcinoma

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1 STUDY OBJECTIVES

Fibroblast growth factor receptor (FGFR) gene aberrations occur in a wide variety of cancers including FGFR2 mutations such as D101Y, S252W, P253R, A314D, A315T, S373C, Y376C, C383R, N550K and K660E in approximately 10–16% of endometrial cancer. In addition to its driving mechanisms in tumorigenesis and metastases via activation of many intracellular signaling pathways, activation of FGFR kinases induces tumor immune suppressive microenvironment and enhances PD-L1 expression, providing a promising strategy to combine a FGFR inhibitor with immune checkpoint blockade, which is supported by preclinical researches as well as pilot clinical studies that the treatment with a FGFR inhibitor in combination with anti-PD-(L)1 therapy demonstrated synergistic antitumor activity in both FGFR wild-type and aberrant malignancies. It is noted that the combination of lenvatinib and pembrolizumab has been approved for the treatment of advanced MSS endometrial carcinoma regardless of the FGFR status. However, the fact that a significant portion of patients (70%) could not tolerate the treatment and require drug interruptions for treatment-related toxicity, urges us to develop less toxic and more effective therapeutic regimens. Therefore, we propose this pilot phase 2 study to explore the combination therapy of futibatinib with pembrolizumab in patients with metastatic microsatellite stable (MSS) endometrial carcinoma to provide a well-tolerated regimen for durable responses.

1.1 Primary Objectives

- To evaluate the objective response rate (ORR) of futibatinib and pembrolizumab in patients with metastatic microsatellite stable (MSS) endometrial carcinoma.
- To evaluate the safety and tolerability.

1.2 Primary Endpoints

- Complete responses (CRs) and partial responses (PRs) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
- Adverse events (AEs: clinical manifestations and laboratory tests) and serious adverse events (SAEs) according to the NCI Common Terminology Criteria for Adverse Events [CTCAE] version 5.0.

1.3 Exploratory Objectives

- To assess patient reported outcomes (PRO).
- To assess survivals.
- To assess changes of blood cytokines and chemokines.
- To assess circulating free DNA (cfDNA).
- To assess tumor potential biomarkers.
- To explore potential biomarkers predicting major clinical outcomes.

1.4 Exploratory Endpoints

- Self-reported symptomatic adverse events using Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™) and the 2-level version of EQ-5D (EQ-5D-3L) for the initial 6 weeks of therapy, and at the end of each cycle thereafter.
- Progression-free survival (PFS), defined as the time from the initiation of the treatment to the occurrence of disease progression or death from any cause, whichever occurs first, and overall survival (OS), defined as the time from the initiation of the treatment to death from any cause.
- Cytokine and chemokine measurement using Multiplex ELISA at baseline, prior to C2D1, and end of therapy or prior to C13D1 if still on therapy.
- Multiple IHC on tumor specimens at baseline (all), prior to C2D1 (patients at stage II), and at relapse in patients with documented SD≥6months/CR/PR.
- Next generation sequencing (NGS) on circulating DNA at baseline, prior to C2D1, and end of therapy or prior to C13D1 if still on therapy.
- NGS on tumor specimens for targeted exome panel including FGFR1-4 genetic aberrations to reveal potential biomarkers at baseline (all), prior to C2D1 (patients at stage II), and at relapse in patients with documented SD≥6months/CR/PR.
- Fisher exact or Log rank test to relate potential biomarkers with ORR, PFS, OS, PRO, and toxicity.

2 BACKGROUND AND STUDY RATIONALE

2.1 FGFR genetic aberrations in endometrial cancer

Receptor tyrosine kinase (RTK) superfamily 1 includes the EGFR, FGFR, INSR, ROR, and EPH groups 2. The fibroblast growth factor receptor (FGFR) group consists of FGFR1-4, CSF1R, VEGFR1-3, RET, KIT, FLT3, PDGFRA/B, TIE1-2, etc. 2. The fibroblast growth factor receptor (FGFR) family consists of four typical RTKs (FGFR1, 2, 3, and 4) that display different tissue distributions and roles in disease plus FGFRL1 lacks the intracellular kinase domain and has less clear function(s) 3.

FGFR gene alterations occur in ~7% of solid tumors including those of the urothelial bladder (32%), breast (18%), endometrium (13%), lung (squamous cell carcinoma 13%, and adenocarcinoma 4%), ovary (9%), glioma (8%), biliary tract (7%), and sarcoma/colon/neuroendocrine/pancreas/kidney (~4% each): FGFR1, 3.5%; FGFR2, 1.5%; FGFR3, 2%; and FGFR4, 0.5%. The majority (66%) of FGFR gene alterations involve gene amplifications, followed by mutations (26%), and rearrangements that produce fusion proteins (8%) 4. he most common FGFR alterations are demonstrated in Figure 12 and somatic mutations in Figure 2 5.

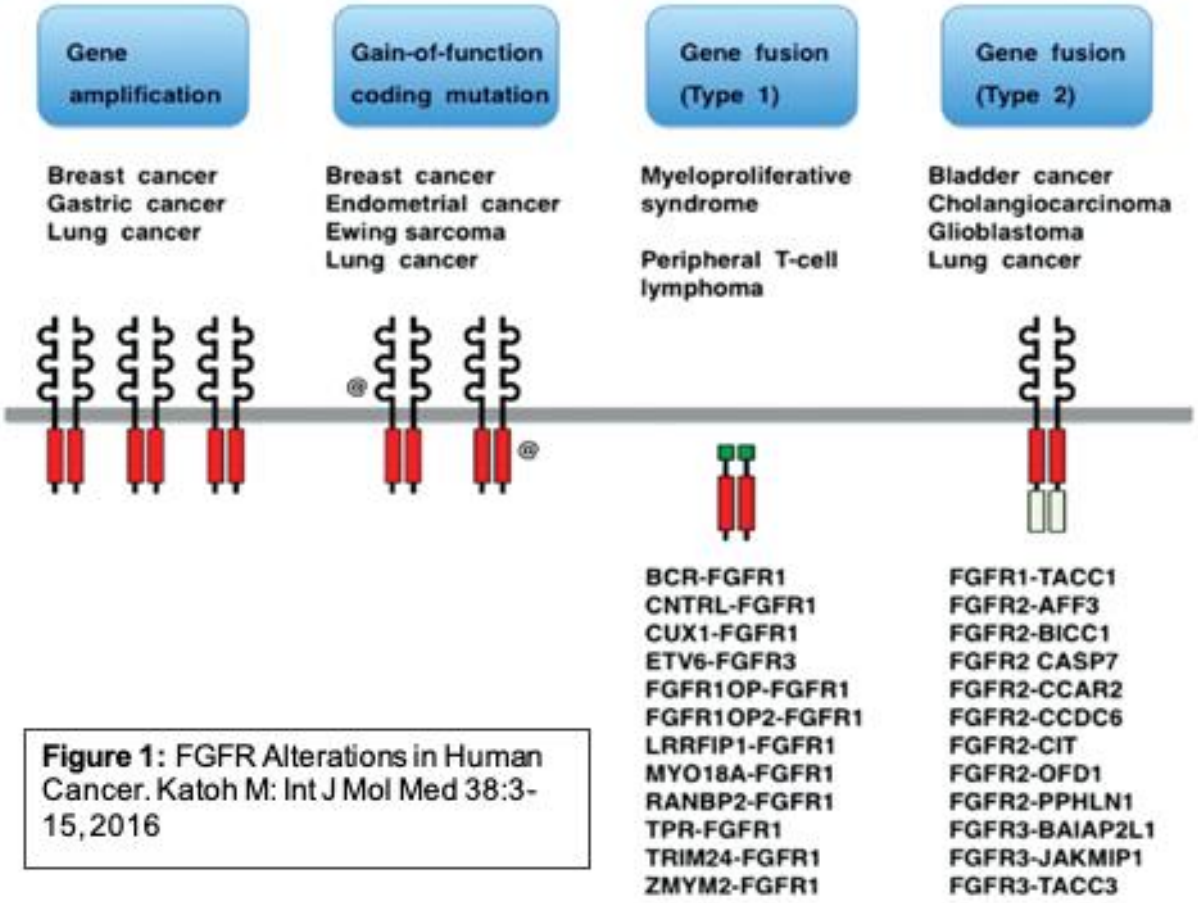

Figure 1: FGFR Alterations in Human Cancer. Katoh M: Int J Mol Med 38:3-15, 2016

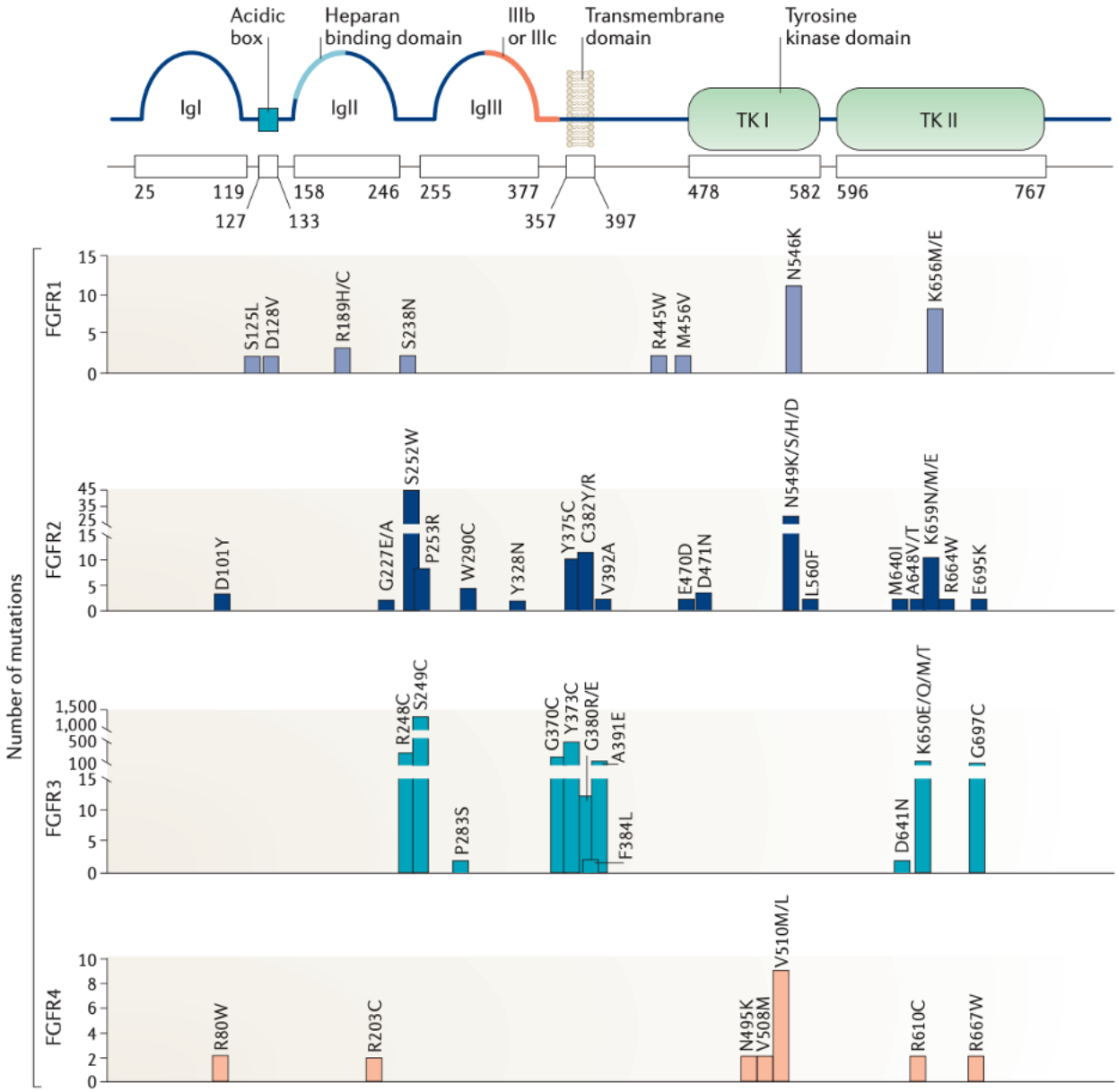

Figure 2: Somatic Mutations of FGFR. Babina IS et al: Nat Rev Cancer 17:318-32, 2017

Endometrial cancer is the most commonly diagnosed gynecologic malignancy. Although a majority of patients can be cured with surgical resection, radiation and cytotoxic chemotherapy, approximately 20% of these patients present persistent or recurrent disease. Endometrial cancer is classified into type I endometrioid endometrial carcinoma (80%) and type II non-endometrioid endometrial carcinoma (20%) with distinct genetical characterization.

While type II uterine serous carcinomas presented with similar genomic features to ovarian serous and basal-like breast carcinomas with frequent TP53, PIK3CA and PPP2R1A mutations and infrequent microsatellite instability (MSI-H), most type I endometrioid

mutations and infrequent microsatellite instability (MSI-H), most type I endometrioid endometrial cancer had few copy number alterations or TP53 mutations, but frequent mutations in PTEN, CTNNB1, PIK3CA, PIK3R1, FGFR2, ARID1A, ARID5B and KRAS [6]; as well as frequent MSI-H that is present in one third of type I endometrial cancer [7], and sensitive to immune checkpoint blockade [8]. One study conducted by NRG Oncology/Gynecologic Oncology Group revealed activating mutations in fibroblast growth factor receptor 2 (FGFR2) in type I endometrial cancer (stage I/II = 12%, and stage III/IV =17%), associated with poor clinical outcomes [9]. Frequent FGFR gene alterations include FGFR2 amplification, FGFR1 T141R and FGFR2 P253R/C382R/N549K/V677I [4].

FGFR2 mutations such as D101Y, S252W, P253R, A314D, A315T, S373C, Y376C, C383R, N550K and K660E were found in approximately 10–16% of endometrial cancer [10,11], which could be the driving force in endometrial cancer tumorigenesis. The majority of somatic FGFR2 mutations in endometrial cancer are identical to germline mutations in developmental disorders, for example craniosynostosis syndromes [12,13]. The most common FGFR2 mutation in endometrial cancer S252W occurs in the linker region between the IgII and IgIII loops, resulting in increased binding affinity of the receptor for a range of FGFs [11], and remaining on the cell surface for an extended period of time to modify protein recruitment and elevate ERK phosphorylation [14]. Mutations in the kinase domain, such as N550K, induce constitutive activation of the receptor, while others, including S373C and Y376C, result in gain of a cysteine residue, allowing formation of intermolecular disulfide bonds [13,15]. Expression of the activating mutations FGFR2N550K and FGFR2Y376C in an inability to polarize intracellular pools of FGFR2 towards the front of migrating cells [15]. All of these mutations then activate downstream signaling pathways, leading to increased cell proliferation, premature differentiation, tumorigenesis and metastases [16]

2.2 The use of FGFR inhibition for cancer therapy

The fibroblast growth factors (FGFs) family consists of 22 members: FGF15 and FGF19 are the same molecule. FGF11-14 that serve as cofactors for voltage-gated sodium channels do not interact with the transmembrane FGFRs. The 18 FGFs that interact with FGFRs are divided to 6 subfamilies based on their similar molecular structures: FGF1-2, FGF4-6, FGF3/7/10/22, FGF8/17/18, FGF9/16/20, and FGF19/21/23 [17]. Upon binding to ligands, FGFRs activate a series of RAS downstream transduction signaling pathways, such as MAPK, PI3K, JAK/STAT3, and phospholipase Cγ (PLCγ), which involve in the regulation a variety of cellular processes, including branching morphogenesis, brain patterning, wound healing, angiogenesis, bone mineralization, proliferation, differentiation, survival, and tumorigenesis [18,19].

Many FGFR inhibitors (non-selective, selective, and ligand trap/antibodies) as shown in Figure 3 and described below have been developed for cancer therapy [5, 20].

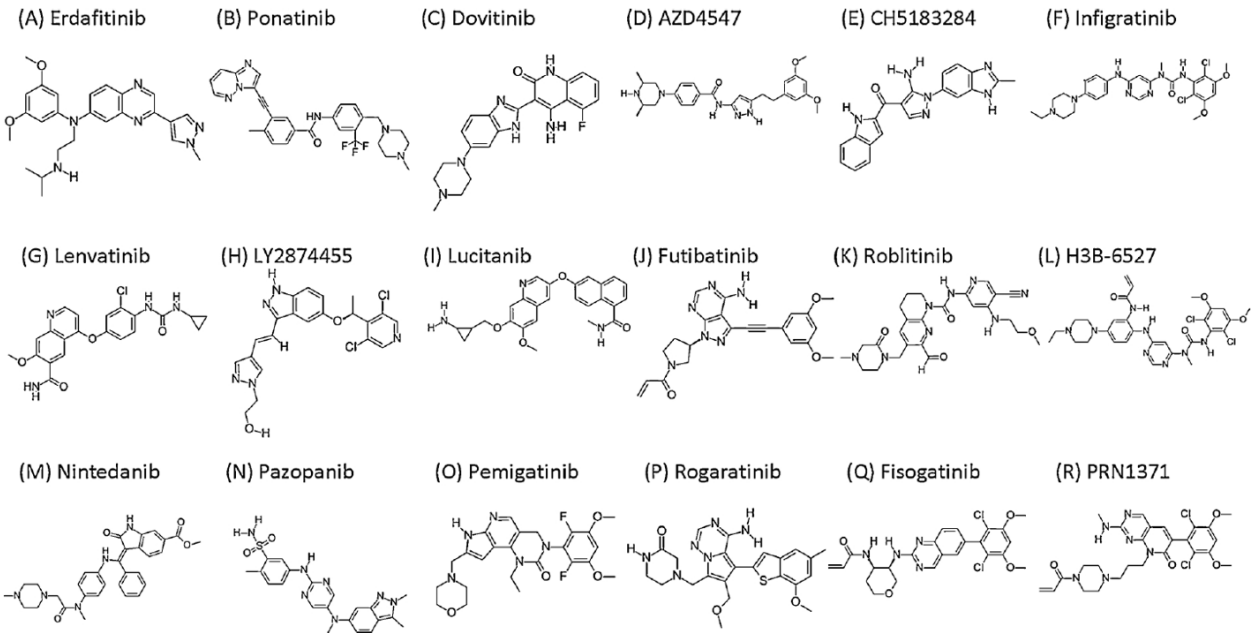

Figure 3: Structures of selected FGFR inhibitors.
Roskoski R: Pharmacological Res 151:104567, 2020

Non-selective inhibitors include dovitinib by Novartis: FLT3 (1 nM), c-KIT (2 nM); FGFR1 (8 nM), VEGFR3 (also known as FLT4) (8 nM), FGFR3 (9 nM) and VEGFR1 (also known as FLT1) (10 nM); ponatinib by ARIAD Pharmaceuticals: ABL (<1 nM), PDGFRα (1.1 nM), VEGFR2 (1.5 nM), FGFR1 (2.2 nM) and c-SRC (5.4 nM); and lucitanib by Clovis Oncology: VEGFR1 (7 nM), VEGFR3 (10 nM), FGFR1 (18 nM), VEGFR2 (25 nM) and FGFR2 (83 nM).

Selective inhibitors include AZD4547 by AstraZeneca: FGFR1 (<1 nM), FGFR3 (1.8 nM), FGFR2 (2.5 nM) and VEGFR2 (24 nM); NVP-BGJ398 by Novartis: FGFR1 (<1 nM), FGFR3

(1 nM), FGFR2 (1.4 nM), FGFR3 (K650E) (4.9 nM) and FGFR4 (60 nM); JNJ-42756493 by Janssen: FGFR1 (<1 nM), FGFR2 (<1 nM), FGFR4 (<1 nM), FGFR3 (1.05 nM) and FGFR3 (G697C) (1.9 nM); LY2874455 by Lilly: FGFR1 (2.8 nM), FGFR2 (2.6 nM), FGFR3 (6.4 nM), FGFR4 (6 nM) and VEGFR2 (7 nM); INCB054828 (pemigatinib) by Incyte: FGFR1 (0.4 nM), FGFR2 (0.5 nM), FGFR3 (1.2 nM) and FGFR4 (30 nM); TAS120 by Taiho Oncology: FGFR1 (3.9 nM), FGFR2 (1.3 nM), FGFR3 (1.6 nM) and FGFR4 (8.3 nM); Debio-1347 by Debiopharm International: FGFR2 (7.6 nM), FGFR1 (9.3 nM) and FGFR3 (22 nM).

Ligand trap and antibodies include FP-1039 by GlaxoSmithKline: FGF2; FPA114 by Five Prime Therapeutics: FGFR2-IIb; and MFGR1877S by Genentech: FGFR3.

Erdafitinib was the first orally effective FGFR antagonist approved by the FDA on April 12, 2019 for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR2* or *FGFR3* alterations, including mutation, amplification or fusion, who have progressed after at least one prior line of platinum-based chemotherapy[21]. It is a potent small-molecule selective pan-FGFR kinase inhibitor with the chemical name N-(3,5 dimethoxyphenyl)-N'-(1-methylethyl)-N-[3-(1-methyl-1H-pyrazol-4-yl) quinoxalin-6-yl] ethane-1,2 diamine and molecular formula of C25H30N6O2 [22]. Erdafitinib inhibited the kinase activity of FGFR1-4 (IC_{50} 1.2, 2.5, 3 and 5.7 nM, respectively) and demonstrated in several FGFR-expressing cell lines and tumors using xenograft mouse models [23]. Erdafitinib is orally bioavailable and has a rapid oral absorption with T_{max} of 2.5 hours, a half-life of 50 to 60 hours, low distribution volume and rapid oral clearance of 26 L and 0.26 L/h, respectively, which were not affected with high-fat or high-calorie food [24]. Over 99% of erdafitinib is bound to plasma protein, particularly to alpha-1-acid glycoprotein. After a single oral dose or erdafitinib, the majority of it was excreted in feces (69%) and in the urine (19%). The primary metabolism of erdafitinib is through CYP2C9 (39%) and CYP3A4 (20%). Patients with CYP2C9*3/*3 genotype (approximately 0.4% to 3% of the population) are expected to have 50% higher exposure and higher toxicity [22].

The overall objective responses (37% PR and 3% CR) were observed in a phase II study of patients with prespecified FGFR alterations (FGFR3 mutations, n=74; and FGFR2/3 fusion, n=25) who had progressed after at least one prior line of chemotherapy or within 12 months of adjuvant or neoadjuvant chemotherapy who received erdafitinib at 8 mg PO daily that can be increased to 9 mg PO daily in case of no side effects and serum phosphate level <5.5 mg/dL. The median duration of progression-free survival and OS were 5.5 and 13.8 months, respectively [21].

Grade 3/4 toxicities occurred in 67% of the participants of the phase II trial of erdafitinib, of which 46% were deemed to be treatment related. The most common grade 3/4 adverse events (AEs) were hyponatremia (11%), stomatitis (10%), asthenia (7%), nail dystrophy (6%), urinary tract infection (5%) and palmar-plantar erythrodysesthesia syndrome (5%). The frequency of hyperphosphatemia of all grades was 77%, with grade 3/4 hyperphosphatemia reported only in 2% of patients [21]. Ocular toxicities, including central serous retinopathy or retinal pigment epithelial detachment, were frequent, with grade 3 or higher toxicity reported in 10% of patients [22].

Pemigatinib or INCB054828, 3-(2,6-difluoro-3,5-dimethoxyphenyl)-1-ethyl-8-[(morpholin-4-yl)methyl]-1,3,4,7-tetrahydro-2Hpyrrolo[3',2':5,6]pyrido[4,3-d]pyrimidin-2-one hydrochloride, potently inhibited the kinase activity of recombinant FGFR1, FGFR2 and FGFR3 enzymes (IC50, 0.4 nM, 0.5 nM, and 1.2 nM, respectively) [20,25].

On April 17, 2020, the US FDA granted accelerated approval to pemigatinib (13.5 mg PO daily x 14 days every 21 days) for patients with advanced cholangiocarcinoma harboring FGFR2 gene fusions or rearrangements (5-8%) based on the FIGHT-202 study (n=107): an objective response of 35.5% plus stable disease of 46.7%, median progression-free survival of 6.9 months, and median overall survival of 21.1 months [26]. The most common adverse reactions are hyperphosphatemia (55%), hypophosphatemia (23%), alopecia (46%),diarrhea (34%), nail toxicity (12%), fatigue (31%), dysgeusia (38%), nausea (23%), constipation (14%), stomatitis (27%), dry eye (21%), dry mouth (29%), decreased appetite (23%), vomiting (9%), arthralgia (11%), abdominal pain (5%), back pain (7%), and dry skin (15%). Approximately 64% of patients had grade 3 or worse adverse events. The most frequent grade 3 or worse adverse events (irrespective of cause) were hypophosphatemia (12%), arthralgia (6%), stomatitis (5%), hyponatremia (5%), abdominal pain (5%), and fatigue (5%). Serous retinal detachment due to subretinal fluid accumulation was observed in 4% patients with 0.7% treatment-unrelated grade 3 ocular toxicity [26].

Futibatinib (TAS-120), 1-[(3S)-3-[4-Amino-3-[2-(3,5-dimethoxyphenyl)ethynyl]-1H-pyrazolo[3,4-d]pyrimidin-1-yl]-1-pyrrolidinyl]-2-propen-1-one, is an irreversible FGFR inhibitor that covalently binds to a highly conserved P-loop cysteine residue in the ATP pocket of FGFR (C492 in the FGFR2-IIIb isoform) [27]. It exhibits *in vitro* potency at low nanomolar concentrations and high specificity against wild-type FGFR1–4 with IC_{50} values of 3.9, 1.3, 1.6, and 8.3 nM respectively [28], as well as against some FGFR2 kinase domain mutations [29]. A phase I basket study of TAS-120 including 45 patients with refractory metastatic intrahepatic cholangiocarcinoma harboring FGF/FGFR genetic aberrations showed an ORR of 25% and a DCR of 79% in 28 patients with *FGFR2* gene fusions, and an ORR of 31% (three with FGFR2 gene fusions and one with FGFR2 amplification) in 13 patients who had received prior therapy with an ATP-competitive FGFR inhibitor [28,30].

In all, more than 460 patients and healthy volunteers have been treated with futibatinib across all trials. Collectively, safety data from these studies suggest that futibatinib is associated with manageable toxicity in multiple patient populations. The most frequently reported treatment-related AE overall has been hyperphosphatemia (a mechanism-based event), mostly of Grades 1-2 and without clinical complications. Other frequently reported treatment-related AEs included the gastrointestinal system disorders of diarrhea, dry mouth, nausea, and stomatitis. Skin toxicity and increased liver enzymes have also been reported, most of which have been mild to moderate in severity. Ocular toxicities, which have been reported with other FGFR inhibitors, were observed with low frequency in all trials (Data from NCCN/Taiho Oncology, Inc. RFP: March 4, 2020). Please see futibatinib Investigator Brochure (IB) for details.

2.3 The use of immune checkpoint blockade for cancer therapy

Accumulated genetic and epigenetic alterations in cancer cells provide a diverse set of antigens that distinguish from their normal counterparts. Immune responses are highly regulated by a balance between co-stimulatory and inhibitory pathways (immune checkpoints) under physiological conditions, which is crucial to minimize collateral tissue damage through modulating the duration and amplitude of immune responses [31]. Dysregulated immune checkpoint proteins such as CTLA4 (cytotoxic T-lymphocyte associated antigen 4, CD152), PD-1 (programmed cell death protein 1, CD279), and ICOS (inducible T-cell costimulator, CD278) play a major role in cancer escape from immune surveillance and provide the most promising approaches to activating antitumor immunity [32]. Because many of the immune checkpoints are initiated by ligand-receptor interactions, antibody blockage provides a promising strategy to overcome dysregulated immune checkpoints for cancer immunotherapy [33]. Ipilimumab, an anti-CTLA4 antibody, was the first of this class of immunotherapeutics to achieve the FDA approval for the treatment of metastatic melanoma [34-36].

Another important immune checkpoint receptor, PD-1, is emerging as a promising target to induce antitumor immune response[37-39]. Similar to CTLA4, PD-1 is highly expressed on Treg cells and enhances their proliferation in the presence of its ligands PD-L1 or L2 [38,40,41], which suppress effector immune responses [32]. In contrast to CTLA4, the major role of PD-1 is to limit the activity of T lymphocytes in peripheral tissues at the time of an inflammatory response, which translates into a major immune resistance mechanism within the tumor microenvironment [32,42,43]. PD-1 is more broadly expressed than CTLA4 and induced on B cells, natural killer (NK) cells as well as tumor-associated macrophages[44-46]. Several anti-PD-1 and anti-PD-L1 antibodies have displayed significant antitumor activities in patients with advanced non-small cell lung cancer (NSCLC), melanoma, renal cell cancer and many others[47,51].

Lambrolizumab (MK-3475, pembrolizumab), is a highly selective, humanized monoclonal IgG4-kappa isotype antibody against PD-1, carrying the variable region sequences of a very high affinity mouse antihuman PD-1 antibody with dissociation constant at 28 pM[50]. . In T-cell activation assays, the 50% effective concentration was 0.1 to 0.3 nM, inhibiting the interaction with its ligands, PD-L1 or L2. PD-L1 is typically expressed at low levels on various non-hematopoietic tissues and induced in the tumor microenvironment of various cancers[52], while PD-L2 is only detectably expressed on antigen-presenting cells in the lymphoid tissue or chronic inflammatory environments[38,53]. Pembrolizumab has demonstrated durable objective responses in patients with melanoma, NSCLC, and many other tumor types. In a phase I trial, pembrolizumab at 10 mg/kg IV every 2 weeks was safe and clinical responses were observed as low as 1 mg/kg[54]. The half-life ($T_{1/2}$) of pembrolizumab ranged from 13 to 21 days, supporting a dosing interval of every 2 or 3 weeks[54]. There was a linear dose-related increase in exposure from 1 to 10 mg/kg: serum concentrations of pembrolizumab were 5-fold higher in the patients receiving 10 mg/kg

every 3 weeks than those in the patients receiving 2 mg/kg every 3 weeks, and steady-state trough concentrations were 20% greater in the patients receiving 10 mg/kg every 2 weeks than in those receiving the same dose every 3 weeks[50].

In a clinical trial P001 of 135 patients with advanced melanoma treated with intravenous pembrolizumab, an overall clinical response of 37% (95%CI, 29-45%) was observed across all dose schedules according to immune-related response: 56% (95% CI, 42-69%) in those receiving 10 mg/kg every 2 weeks was significantly greater than 27% (95% CI, 16-40%) in those receiving 10 mg/kg every 3 weeks (p=0.002); and 14% (95% CI, 3-35%) in those receiving 2 mg/kg every 3 weeks (p<0.001) [50]. The majority of responses were seen at the time the first imaging was performed at 12 weeks. Similar responses were observed in patients who had received ipilimumab treatment and in those who had not. The median PFS was estimated to be longer than 7 months and the median OS had not been reached, and 81% of the patients who had a response were still receiving treatment at a median follow-up time of 11 months [50].

The treatment with pembrolizumab was well tolerated: most of the adverse events were low grade. Treatment-related pneumonitis was reported in 4%: none of the cases were grade 3 or higher. Other severe adverse events included elevated aminotransferase levels (<2%), renal failure (<2%), thyroid dysfunction (<1%), and diarrhea (<1%). Common adverse events attributed to pembrolizumab were fatigue, rash, pruritus, and diarrhea. The highest incidence of overall treatment-related adverse events was seen in patients receiving 10 mg/kg of pembrolizumab every 2 weeks (23%), as compared with those receiving 10 mg/kg every 3 weeks (4%), and 2 mg/kg every 3 weeks (9%) [50]. An ongoing randomized clinical trial comparing patients receiving 10 mg/kg of pembrolizumab every 2 weeks with those receiving the treatment every 3 weeks will provide valuable information to define the optimal dose schedule.

On September 4, 2014, the US FDA granted accelerated approval to pembrolizumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor based on the results of the above phase I trial P001 including additional 38 patients. Subsequently many anti-PD-1 and anti-PD-L1 antibodies have been FDA approved for cancer immunotherapy: anti-PD-1 (US FDA approved: cemiplimab, nivolumab, pembrolizumab, spartalizumab, and tislelizumab; Experimental: AMP-224, AMP-514, camrelizumab, INCMGA00012, sintilimab, and toripalimab); and anti-PD-L1 (FDA approved: atezolizumab, avelumab, and durvalumab; and Experimental: AUNP12, BMS-986189, CA-170, CK-301, and KN035).

In 24 patients with locally advanced or metastatic PD-L1-positive endometrial cancer who had experienced progression after standard therapy, the treatment with pembrolizumab achieved confirmed 13% partial responses (95% CI, 2.8% to 33.6%) with the median duration of response not reached, plus 13% stable disease with a median duration of 24.6 weeks. Pembrolizumab showed durable antitumor activity in a subgroup of patients with heavily pretreated advanced PD-L1-positive endometrial cancer [55].

2.4 Futibatinib and pembrolizumab for synergistic anticancer therapy

FGFR and Tumor Immune Microenvironment

Figure 4 showed that activation of FGFR1 induces macrophage recruitment and cytokine production, leading to protumorigenic alterations via tumor immunosuppressive microenvironment that consists of cancer, stromal and immune cells: cancer-associated fibroblasts (CAFs), endothelial cells, M2-type tumor-associating macrophages (M2-TAMs), myeloid-derived suppressor cells (MDSCs) and regulatory T cells [56,57].

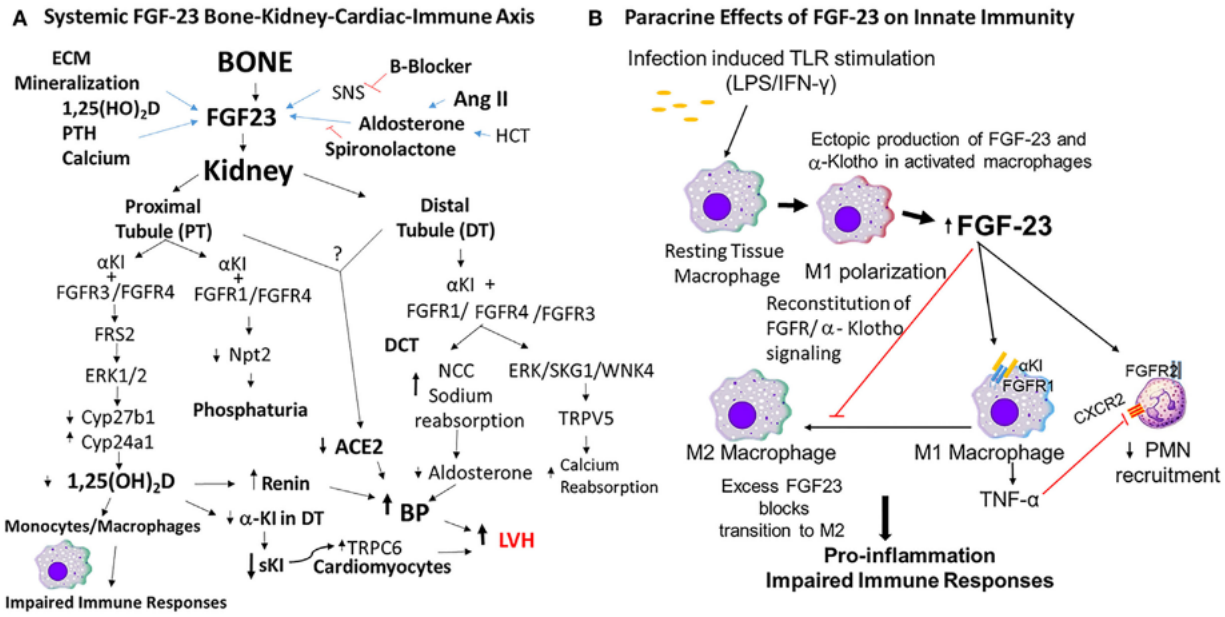

Figure 4: Mechanisms of FGF-FGFR effects to impair innate immune response.
Fitzpatrick EA et al: Front Endo 9:320, 2018 doi: 10.3389/fendo.2018.00320

FGF-23 was markedly up-regulated in LPS/INF-γ-induced proinflammatory M1 macrophages and *Hyp* (a murine model of human X-linked hypophosphatemia harboring a large deletion in the PHEX gene) mouse-derived peritoneal macrophages, but not in IL-4-induced M2 anti-inflammatory macrophages. NF-κB and JAK/STAT1 pathways mediated the increased transcription of FGF-23 in response to M1 polarization. FGF-23 stimulated TNF-α, but not IL-6, expression in M0 macrophages and suppressed arginase-1 expression in M2 macrophages through FGFR-mediated mechanisms. FGF-23 has proinflammatory paracrine functions and counter-regulatory actions to 1,25(OH)2 D on innate immune responses [57,58].

Treatment with a selective FGFR1-3 inhibitor AZD4547 not only can directly suppress the proliferation of breast cancer cell lines, but also restrain MDSCs and therefore restore immune surveillance, leading clearance of 4T1 tumor in the immune competent mice [59]. AZD4547 significantly alleviated the expression of the pro-inflammatory factors IL-1β, IL-6, TNF-α, MMP9, and CXCL10 both *in vivo* and *in vitro*. In addition, AZD4547 suppressed the proliferative activity of macrophages in lung tissue and RAW264.7 macrophages. In

addition, the LPS-induced phosphorylation of key proteins of NF-κB/MAPK/STAT3 pathways in RAW264.7 macrophages, such as p65, IκB-α, Erk1/2, JNK, and STAT3 proteins, could be inhibited by AZD4547 pretreatment [59,60].

Treatment with BGJ398, another potent selective FGFR1-3 inhibitor, resulted in rapid tumor regression, leaving a nonpalpable mass of dormant tumor cells organized into a luminal and basal epithelial layer similar to the normal mammary gland, but surrounded by dense stroma with markedly reduced levels of MDSCs and decreased tumor vasculature [61]..

FGFR and PD-L1 Expression

FGFR2 causes the tyrosine kinase domains to initiate a cascade of intracellular signals by binding to FGFs and dimerization to activate multiple signaling pathways involved in tumorigenesis and metastases [62,63]. FGFR2 expression was significantly associated with lymph node metastasis, clinical stage, and poor survival. PD-L1 expression was positively correlated with FGFR2 expression in colon cancer cells. Tumor-derived–activated FGFR2 induced PD-L1 expression via the PI3K–AKT, ERK and JAK/STAT3 signaling pathway in cancer cells as shown in Figure 5, and also promoted the expression of PD-L1 in a xenograft mouse model of colon cancer [64][64].

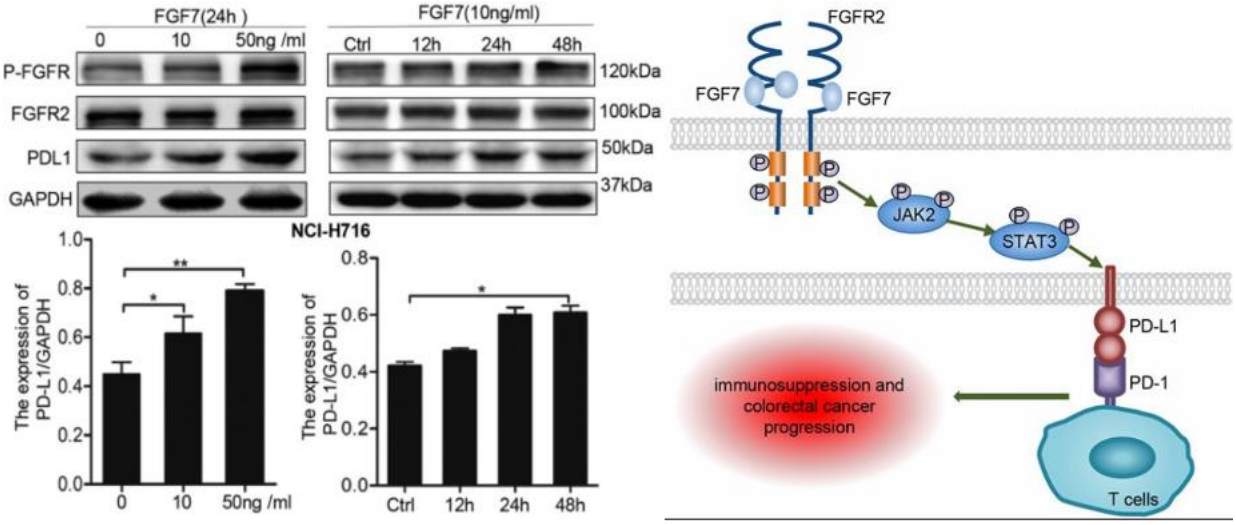

Figure 5: FGF7-FGFR2 promotes PD-L1 expression. Li P et al: J Imm 202:3065-75, 2019

Synergistic Antitumor Activity with FGFR Inhibition and Anti-PD-1

FGF-2 expression is associated with EMT and poor prognosis in primary human bladder carcinomas, promoting epithelial to mesenchymal transition (EMT) and stemness, as well as with the expression of mesenchymal markers, associated with immune checkpoint activation that overexpresses CTLA-4, PD-1 and PD-L1 in bladder carcinoma [65][65]. Although immune checkpoint activation is associated with bad prognosis, such tumors are also more likely to respond to immune checkpoint inhibitors [49][49]. In an autochthonous $FGFR2^{K660N}/p53^{mut}$ lung cancer mouse model, erdafitinib monotherapy treatment resulted in substantial tumor control but no significant survival benefit, while anti–PD-1 alone was ineffective[66]. In contrast to monotherapy, the erdafitinib and anti–PD-1 combination induced

significant tumor regression and improved survival [66], as shown in Figure 6. For both erdafitinib monotherapy and combination treatments, tumor control was accompanied by tumor-intrinsic, FGFR pathway inhibition, increased T-cell infiltration, decreased regulatory T cells, and downregulation of PD-L1 expression on tumor cells. A decreased fraction of tumor-associated macrophages also occurred but only in combination-treated tumors [66][66].

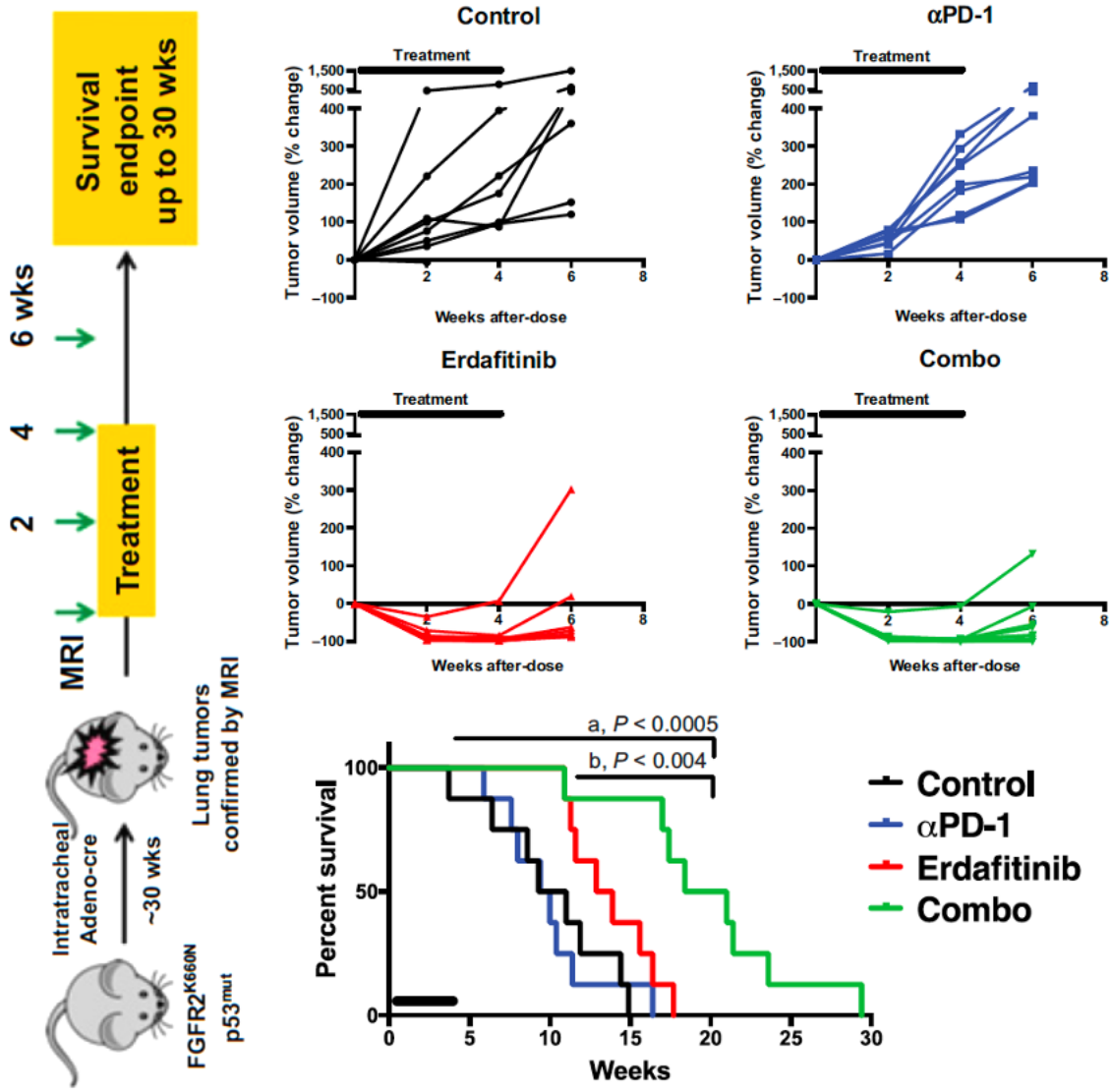

Figure 6: Antitumor response and improved survival with erdafitinib and anti-PD-1 combination. Palakurthi S et al: Cancer Immunol Res 7:1457-71, 2019

In consistence with preclinical studies, the FIERCE-22 Study of patients with metastatic urothelial carcinoma with failure to ≥ 1 prior line therapy or recurrence ≤ 12 months of (neo)adjuvant chemotherapy and anti-PD-1/L1 naïve showed that treatment with vofatamab (a fully human monoclonal antibody against FGFR3 that blocks activation of both the wildtype and genetically activated receptor) and pembrolizumab achieved similar objective responses regardless FGFR3 status (33% for wild type FGFR3 and 43% for FGFR3 mutations or fusions) [67], which compared favorably with monotherapy with either pembrolizumab [68] or vofatamab [69], as shown in Figure 7 [67].

Clinical Trial	ORR
Keynote-45 (anti-PD-1/L1 naïve)	21% (n=270)
FIERCE-21 (vofatamab in FGFR3 mut/fus)	10% (n=21)
FIERCE-22 (vofatamab + pembrolizumab)	36% (n=22)

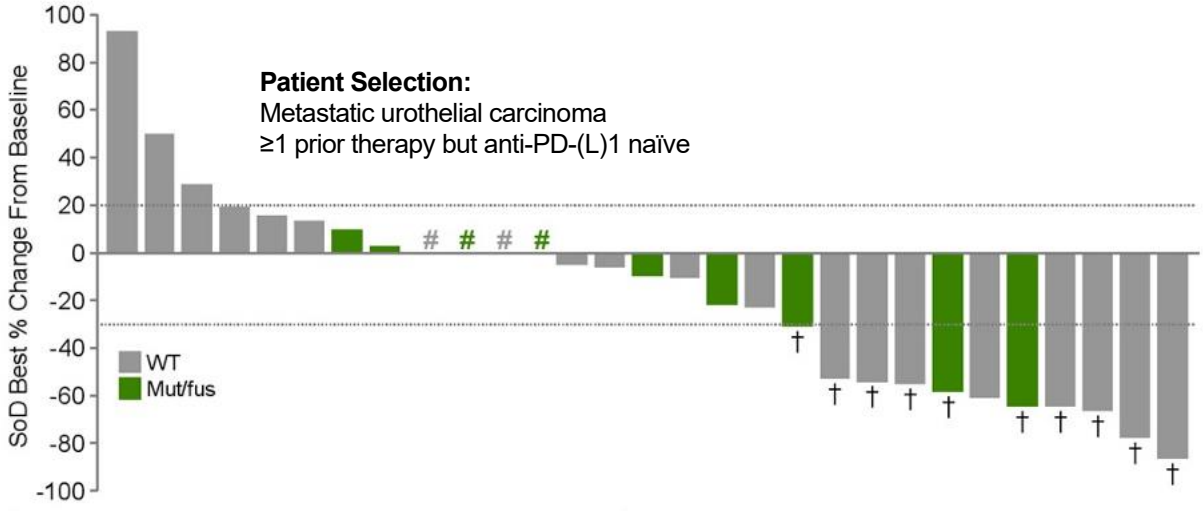

Figure 7: Responses Similar Regardless FGFR3 Status**:** WT: 33% (n=15) and MT/FUS: 43% (n=7). Siefker-Radtke A et al: ASCO 2019 Abstract #4511

Lenvatinib, a potent RTK inhibitor of VEGFR1-3, FGFR1-4, PDGFR-a, RET and KIT [70][70], modulates cancer immunity in the tumor microenvironment by reducing TAMs and, when combined with PD-1 blockade, shows enhanced antitumor activity via the IFN signaling pathway. These findings provide a scientific rationale for combination therapy of lenvatinib with PD-1 blockade to improve cancer immunotherapy [71][71].

On September 17, 2019, FDA granted accelerated approval to pembrolizumab plus lenvatinib for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation [72]. This was based on a single-arm trial of 94 patients, with previously treated metastatic endometrial cancer whose tumors were not MSI-H/dMMR (MSS: microsatellite stable). An objective response rate of 38% (95% CI: 28.5%, 48.9%) with 11% complete response was observed [73,74], which compared favorably with historically reported monotherapy with an objective response rate of 14.3% with lenvatinib [75] or 13% with pembrolizumab [55].

Grade 3 or 4 treatment-related adverse events occurred in 67% of patients. Any-grade treatment-related adverse events occurred in 97% of patients. Overall, 18% of patients discontinued one or both agents because of treatment-related toxicity (15% for lenvatinib,

12% for pembrolizumab, and 9% for both). Treatment-related toxicity such as hypertension, diarrhea, fatigue and hypothyroidism led to dose interruptions of lenvatinib and/or pembrolizumab in 70% of patients [74][74].

Current Status and Safety Overview of Ongoing Combination Studies for Futibatinib plus Pembrolizumab (Data from Taiho Oncology, Inc.)

As of June 2021, there are two Taiho sponsored clinical trials for futibatinib in combination with pembrolizumab ongoing.

- Phase 1b Study to Assess the Safety, Tolerability, and Efficacy of TAS-120 (Futibatinib) in Combination with MK-3475 (Pembrolizumab) in Patients with Solid Tumors (Protocol Number: 10059030) in Japan.
- Phase 2 Study Evaluating Futibatinib (TAS-120) Plus Pembrolizumab in the Treatment of Advanced or Metastatic Urothelial Carcinoma (Protocol TAS-120-203) in US and Europe

This document summarizes the current status, including key safety observations from both studies.

Phase 1b Study to Assess the Safety, Tolerability, and Efficacy of TAS-120 (Futibatinib) in Combination with MK-3475 (Pembrolizumab) in Patients with Solid Tumors (Protocol Number: 10059030)

Study Design:
Study 10059030 is a phase 1b, open-label, nonrandomized, multicenter study conducted in Japan. This study consists of two parts:

- **Feasibility part**: to assess the safety and tolerability of futibatinib in combination with pembrolizumab in patients with advanced or metastatic solid tumors (N = up to 38 pts planned)
- **Expansion part**: to evaluate the efficacy and safety in patients with advanced or metastatic cancer patients in each of the following three cohorts:
  - Cohort A: anti-PD-1/PD-L1 monoclonal antibody naive for advanced or metastatic esophageal carcinoma (N= 35 pts planned)
  - Cohort B: anti-PD-1/PD-L1 monoclonal antibody refractory for advanced or metastatic esophageal carcinoma (N= 35 pts planned)
    Cohort C: anti-PD-1/PD-L1 monoclonal antibody refractory for advanced or metastatic NSCLC (N= 35 pts planned)

The primary objective of this study is to assess the safety and tolerability for futibatinib in combination with pembrolizumab (feasibility part) and a preliminary evaluation of the anti-tumor activity of this combination in advanced esophageal carcinoma and NSCLC patients (expansion part).

Dose and Schedule of futibatinib and pembrolizumab

The starting dose and schedule in the feasibility part for combination treatment with futibatinib and pembrolizumab will be the RPTD of futibatinib monotherapy (i.e., 20mg once daily (QD)) and the approved dose of pembrolizumab (i.e., 200mg every 3 weeks (Q3W), respectively (Table 1). If considered intolerable during cycle 1 (21 days), a lower dose of futibatinib in combination with pembrolizumab 200mg Q3W will be explored as shown in Table 1. Dose modifications of futibatinib are not permitted during cycle 1 in the feasibility part.

Table 1: Dose Level for futibatinib and pembrolizumab for the feasibility part

Dose level	Pembrolizumab	Futibatinib
Level 1 (starting dose)	200 mg Q3W	20 mg QD
Level −1	200 mg Q3W	16 mg QD
Level −2	200 mg Q3W	12 mg QD

Based on the results observed in the feasibility part, the dose of futibatinib in combination with pembrolizumab 200mg Q3W will be determined for the expansion part.

Current Status

As of 23 January 2021, a total of 13 patients were enrolled and treated in Study 10059030. This included 11 patients enrolled in the feasibility part and 2 patients enrolled in the expansion part. All patients enrolled were treated with futibatinib 20mg QD in combination with pembrolizumab 200mg Q3W.

Safety

All 13 patients included in the analysis experienced at least 1 treatment-emergent adverse event (TEAE). No Dose limiting toxicity were observed in any of these patients. Table 2 summarizes the most common AEs (≥20% incidence rate) observed as of the cut-off date in this study regardless of relationship to study treatment.

The most frequently reported TEAE was hyperphosphatemia, with an incidence of 92.3% (including 4 patients [30.8%] with Grade ≥3 AEs defined as serum phosphate level >7mg/dl irrespective of clinical symptoms). Hyperphosphatemia is a known on-target effect of FGFR inhibitors and has been reported to a similar frequency and grade for single agent treatment with futibatinib.

Other common AEs (≥ 20% incidence rate) included constipation, diarrhea, nausea, stomatitis, decreased appetite and dermatitis acneiform.

Table 2: Adverse Events by Preferred Term All-Grade Incidence ≥20% Regardless of Relationship to Study Treatment (Safety Population)

MedDRA(ver.23.1)	TAS-120+Pembro (N=13)	
System Organ Class	All Grades	>/=Grade 3
Preferred Term	N (%)	N (%)
Any Event	13 (100.0)	7 (53.8)
Gastrointestinal disorders	13 (100.0)	1 (7.7)
Constipation	3 (23.1)	0 (0.0)
Diarrhea	7 (53.8)	0 (0.0)
Nausea	8 (61.5)	0 (0.0)
Stomatitis	6 (46.2)	0 (0.0)
Metabolism and nutrition disorders	12 (92.3)	5 (38.5)
Hyperphosphatemia	12 (92.3)	4 (30.8)
Decreased appetite	3 (23.1)	0 (0.0)
Skin and subcutaneous tissue disorders	8 (61.5)	1 (7.7)
Dermatitis acneiform	3 (23.1)	0 (0.0)

A total of 7 patients (53.8%) experienced at least 1 event of Grade ≥3 regardless of relationship to futibatinib; PTs for which the incidence of Grade ≥3 events was at least 5% comprised only hyperphosphatemia.

A total of 5 patients (38.5%) experienced at least 1 treatment-related AE of Grade ≥3. The most common of the treatment-related AE was hyperphosphatemia (n=4; 30.8%). Seven SAEs were reported for 6 patients (46.2%). Among them 3 SARs were assessed as either related to futibatinib and/or pembrolizumab in 3 patients, including 1 Grade 2 fatigue considered by the investigator to be related to futibatinib and considered by the company to be related to futibatinib and pembrolizumab in 1 patient, 1 event of Grade 3 rash considered to be related to pembrolizumab in 1 patient, and 1 event of Grade 3 Type 1 diabetes mellitus considered to be related to pembrolizumab in 1 patient.

In summary, the safety profile observed as of the cut-off date in this study for futibatinib 20mg QD in combination with pembrolizumab 200mg Q3W is largely consistent with the known safety profile for single agent futibatinib and pembrolizumab, respectively. There were no DLTs reported and beside hyperphosphatemia only few ≥ Grade 3 TEAE observed. Enrollment of further patients at the futibatinib 20mg QD plus pembrolizumab 200mg Q3W dose level into the tumor type specific expansion part is currently ongoing.

Phase 2 Study Evaluating Futibatinib (TAS-120) Plus Pembrolizumab in the Treatment of Advanced or Metastatic Urothelial Carcinoma (Protocol TAS-120-203)

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

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

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

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

The primary objective of this study is to evaluate the efficacy of futibatinib in combination with pembrolizumab as assessed by ORR according to RECIST 1.1 in UC patients. Safety and tolerability of futibatinib plus pembrolizumab is a secondary objective of this study.

Dose and Schedule of futibatinib and pembrolizumab
Futibatinib and pembrolizumab will be administered at the RPTD of futibatinib monotherapy (i.e., 20mg once daily (QD)) and the approved dose of pembrolizumab (i.e., 200mg every 3 weeks (Q3W), respectively. If considered intolerable based on incidence of unacceptable toxicity including dose-limiting toxicity during cycle 1, the study may continue with a reduced dose of futibatinib (16 mg QD) in combination with pembrolizumab 200mg Q3W.

Current Status
As of 29 May 2021, a total of 4 patients were enrolled and treated in the safety lead-in part of Study TAS-120-203. All patients enrolled were treated with futibatinib 20mg QD in combination with pembrolizumab 200mg Q3W. Out of the 4 patients enrolled, 3 patients have completed the first cycle and there have been no DLT reported. Based on investigator calls and continuous safety monitoring by the sponsor, the safety profile observed in this study for futibatinib 20mg QD plus pembrolizumab 200mg Q3W is largely consistent with the known safety profile for single agent futibatinib and pembrolizumab, respectively.

FGFR gene aberrations occur in a wide variety of cancers including FGFR2 mutations such as D101Y, S252W, P253R, A314D, A315T, S373C, Y376C, C383R, N550K and K660E in

approximately 10–16% of endometrial cancer [9-11]. In addition to its driving mechanisms in tumorigenesis and metastases via activation of many intracellular signaling pathways [20,57,62], activation of FGFR kinases induces tumor immune suppressive microenvironment and enhances PD-L1 expression, providing a promising strategy to combine a FGFR inhibitor with immune checkpoint blockade, which is supported by preclinical researches [2,19,56,64,66] aswell as pilot clinical studies [67,74]. It is noted that the combination of lenvatinib and pembrolizumab has been approved for the treatment of advanced MSS endometrial carcinoma regardless of the FGFR status [74]. However, the fact that a significant portion of patients (70%) could not tolerate the treatment and require drug interruptions for treatment- related toxicity [74] urges us to develop less toxic and more effective therapeutic regimens.

Therefore, we propose this pilot phase 2 study to explore the combination therapy of futibatinib with pembrolizumab in patients with metastatic MSS and FGFR aberrant endometrial carcinoma to provide a well-tolerated regimen for durable responses.

3 PATIENT SELECTION

3.1 Inclusion Criteria

To be eligible for this trial, patients must meet all of the following eligibility criteria.

1. Patients with histologically confirmed locally advanced or metastatic endometrial carcinoma that is not amenable to curative surgical- or radiation-based intervention, who have received or declined at least one-line systemic chemotherapy.

2. Known microsatellite stable (MSS) and *FGFR1-4* aberration (activating mutations or amplification) as pre-identified in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory

3. At least one measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

4. Age ≥18 years.

5. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test prior to administration of the first dose of futibatinib within 7 days prior to initiation of therapy (C1D1), and must agree to use effective birth control initiated immediately following negative serum pregnancy test during screening period, during the study, and for at least 180 days after the last dose (or longer based on local requirements). Female patients are not considered to be of child-bearing potential if they are post-menopausal (no menses for 12 months without an alternative medical cause) or permanently sterile (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).

6. Adequate organ functions as defined below:
   - Absolute neutrophil count (ANC) ≥ 1,000 /μL.
   - Hemoglobin (Hb) ≥ 9 g/dL.
   - Platelets ≥ 75,000 /μL.
   - Total bilirubin ≤ 1.5 x ULN (upper limit of normal); or total bilirubin < 3 x ULN with direct bilirubin ≤ ULN in patients with well documented Gilbert's Syndrome.
   - ALT ≤ 3 x ULN or ≤ 5 x ULN if liver metastases persist.
   - Serum phosphate ≤ 1.5 x ULN.
   - Serum calcium ≤ ULN.
   - Serum albumin ≥ 3 g/dL.
   - Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance (CrCl) ≥ 40 mL/min by the Cockcroft-Gault method* or 24-hour urine collection.

   *CrCl = (140-age) x (weight [kg]) x 0.85 / (72 x serum creatinine mg/dL)

7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

8. No prior combination treatment with anti-PD-(L)1 therapy and a FGFR inhibitor.

9. Ability to read and fully understand the requirements of the trial, willingness to comply with all trial visits and assessments, and willingness and ability to sign an institutional review board (IRB)-approved written informed consent document.

10. Any prior radiation must have been completed at least 14 days prior to the start of study drugs, and patients must have recovered from any acute adverse effects prior to the start of study treatment (Radiotherapy for extended field within 4 weeks or limited field radiotherapy within 2 weeks).

11. Ability to take oral medications without medical history of malabsorption or other chronic gastrointestinal disease, or other conditions that may hamper compliance and/or absorption of the study agents (feeding tube is not permitted).

12. Provision of an archival tissue block, or 10 formalin-fixed paraffin-embedded (FFPE) slides obtained within 6 months prior to study entry; or agreeing to have biopsies if archival tissues are not available.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be not eligible for the study:

1. Uncontrolled intercurrent illness including but not limited to ongoing or active infection requiring intravenous antibiotics, symptomatic congestive heart failure (New York Heart Association Class III or IV), history of myocardial infarction, unstable angina, stroke or transient ischemic attack within 6 months before study enrollment, history or current evidence of uncontrolled ventricular arrhythmia. Congenital long QT syndrome, or any known history of torsade de pointes, or family history of unexplained sudden death. Chronic diarrhea diseases considered to be clinically significant in the opinion of the Investigator. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or futibatinib and pembrolizumab administration, or may interfere with the interpretation of study results, and in the judgment of the Investigator would make the patient inappropriate for entry into this study.

2. History and/or current evidence of any of the following disorders: Non-tumor related alteration of the calcium-phosphorus homeostasis that is considered clinically significant in the opinion of the Investigator; Ectopic mineralization/calcification, including but not limited to soft tissue, kidneys, intestine, or myocardia and lung, considered clinically significant in the opinion of the Investigator; and Retinal or corneal disorder confirmed by retinal/corneal examination and considered clinically significant in the opinion of the Investigator and a trained ophthalmologist who performs the test.

3. Having not recovered from a major surgical procedure or significant traumatic injury (i.e., still needing additional surgical or medical care for these issues): major surgical procedures ≤ 28 days of treatment entry, or minor surgical procedures ≤ 7 days. No waiting period required following port-a-cath or other central venous access placement.

4. Unresolved clinically significant Grade 2 toxicity from prior therapy.

5. Patient has an inability to swallow oral medications. Note: Patient may not have a percutaneous endoscopic gastrostomy (PEG) tube or be receiving total parenteral nutrition (TPN).

6. Clinically active bleeding, or active gastric or duodenal ulcer.

7. Fridericia's corrected QT interval (QTcF =QT/$\sqrt[3]{60/HR}$) > 470 ms on ECG conducted during Screening. Patients with an atrioventricular pacemaker or other condition (for example, right bundle branch block) that renders the QT measurement invalid are an exception and the criterion does not apply.

8. History of allergic reactions to the study drugs, or any component of the products.

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

10. Any treatment specifically for systemic tumor control given within 3 weeks before the initiation of the study drugs, within 2 weeks if cytotoxic agents were given weekly, within 6 weeks for nitrosoureas or mitomycin C, within 5 half-lives for targeted agents with half-lives and pharmacodynamic effects lasting < 5 days, or failure to recover from toxic effects of any therapy before the initiation of the study drugs. A drug that has not received regulatory approval for any indication within 14 or 21 days of treatment for a non-myelosuppressive or myelosuppressive agent, respectively.

11. Has received a live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: Bacille Calmette-Guérin vaccine, measles, mumps, rabies, rubella, typhoid vaccine, varicella/zoster, and yellow fever. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines are live attenuated vaccines and are not allowed.

12. Received strong inhibitors and inducers and sensitive substrates of CYP3A4 within 2 weeks, and avoid coadministration of strong inhibitors of CYP3A4 (see appendix A).

13. Symptomatic primary tumors or metastasis in the brain and/or central nervous system that are uncontrolled with antiepileptics and require steroids at a dose of prednisone > 10 mg/day or equivalent.

14. Evidence of leptomeningeal or lymphangitic carcinomatosis.

15. A history of another primary malignancy that is currently clinically significant, requiring active intervention except for hormone therapy.

16. Concurrent immunosuppressive therapy or steroid (> 10 mg/day prednisone or equivalent).

17. Previously documented or suspected autoimmune disease requiring active immunosuppressive therapy (adequately treated skin rash or replacement therapy for endocrinopathies is not excluded), and history of or current pneumonitis.

18. Lactation or pregnancy.

19. Known human immunodeficiency virus requiring HAART treatment due to unknown drug-drug interactions or known active hepatitis B or C virus infection.

4 STUDY DESIGN AND TREATMENT PLAN

4.1 Study Design

This is an investigator-initiated NCCN (National Comprehensive Cancer Network)-supported phase II clinical trial (2020-IST-FUTI-000032) conducted at The University of Texas MD Anderson Cancer Center who will hold the Investigational New Drug (IND) for this study.

After patients with metastatic MSS endometrial carcinoma have signed the informed consent, patients will be enrolled to receive therapy for toxicity and efficacy evaluation.

The dose limiting toxicity (DLT) window is the initial 21 days of therapy.

- Enroll 6 lead-in patients to receive futibatinib 20 mg PO daily plus pembrolizumab 200 mg IV once every 3 weeks on day 1 of each cycle (dose level 1 in Table 1). If there is one or less DLT, the study will continue following a Bayesian optimal phase 2 (BOP2) design at dose level 1.
- If there are two or more DLTs, enroll another 6 lead-in patients to receive futibatinib 16 mg PO daily plus pembrolizumab 200 mg IV once every 3 weeks on day 1 of each cycle (dose level -1 in Table 1).
- If there are two or more DLTs at this dose level, the study will be terminated.
- If there is one or less DLT, the study will continue following a BOP2 design at dose level -1.
- The lead-in patients will be counted as the patients who are enrolled to stage I at the same dose level.

4.2 Treatment Plan

Table 3: Dose De-escalation for Futibatinib and Pembrolizumab

Dose Level	Futibatinib	Pembrolizumab
-1	16 mg PO daily	200 mg IV on Day 1
1	20 mg PO daily	200 mg IV on Day 1

As described in Section 2.4, the current clinical evidence supported the safety of futibatinib 20 mg PO daily in combination with pembrolizumab 200 mg IV once every 3 weeks in patients with advanced solid tumors.

One cycle of therapy is 21 days. As seen in Table 3, futibatinib will be administered by mouth with or without food once a day and pembrolizumab will be given intravenously once every 21 days. Patients will be monitored for 60 minutes post pembrolizumab administration at C1D1, and then 30 to 60 minutes post infusion subsequently as clinically indicated. Appropriate dose modifications and interruptions for futibatinib, and interruptions for pembrolizumab without dose modification are allowed. No other investigational or commercially available agents specific for cancer control are permitted. Local palliation is allowed, but it is not allowed to the sole target lesion.

Investigational treatment with intravenous pembrolizumab 200 mg once every 3 weeks and oral futibatinib will be administered for up to 2 years as long as the patient is receiving benefit, tolerating the regimen, and does not meet any criteria for discontinuation of study treatment. At the discretion of treating physician, patients may receive intravenous pembrolizumab 400 mg once every 6 weeks subsequently.

4.3 Criteria for Subsequent Therapy

All patients must meet the minimal criteria for subsequent therapy: the absolute neutrophil count ≥1,000 /μL, the platelet count ≥50,000 /μL, and the resolution of toxicity to ≤Grade 1, pre-therapy baseline, or Grade 2 that is not clinically significant. Toxicities are graded by using NCI CTCAE v5.0 toxicity criteria.

In general, treatment should be on hold if the minimal criteria for subsequent therapy are not met. However, the patient may resume therapy if and when the physician and the patient believe that further treatment will benefit the patient. Supportive care will be allowed according to good clinical practice.

Remote Procedures

In case of any unexpected incidents that patients can't come back to MD Anderson Cancer Center for study treatment and assessments, remote procedures can be applied for this trial conduction, including remote consent, remote toxicity assessment via phone calls, virtual visit, etc., with compliance with institutional policies. Patients can have lab work, scheduled scans, physical exams and receive treatment locally if applicable. Laboratory work done at an outside facility is to be forwarded to the subject's attending physician at MD Anderson or the PI of the study, who will date and sign off on the labs to verify the results were reviewed. Remote monitoring can be applied as needed. Study drug may be mailed to the patient per institutional guidelines/approval.

4.4 Dose Delays and Modifications

In addition to the following general guidelines for dose delays and modifications, the treating physicians as well as the study chair may institute additional remedies in the best interests of their patients according to their best medical knowledge.

The patients may interrupt treatment during study for palliative radiation or surgery, and may resume therapy when they recover, according to good medical practice.

If a patient experiences a clinically relevant toxicity which is known to be related to one drug in the regimen, then that drug may be modified according to the recommendation for that drug. Patient continuation on one single agent is allowed.

If a patient experiences a clinically relevant toxicity for which it is unclear which drug is the cause of the toxicity, then both agents may be modified according to the recommendation for each agent.

After a dose reduction for any toxicity, re-escalation is not permitted. For Grade 4 or recurrent G3 eye-related toxicities, the investigational treatment must be permanently discontinued.

Dose Delays and Modification Specific for Futibatinib

Description of Futibatinib – please see investigator's brochure (IB).
Futibatinib is a novel and selective small molecule irreversible, covalent inhibitor of fibroblast growth factor receptor (*FGFR*) 1–4.

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

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

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

Handling and Storage
Futibatinib tablets should be stored in accordance with the label.

Treatment Administration
Futibatinib is supplied as 4 mg tablets and will be taken orally at a dose of 20 mg daily until the patient meets any of the administration discontinuation or dose reduction criteria.

Futibatinib should be administered without or with food, with a glass of water.

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

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

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

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

Dose Modifications for Nonhematologic Toxicities

Dosing modification guidelines for nonhematologic and eye toxicities are provided in Table 4 Please see futibatinib package insert for details. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/214801Orig1s000lbledt.pdf)

Table 4: Recommended Dose Modifications for Related Nonhematologic Toxicities

Adverse Reaction	Severity	Futibatinib Dosage Modifications
Retinal Pigment Epithelial Detachment (RPED)	Not applicable	Continue at the current dose and continue periodic ophthalmic evaluation: • If resolving within 14 days, continue at the current dose. • If not resolving within 14 days, withhold until resolving; then resume at previous or a lower dose
Hyperphosphatemia	Serum phosphate ≥ 5.5 – ≤ 7 mg/dL	Continue at the current dose and initiate phosphate lowering therapy. Monitor serum phosphate weekly.
	Serum phosphate > 7 – ≤ 10 mg/dL	• Initiate or adjust phosphate lowering therapy. Monitor serum phosphate weekly and Dose reduced to next lower dose - If the serum phosphate resolves to ≤ 7 mg/dL within 2 weeks after dose reduction, continue at this reduced dose. - If serum phosphate is not ≤ 7 mg/dL within 2 weeks, further reduce to the next lower dose. - If serum phosphate is not ≤ 7 mg/dL within 2 weeks after the second dose reduction,
	Serum phosphate >10 mg/dL	withhold until serum phosphate is ≤ 7 mg/dL and resume at the dose prior to suspending. Initiate or adjust phosphate lowering therapy and monitor serum phosphate weekly and • Withhold until phosphate is ≤ 7 mg/dL and resume at the next lower dose. - Permanently discontinue if serum phosphate is not ≤ 7 mg/dL within 2

		weeks following 2 dose interruptions and reductions.
Other Adverse Reactions	Grade 3 [a] Grade 4 [a]	Withhold until toxicity resolves to Grade 1 or baseline, then resume - for hematological toxicities resolving within 1 week, at the dose prior to suspending. - for other adverse reactions, at next lower dose. Permanently discontinue

[a] Severity as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0).

Dose Modifications for Hematologic Toxicities are presented in Table 5.

Table 5: Futibatinib Dose Interruption and Modification for Related Hematologic Toxicities

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

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

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

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

Futibatinib will be permanently discontinued (pembrolizumab is allowed to be administered as a single agent if there is no tumor progression and no pembrolizumab related prohibitive toxicity) if liver function test abnormalities fulfill Hy's Law criteria defined as concurrent observation of the following, with no other reason found to explain the findings (such as viral hepatitis A, B, or C; preexisting or acute liver disease; liver metastases; or another drug capable of causing the observed liver injury):

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

Dose Delays and Interruptions Specific for Pembrolizumab

Description of Pembrolizumab: please see pembrolizumab packaging insert.

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

Pembrolizumab will be obtained commercially and its cost will be covered by patients and/or their insurance companies.

Administration

Intravenous pembrolizumab 200 mg will be administered once every 3 weeks for up to 2 years as long as the patient is receiving benefit, tolerating the regimen, and does not meet any criteria for discontinuation of study treatment.

Recommended Dose Delays and Interruptions for Pembrolizumab

No dose reductions of KEYTRUDA are recommended. Withhold or discontinue KEYTRUDA to manage adverse reactions as described in Table 6. Severity and type of reaction are graded according CTCAE 5.0. Please see Pembrolizumab package insert for details.

Table 6. Pembrolizumab Dose Delays and Interruptions Guidelines

Adverse Reaction	Severity	Dose Delays/Interruptions
Other immune-mediated adverse reaction	Grades 2 or 3 based on the severity and type of reaction	Withhold Resume when the immune-mediated adverse reaction resolves to Grade 1 or 0 following corticosteroid taper
	Grade 3 based on the severity and type of reaction or Grade 4	Permanently discontinue
Recurrent immune-mediated adverse reactions	Recurrent Grade 2 pneumonitis	Permanently discontinue
	Recurrent Grades 3 or 4	
Inability to taper corticosteroid	Requirement for 10 mg/day or greater prednisone or equivalent for more than 12 weeks after last dose of pembrolizumab.	Permanently discontinue
Persistent Grade 2 or 3 (excluding endocrinopathy)	Grades 2 or 3 adverse reactions lasting 12 weeks or longer after last dose of pembrolizumab	Permanently discontinue

Concomitant Medications and Therapies

Prohibitive Medications and Therapies

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

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

Immunosuppressive therapy including steroids (> 10 mg/day prednisone or equivalent) is not permitted with pembrolizumab.

Concomitant strong inhibitors and inducers and sensitive substrates of CYP3A4 should be avoided, if possible, with futibatinib. Caution is advised if these drugs are given concomitantly (see Appendix A: CYP3A4 and Transporters – Classification of Substrates, Inhibitors, and Inducers of CYP Enzymes and Transporters). Alternative replacement is highly recommended.

Concomitant Medications and Therapies Requiring Precautions

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

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

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

Hematologic Support: may be administered as medically indicated (that is, blood transfusions, granulocyte colony-stimulating factor, erythropoietin stimulating agents) according to the institutional site standards or American Society of Clinical Oncology (ASCO) guidelines [76].[76].

Management of Diarrhea: Prophylactic treatment for diarrhea is permitted during the study if clinically indicated according to the institutional or published guidelines [77].

Management of Nausea/Vomiting: Antiemetics may be administered as clinically indicated according to institutional standards or ASCO guidelines [78].

Drug Interactions
Threeclinical drug-drug interaction studies and 1 PK model analysis in humans showed that moderate to strong inhibitors or inducers of CYP3A have potential clinical drug-drug interactions with futibatinib: please see IB and futibatinib package insert for details.

Futibatinib is a substrate of CYP3A and P-gp.

Dual P-gp and Strong CYP3A Inhibitors

• Avoid concomitant use of drugs that are dual P-gp and strong CYP3A inhibitors with futibatinib.

• Concomitant use of drugs that are dual P-gp and strong CYP3A inhibitors with futibatinib may increase futibatinib exposure, which may increase the incidence and severity of adverse reactions.

Dual P-gp and Strong CYP3A Inducers
• Avoid concomitant use of dual P-gp and strong CYP3A inducers with futibatinib.

• Concomitant use of drugs that are dual P-gp and strong CYP3A inducers may decrease futibatinib exposure, which may reduce the efficacy of futibatinib.

Overdose
As of the cut-off date for the Development Update Safety Report (DSUR) for futibatinib (23 January 2020), there were 2 cases of overdose reported in the TAS-120-101 trial. Two patients with cholangiocarcinoma took a higher than planned dose of futibatinib for 1 day. There were no adverse events associated with the overdose.

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

For WOCBP, including female study participants and partners of male participants, effective contraception is required during the study and for 180 days after the last dose of study medication, or longer if necessary based on local requirements. Effective contraception is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  – Oral – Intravaginal – Transdermal• Progestogen-only hormonal contraception associated with inhibition of ovulation:– Oral – Injectable – Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner with documentation of the success of the vasectomy

• Complete abstinence from heterosexual intercourse (periodic abstinence is not a safe method)

Donation of ova is not allowed during the study and for 180 days or longer based on local requirements following the last dose of study drug.

Definitions of "Women of Childbearing Potential", "Women of No Childbearing Potential"

As defined in this protocol, "women of childbearing potential" are females who are physiologically capable of becoming pregnant.

Conversely, "women of no childbearing potential" are defined as females meeting any of the following criteria:

- Surgically sterile (i.e., through bilateral salpingectomy, bilateral oophorectomy, or hysterectomy)
- Postmenopausal, defined as:
  - ≥ 55 years of age with no spontaneous menses for ≥ 12 months OR
  - < 55 years of age with no spontaneous menses for ≥ 12 months AND with a postmenopausal follicle-stimulating hormone concentration > 30 IU/mL and all alternative medical causes for the lack of spontaneous menses for ≥ 12 months have been ruled out, such as polycystic ovarian syndrome, hyperprolactinemia, etc.

If an FSH measurement is required to confirm postmenopausal state, concomitant use of hormonal contraception or hormonal replacement therapy should be excluded.

5 STUDY PROCEDURES

All patients will be evaluated as outlined in Study Calendars (See ATTACHMENT A). Dosing, laboratory tests, imaging studies and office visits/telemedicine will occur per protocol (within ± 4 days) unless patients' medical or logistical issues necessitate adjustment.

5.1 Pretreatment Evaluations

To be completed within 4 weeks prior to initiation of therapy:

- Medical history, including list of current medications
- Imaging studies with CT scans of chest, abdomen and pelvis
- Tumor markers, CA125 and/or CA15.3
- ECHO or MUGA, and then as clinically indicated
- A copy of microsatellite stable (MSS) and FGFR1-4 aberration (activating mutations or amplification) as pre-identified in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory A comprehensive ophthalmological examination, including optical coherence
  tomography (OCT) of the macula, prior to initiation of therapy, every 2 months for the first 6 months, and every 3 months thereafter
- Informed consent signed by patient and investigator

To be completed within 7 days of initiation of therapy:

- Physical exam including symptoms and signs
- ECOG performance status (See ATTACHMENT B)
- Complete blood count with leukocyte differential and platelet count
- Serum chemistries including sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, phosphate, magnesium, albumin, alkaline phosphatase, total bilirubin, AST, ALT, TSH and free T4
- ECG
- Urinalysis
- Tumor markers, CA125 and/or CA15.3 if elevated at screening
- Women of childbearing potential will have a pregnancy test using blood

5.2 On Study Evaluations

To be obtained weekly during the initial 3 weeks and then as clinically indicated:

- Complete blood count and leukocyte differential and platelet count
- Serum chemistries including sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, phosphate, magnesium, albumin, alkaline phosphatase, total bilirubin, AST and ALT
- Physical exam including symptoms and signs

ECOG performance status

To be obtained at the beginning of each subsequent cycle:

- Medical history and physical exam
- ECOG performance status
- Assessment of treatment-related and -unrelated toxicities
- Complete blood count with leukocyte differential and platelet count
- Serum chemistries including sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, phosphate, magnesium, albumin, alkaline phosphatase, total bilirubin, AST, ALT, TSH and free T4
- ECG
- Urinalysis
- Tumor markers, CA125 and/or CA15.3 if elevated at screening
- Women of childbearing potential will have a pregnancy test using blood
- A comprehensive ophthalmological examination, including optical coherence tomography (OCT) of the macula, prior to initiation of therapy, every 2 months for the first6 months, and every 3 months thereafter will be performed. For onset of visualsymptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of futibatinib.

To be obtained once every 6-9 weeks for tumor measurement:

- Evaluation of tumor: the same imaging technique or more sophisticated studies will be performed once every 6 weeks of therapy (6 weeks ± 7 days) for the initial 12 weeks after starting the treatment, and then once every 9 weeks (9 weeks ± 7 days), or sooner as clinically indicated

Patients will be seen by a physician at the start of treatment and then prior to initiating subsequent cycles (+/- 7 days). In order to more precisely determine time of progression more precisely, the investigator is encouraged to obtain radiological assessments earlier if there is a strong clinical suspicion of progression of disease to either confirm or refute the clinical impression. Possible adverse events will be discussed in detail with each patient and assessed on a continuing basis. ECG, echocardiogram, and other radiological-laboratory tests will be monitored throughout treatment if clinically indicated.

Ophthalmological Examination
The cornea and conjunctiva are readily visible tissues, and therefore, abnormalities of the cornea and conjunctiva can usually be recognized via external ocular examination and routine slit lamp biomicroscopy. The retina is visible through fundoscopy after dilation of the pupil. Ophthalmologic examination will be performed by a trained ophthalmologist or qualified delegate.

A comprehensive ophthalmological examination, including optical coherence tomography (OCT) of the macula, prior to initiation of therapy, every 2 months for the first 6 months, and every 3 months thereafter will be performed. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently,

Each evaluation will encompass:

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

Patient-Reported Outcome (PRO) Measurement Tools (optional)
Patients will be instructed to capture symptomatic adverse events weekly for the initial 6 weeks after starting the treatment (cycle 1 and 2), and at the end of each cycle (subsequent cycles) thereafter through paper, online and/or portal device according to Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™ https://healthcaredelivery.cancer.gov/pro-ctcae), and the 2-level version of EQ-5D (EQ-5D-3L: https://euroqol.org/eq-5d-instruments/eq-5d-3l-about/).

5.3 Translational Research

Exploratory Objectives: To identify plasma and tissue biomarkers associated with response to futibatinib and pembrolizumab in patients with metastatic microsatellite stable (MSS) endometrial carcinoma.

Rationale: Growing evidence suggests that activation of FGFR induces macrophage recruitment and cytokine production, leading to protumorigenic alterations via tumor immunosuppressive microenvironment [56,57]. Moreover, preclinical studies demonstrate that combination therapy of lenvatinib (VEGF/FGFR inhibitor) with PD-1 blockade improved cancer immunotherapy by reducing TAMs and enhancing antitumor activity via the IFN signaling pathway[71]. FGFR pathway inhibition, increased T-cell infiltration, decreased regulatory T cells, and downregulation of PD-L1 expression on tumor cells [66]. However, mechanisms underlying this combination effects of futibatinib and pembrolizumab in endometrial cancer are unknown. TCGA data revealed that high expression of FGFR3 is significantly correlated with poor survival in endometrial cancer ($p<0.001$). In addition, preliminary data using the ImmGen database revealed that FGFR1 is highly expressed in macrophages and FGFR2-4 are expressed on stromal cells (Figure 8).

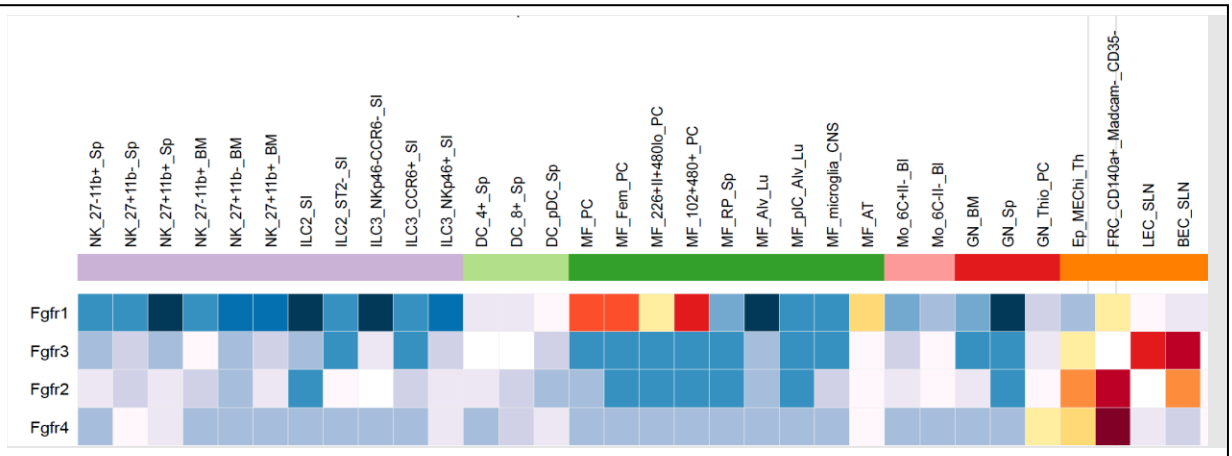

Fig. 8. Expression of FGFR1-4 on immune cells and stromal cells.

On the basis of the compelling preclinical and pilot clinical data, we hypothesized that *dynamic changes in TAM-related biomarkers and inflammatory cytokines will be associated with response to futibatinib and pembrolizumab in patients with metastatic endometrial carcinoma.* Our translational endpoints will be to assess plasma markers (inflammatory cytokines/chemokines) and tissue markers (M2-like and M1-like markers, MDSCs, CD8, CD25, CD34, CD56), and pAKT, pERK2, FGFR1-4, PD-L1, and PD-1 at baseline, within 1 week prior to cycle 2 day 1 (C2D1), and at time of relapse in patients who have displayed stable disease (SD)≥6months, CR or PR (SD≥6months/CR/PR).

Pre- and post-biopsy tissues will be used for monitoring dynamic changes in macrophages (with phenotype of M2-like CD markers, and MHCII), and CD4/CD8, MDSCs, NK, and T-regs using multiplex IHC. PBMCs will be used for monitoring dynamic gene changes in classical (CD14+/CD16-) and non-classical monocytes (CD14low/CD16+) by RNA sequencing. NGS will be utilized on tumor specimens and cfDNA for targeted exome panel including FGFR1-4 genetic aberrations at baseline, within 1 week prior to cycle 2 day 1 (C2D1), and at time of relapse in patients who have displayed SD≥6months/CR/PR.

Sample Collections
For purposes of collecting blood and tumor samples, the Investigational Cancer Research services (ICRS) at MD Anderson will provide bulk tubes and reagents for PD and biopsies, tube labels, and subject requisition forms.

Blood sample collections:
After the informed consent is obtained, 20 mL blood will be collected into CPT tubes at each of the following time-points (optional): prior to the initiation of treatment (pre-study), prior to the initiation of cycle 2 day 1 (C2D1), and at end of therapy if available or prior to cycle 13 day 1 (C13D1) if still on therapy. PBMCs will be collected for RNA sequencing. Plasma will be collected for multiplex ELISA and DNA NGS.

Blood samples will be collected in green-topped Vacutainer tubes containing sodium heparin. Plasma at 0.5-1 mL/vial and peripheral blood mononuclear cells (PBMCs) will be isolated and cryopreserved in 10% DMSO and 90% human AB serum at 10×10^6 cells/vial and stored at -70^{0}C to -80°C until later analysis (Dr. Anil Sood at Gynecologic Oncology).

Tumor sample collections:
After informed consent is obtained, tumor core biopsy samples will be collected as follows:
1. Ten 5-μm thick FFPE slides, or tumor block – all patients
2. Pre-treatment core biopsy – all patients if archival samples are not available
3. Tumor core biopsy within 1 week before C2D1 – 12 patients at stage II
4. After-study tumor core biopsy at time of relapse in patients who have displayed SD≥6months/CR/PR – optional

The time of drug administration and the time of biopsy will be documented. The treating physician, principal investigator, and interventional radiologist will work together to ensure that patients will not be subject to a significant risk procedure for the purpose of obtaining tissue for this study. In particular, a significant risk procedure is generally considered to be one for which the procedure associated absolute risk of mortality or major morbidity in the patient's clinical setting and at the institution completing the procedure, is 2% or higher. Procedures more invasive than a core biopsy are not utilized. The core biopsies will be snap frozen and stored in cryogenic storage tubes. The sample should be frozen by total immersion in liquid nitrogen or an alcohol dry-ice bath and kept in liquid nitrogen or an alcohol dry-ice bath or buried in dry ice pellets from the time of freezing until the time of storage in the -70°C to -80°C freezer (Dr. Anil Sood at Gynecologic Oncology). Part of the biopsies will be formalin-fixed paraffin-embedded (FFPE) for IHC and pathologic diagnosis.

Sample processing
Samples may be processed and tested as designed or via a more sophisticated technique when available:
1. Cytokine and chemokine measurement using Multiplex ELISA at baseline, prior to C2D1, at end of therapy if available or prior to C13D1 if still on therapy.
2. Multiple IHC on tumor specimens at baseline (all), prior to C2D1 (patients at stage II), and at relapse in patients with documented SD≥6months/CR/PR.
3. NGS on circulating DNA at baseline, prior to C2D1, at end of therapy if available or prior to C13D1 if still on therapy.
4. NGS on tumor specimens for targeted exome panel including FGFR1-4 genetic aberrations to reveal potential biomarkers at baseline (all), prior to C2D1 (patients at stage II), and at relapse in patients with documented SD≥6months/CR/PR.

Methods: To assess the utility of surrogate biomarkers and the anti-tumor response to therapy with the combination treatment of futibatinib and pembrolizumab in patients with metastatic endometrial cancer, we will draw 20 ml blood for plasma markers (inflammatory cytokines/Chemokines) and PBMC RNA sequencing and cfDNA NGS, prior to the initiation of cycle 2 day 1 (C2D1), and at end of therapy if available or prior to cycle13 day 1 (C13D1) if still on therapy. The biopsied tissues will be used for DNA extraction for NGS using exome panel including FGFR1-4 genetic aberrations, and multiplex IHC for monitoring dynamic changes in M2 like macrophages (with phenotype of M2-like and M1-like CD markers), and CD4/CD8, MDSCs, NK, and Treg.

Multiplex ELISA for detecting cytokines/chemokines. 5 ml blood will be drawn for detecting both human inflammation cytokines/chemokine panels in plasma collected at baseline, prior to C2D1, at end of therapy if available or prior to C13D1 if still on therapy. Plasma will be collected, aliquoted and stored at -80℃ for further processing. Multiplex ELISA will be performed on the manufacturer's instruction[79].

Tumor biopsy and tumor marker analysis: Core needle biopsy will be performed in the Diagnostic Imaging Department at baseline if archival tumor tissues are not available, prior to the initiation of cycle 2 day 1 (C2D1), and at relapse in patients with documented SD≥6months/CR/PR (optional). Sample will be frozen for detecting surface markers of M2-like macrophages, CD4/ CD8, MDSCs, NK and Treg cells by multiplex IHC at the Pathology Core at MDACC[80]. Freshly frozen tumor samples will be analyzed for FGFR1-4 mutations by NGS at the Genomic core at MDACC.

Detection of monocyte- and CD8-enriched genes in PBMCs: 5 ml blood will be collected into CPT tubes at baseline, prior to C2D1, at end of therapy if available or prior to C13D1 if still on therapy. PBMCs will be collected and frozen and stored at -80℃ for further processing. RNA will be extracted from PBMCs obtained from these patients before and after treatment. RNA sequencing will be carried out for detecting monocyte- and CD8-preselected genes in PBMCs[81].

cfDNA NGS: 10 ml blood will be collected into CPT tubes at baseline, prior to C2D1, at end of therapy if available or prior to C13D1 if still on therapy. Utilizing the quick-cfDNA serum/plasma Kit (Zymo Research), DNA will be extracted from plasma obtained from these patients before and after treatment and stored at -80℃ for further DNA sequencing [82-84].

5.4 Off Study and Follow-Up Evaluations

To be obtained within 30 days of the last dose of study drugs if feasible:

- Medical history and complete physical exam
- ECOG performance status
- Tumor markers, CA125 and/or CA15.3 if elevated at screening
- Complete blood count with leukocyte differential and platelet count
- Serum chemistries including sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, phosphate, magnesium, albumin, alkaline phosphatase, total bilirubin, AST, ALT, TSH, and free T4
- Assessment of treatment-related and -unrelated toxicities
- Evaluation of tumor: the same imaging technique used during the initial evaluation or more sophisticated studies
- Women of childbearing potential will have a pregnancy test using blood monthly until 3 months after the last dose of the study agents if feasible.

5.5 Guidelines for Evaluation of Tumor Markers and Tumor Responses

Evaluate tumor markers in those who have elevated tumor markers before treatment

Complete Response (CR):	Tumor marker is below normal limit.
Partial Response (PR):	More than 50% of tumor marker reduction.
Progressive Disease (PD):	More than 25% of tumor marker increase.
Stable Disease (SD):	Change not sufficiently defined as PR or PD.

Assessment of Tumor Response (RECIST version 1.1)[85]:
The baseline imaging studies will be reviewed prior to the initial therapy. Tumor measurement and documentation will be performed after the first restaging workup.

Measurable Disease is defined by the presence of at least one measurable lesion.
Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

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

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

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

Target and Non-target Lesions
When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Lymph nodes merit special mention since they are normal anatomical structures, which may be visible by imaging even if not involved by tumor. Pathological nodes, which are defined as measurable and may be identified as target lesions, must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in

which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) will be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and will not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Guidelines for Evaluation of Measurable Disease: All measurements should be taken and recorded in metric notation. All evaluations should be performed as closely as possible to the beginning of treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Chest x-ray: Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Helical (or Spiral) CT and MRI: These techniques should be performed with cuts of 10mm or less in slice thickness contiguously. Spiral CT should be performed using a ≤5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US): When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, and Laparoscopy: These will not be used to assess response on this study.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in CR.

Cytology, and Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) if clinically indicated.

Response Criteria for Evaluation of Target Lesions (Table 7)
Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (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 5mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient decrease to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Response Criteria for Evaluation of Non-target Lesions (Table 8)
Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Evaluation of Best Overall Response (Table 9)
The best overall response is the best response recorded from the start of the study treatment until the end of treatment, taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Confirmatory Measurement
To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed ≥ 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks.

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is

objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease occurs.

Duration of SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Time to response is measured as time to initial response and time to best response. The time to initial response is defined from study entry to the date that initial response criteria are met. The time to best response is defined from study entry to the date that best response criteria are met.

Time to treatment failure is measured from study entry to the point of relapse for responders or the point of progression for non-responders. Patients with treatment failure are removed.

Time to tumor progression is the time from date of initial treatment to first objective documentation of disease progression.

Time to death is the time from date of initial treatment to date of death.

Table 7: Time point response: patients with target (+/- non-target) disease			
Target lesions	Non-Target 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
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.			

Table 8: Time point response: patients with non-target disease only		
Non-target lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease, and NE = not evaluable. A “Non-CR/non-PD” is preferred over “stable disease” for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

Table 9: Best overall response when confirmation of CR and PR required.		
Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR
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
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable. If a CR is met at the first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that time point (since disease must have reappeared after CR). Best response would depend on whether the 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 patient had a PR, not a CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is a PR.		

Efficacy analysis: All patients who have received one dose of any study agent will be considered evaluable for efficacy. Patients who are removed from the study before the first scheduled restaging workup because of progression, serious drug-related adverse events, or any other reasons are also considered evaluable for efficacy. If the restaging workups are not done, these patients will be denoted the same as the patients who have new lesions.

Other Assessment
Patients' functional performance status will be graded according to ECOG criteria as seen ATTACHMENT B.

5.6 Evaluation of Toxicity

This is an open-label phase II study. MD Anderson will have access to the Safety Data on a regular basis.

The lead-in patients have to be evaluated for DLT. The DLT window is 21 days.

Hematological DLT is defined as study drug-related toxicity:
- Platelets < 25,000 /μL or bleeding associated with platelets < 50,000 /μL
- Grade 4 neutropenia lasting 7 or more days
- Neutropenic fever

Non-hematological toxicities are graded using NCI CTCAE v5.0 toxicity criteria and the DLT is defined as study drug-related toxicity:
- Grade 3 or greater non-hematological toxicity other than nausea, vomiting, or fatigue
- Grade 3 or greater clinically significant electrolyte abnormalities
- Grade 3 nausea and vomiting related to study drug treatment that is not controlled at 72 hours despite appropriate antiemetic therapy
- Evaluation of liver toxicity as defined by Hy's Law:
  - The drug causes hepatocellular injury with ALT or AST ≥ 3 x ULN or baseline
  - Total Bilirubin > 2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase < 2 x ULN)
  - No other reason can be found to explain the combination of increased ALT/AST and total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, preexisting liver disease, or another non-study agent capable of causing the observed injury
- Persistent Grade 2 toxicity or laboratory tests such as hyperphosphatemia or hypophosphatemia that cannot be resolved by administering phosphate binders, and requires a dose reduction will be considered a DLT if the treating physician and the principal investigator concur.
- Any death not clearly due to underlying disease or extraneous causes

The following types of toxic effects would not be considered in the definition of DLT:

- Alopecia, or nausea and vomiting in the absence of appropriate antiemetics, or insomnia, obesity/weight gain, infertility, amenorrhea, galactorrhea, or glucose intolerance that is believed to be due to dexamethasone used as antiemetic.

- The laboratory tests if asymptomatic despite being Grade 3, except for phosphate levels as described above.

Safety analysis: All patients who receive therapy will be considered evaluable for safety. Lead-in patients will be monitored for DLT in cycle one. Patients are evaluable if they have received at least 75% of total scheduled study agents in initial 21 days or have experienced a treatment related DLT. Patients are non-evaluable if they meet all the following criteria in cycle one: they have not experienced a treatment-related DLT, they have not received 75% of total scheduled study agents, and therapy is held for logistic and underlying medical issues but not for treatment-related toxicity. Non-evaluable patients may be replaced.

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for adverse event reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP home page (http:/www.ctep.info.nih.gov) and is appended to this protocol. Life-threatening toxicities should be reported immediately to the study chair who, in turn, must notify the IRB. Reporting of adverse reactions does not supplant the reporting of toxicities as part of the results of the clinical trial. Follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

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

Please note: Progression of the cancer under study is not considered an adverse event.

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

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

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

Anticipated day-to-day fluctuations (intermittent) of pre-existing conditions or clinical labs, including the disease under study, need not be considered adverse experiences unless deemed clinically significant, worse than baseline, and at least possibly related to study drug/research procedure. An unexpected adverse drug reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information. Abnormal laboratory findings considered by the reporting investigator to be clinically significant, e.g., those that are unusual or unusually severe for the population being studied or known toxicity of study drug(s) should be documented as adverse events if felt to at least possibly related to study drug/research procedure. AEs may be documented by dictation or toxicity template forms at choice of physician.

Eliciting Adverse Event Information: Adverse events will be elicited at each clinic visit during participation in the study. All adverse events that are directly observed and all adverse events that are spontaneously reported by the patient are to be documented by the investigator. The study chair or physician designee is responsible for determining the attribution of adverse events to study drug.

All adverse experiences occurring during the study should be documented. At each scheduled protocol visit, patients will be asked a non-leading question to elicit adverse experiences. Adverse experiences should be documented in terms of a medical diagnosis if possible. When this is not possible, the adverse experience should be documented in terms of signs and/or symptoms observed by the Investigator (death is not an AE; death is an outcome).

At each scheduled protocol visit/assessment, the Investigator or designee will evaluate adverse experiences. The description of the event should include:

- Description of each adverse experience (diagnosis whenever possible).
- Date of onset and resolution (and time, where appropriate).
- Timing (i.e., intermittent, continuous).
- Maximum intensity with final decision made by attending physician if there are differing assessments.
- Causality should be assessed initially at the best knowledge of the investigator, especially when a SAE has occurred with minimal information available, and may be re-assessed at a later time after subsequent labs, tests, physical exam, etc. If there is a difference in opinion of causality between practitioners, the attending physician or PI attribution will be final determinant. There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always makes assessment of causality for every event prior to transmission of the SAE report/eCRF to the sponsor. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE report/eCRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The Investigator is responsible for assessing the severity of the AE and/or the ADE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution.

Attribution - the determination of whether an adverse event is related to a medical treatment or procedure.

- **Definite** - the adverse event is clearly related to the investigational agent(s).
- **Probable** - the adverse event is likely related to the investigational agent(s).
- **Possible** - the adverse event may be related to the investigational agent(s).
- **Unlikely** - The adverse event is doubtfully related to the investigational agent(s).
- **Unrelated** - The adverse event is clearly NOT related to the investigational agent(s).

Outcome and sequelae, and action taken, including but not limited to changes in the dosing regimen of the assigned treatment medication. Details of changes to the dosage schedule or any corrective treatment should be recorded.

If an adverse experience increases in frequency or severity during a study period, a new record of the experience will be started, if felt to be related to study drug. Abnormal laboratory results and/or vital signs will not be recorded as adverse experiences unless deemed clinically significant by the Investigator. The CTEP active version of NCI Toxicity Criteria may be used by the Investigator as a guide in determining the severity of abnormal laboratory values.

Assessment of Intensity: Maximum intensity should be assigned to an adverse experience. Intensity will be assigned a grade of 1-5 based upon the most current version of the NCI Common Terminology Criteria (http:/www.ctep.info.nih.gov). Final arbitration of intensity in cases of differing assessments by different practitioners will be the attending physician and/or the principal investigator. Day to day fluctuations of intensity may not be recorded but rather the worst grade over the longest time period may be recorded.

- **Grade 1:** Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.
- **Grade 2:** Moderate: discomfort present with some disruption of daily activity, require treatment.
- **Grade 3:** Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.
- **Grade 4:** Life Threatening: discomfort that represents immediate risk of death
- **Grade 5:** Death

Assessment of Causality: Every effort should be made to explain each adverse experience and to assess its relationship, if any, to the study medication. Assignment of causality will be made using the following question whether there is a reasonable possibility that the event may have been caused by the study medication.

This is a Phase II study, AEs will be recorded as per the guidelines for phase II on the Table 10 below:

Table 10: Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

6 REGULATORY AND REPORTING REQUIREMENTS

6.1 Evaluation of Toxicity/Adverse Events

Evaluation of toxicity will be done in accordance with the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50).

All clinically insignificant abnormal laboratory tests will not be documented. Grade 1 toxicities (related or unrelated) will not be collected or documented as these are not considered clinically significant in this patient population and/or they are expected for these study agents. Grade 2 or higher toxicities that are felt to be treatment related and unexpected will be documented. Unless otherwise documented in the electronic medical record as clinically significant and study drug related, all laboratory abnormalities will be assumed to be related to the patient's other co-morbid conditions, prior therapies, other concomitant therapies/medications, or underlying cancer.

The principal investigator is responsible for monitoring the safety of patients who enroll in the study. All AEs occurring after any administration of the study drug will be followed until resolution, stabilization, death, loss to follow up, or commencement of new therapy. The descriptions and grading scales found in the revised NCI CTCAE version 5.0 will be used for adverse event reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled. Attribution and outcome should be assigned separately for each drug and noted on the CRF.

The Investigator is responsible for completing a toxicity/efficacy summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval.

Planned interim analyses occur at two time points: one cohort for the lead-in patients after all patients have completed the initial 21 days of study treatment (lead-in cohort summary), and the other for patients who are enrolled to the stage I (stage I cohort summary). The cohort summary should be submitted before study advancing/changing dose levels. A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

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

An AE is considered to be "Related" if the event follows a reasonable temporal sequence from administration of study drug and there is a reasonable possibility that at least one of the following conditions is true:

- A positive dechallenge: This means that the event improves or resolves after the drug is stopped (temporarily or permanently).
- A positive rechallenge: This means that the event reappears after the drug is restarted.
- The event cannot be reasonably explained by the patient's clinical state and/or other therapies administered.
- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, Stevens-Johnson syndrome).

An AE is considered to be "Not related" if there is no reasonable possibility that at least one of the following conditions is true:

- The event occurred prior to study drug administration.
- There is no reasonable possibility that the study drug caused the event. ("no reasonable possibility" means there is no evidence to suggest a causal relationship between the study drug and the AE)
- The event does not follow a reasonable temporal sequence from administration of study drug and could have been produced by a documented pre-existing condition, concomitant medication or patient's clinical state.

Outcome of Adverse Events

Record the outcome of AEs as follows:

- Resolved
- Not resolved
- Fatal
- Recovered with sequalae
- Recovering
- Unknown

Follow-up of Adverse Events

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

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

Laboratory Assessments

All laboratory results must be reviewed by the Investigator. A new laboratory or instrumental abnormality that has a clinical impact on a patient (including e.g., resulting in study drug dose reduction, treatment delay, treatment discontinuation or requirement of intervention) is considered an AE, unless it is considered part of clinical manifestations to a clinical diagnosis that is already reported as an AE. All laboratory values that are out of the normal range are to be evaluated for their clinical impact before next dosing is given.

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

6.2 Serious Adverse Events

Serious Adverse Events will be reported per standard IRB reporting requirements.
Serious Unexpected problems will be reported per standard IRB reporting requirements.

Assessment of Intensity
Maximum intensity should be assigned to an adverse experience. Intensity will be assigned a grade of 1-5. Final arbitration of intensity in cases of differing assessments by different practitioners will be the attending physician. Day to day fluctuations of intensity may not be recorded but rather the worst grade over the longest time period may be recorded.

Assessment of Seriousness
Definition of Serious Adverse Experience (SAE)
A serious adverse drug experience is any adverse experience occurring at any dose that results in any of the following outcomes:

Death: Is immediately life threatening (immediate risk of death from the reaction as it occurred). This does not include a reaction that, had it occurred in a more severe form, might have caused death. Death due to disease progression or relapse is not considered an SAE unless the investigator deems it possibly related to study drug. Death due to progression of disease will be reported per MD Anderson IRB standard guidelines.

Disability/Incapacitation
Results in persistent or significant disability/incapacity (permanent or substantial disruption of a person's ability to conduct normal life functions).

Congenital anomaly/birth defect
Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

Hospitalization
In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse experience should be considered serious. Results in or prolongs an existing inpatient hospitalization. Hospitalization for elective surgery or routine clinical procedures** that are not the result of an adverse experience (e.g., elective surgery for a pre-existing condition) need not be considered adverse experiences and should be documented as appropriate. If anything untoward is reported during the procedure, that occurrence must be reported as an adverse experience, either 'serious' or 'non-serious' according to the usual criteria. New

hospitalization or prolonging of current hospitalization for disease progression or disease-related symptom management will not be considered a Serious Adverse Event.

Routine Clinical Procedure: one which is defined in the protocol as a procedure which may take place during the study period and should not interfere with the study drug administration or any of the ongoing protocol specific procedures.

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

The following are not considered hospitalizations for the purposes of assessing seriousness (however, one of the other serious criteria may apply):
- Hospitalizations for preplanned procedures;
- Hospitalization for study-related treatment and procedures.

Assessment of Causality
Every effort should be made by the investigator to explain clinically significant adverse experience and to assess its relationship, if any, to the study medication.

Immediate Reporting of Serious Adverse Experiences within 24 hours
Serious adverse experiences (SAEs) which occur at any time after first dose of study drug or performance of protocol mandated research procedure and within 30 days after receiving the last dose of study drug(s) or prior to commencement of new therapy will be reported to the IRB per institutional standard policy. All SAEs should be documented in the patient's medical records or on the institutional standard forms (immediate reporting versus AE log). All patients with serious adverse experiences should be followed until resolution, stabilization, death, or commencement of new therapy.

Instances of death, cancer, or congenital abnormality brought to the attention of the Investigator at any time after cessation of study medication and considered by the Investigator to be possibly related to study medication should be reported to the MD Anderson Cancer Center Institutional Review Board within 30 days.

Serious Adverse Event (SAE) Reporting Requirements for M D Anderson Sponsor Single Site IND Protocol
An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:
- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Note: grade 3 and 4 eye related toxicities will be reported as SAEs.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Adverse Events for Drugs and Devices".
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent.
- Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office **within 5 working days of knowledge of the event** regardless of the attribution**.**
- Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Office **within 24 hours of knowledge of the event**
- Additionally, any serious adverse events that occur after the 30-day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.
- The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MD Anderson IRB.
- All events reported to the supporting company must also be reported to the IND Office

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Pregnancy
If a patient becomes pregnant while in the study, the study treatment must be immediately discontinued. Pregnancy information in a female patient (or for the female partner of a male patient) should be reported **as soon as possible** from the time the Investigator first becomes aware of a pregnancy or its outcome. This should be performed by completing a Pregnancy Form and faxing or e-mailing it to Taiho's Pharmacovigilance or designee. The eSAE application will be used to report pregnancy as "Other Important Medical Event" to the IND Office.

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

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

Overdose
An overdose is defined as the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. An overdose that results in an AE should be reported to Taiho's Pharmacovigilance or designee within 24 hours from the time the Investigator first becomes aware of its occurrence.

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

Investigator Communication with NCCN/Taiho Oncology, Inc.:

For expedited reports, Investigator- will send either the MedWatch report form or MD Anderson IND office eSAE report form to NCCN/Taiho Oncology, Inc. at the time of the regulatory authority submission to applicable regulatory authority (e.g.; US FDA) no later than seven (7) days for initial AND follow-up life-threatening and death reports, and fifteen (15) days for all other initial or follow-up serious and unexpected suspected adverse reactions (SUSARs), from the time of receipt of the SAE by Investigator-

All other SAEs/non-expedited Reports: For non-expedited SAE reports (i.e., unrelated to Study Drug or listed/expected event), Investigator- will send a quarterly safety line listing to NCCN/Taiho Oncology, Inc. within 10 days after the start of each quarter (e.g.; April 10th for Quarter 1 data due each year).

NCCN/Taiho Oncology, Inc. Email inbox for individual MedWatch report forms or MD Anderson IND office eSAE report forms and safety line listings: Investigator will send all individual SUSAR MedWatch reports or MD Anderson IND office eSAE report form and quarterly line listings to NCCN/Taiho Oncology, Inc. via email

NCCN SAE Email Address: ORPreports@nccn.org (preferred option)
NCCN SAE Facsimile Number: 215-358-7699 (back-up)

AND

Taiho Oncology, Inc. Email: TaihoCTSafetyreporting@taihooncology.com (preferred option)
Fax: +1 609-750-7371 (back-up)

6.3 Statement of Good Clinical Practices

This trial will be conducted in adherence to the study protocol, Good Clinical Practices as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54 56, 312 and Part 11 as well as ICH GCP consolidated guidelines (E6) and applicable regulatory requirements. http://www.fda.gov/cder/guidance/index.htm

Destruction of the expired/unused investigational product will be performed per the MDACC policy. NCCN/Taiho will be informed prior to destruction of the investigational product.

6.4 Data Collection

All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research Database at MD Anderson Cancer Center.

Data Protection and Confidentiality

All patients who meet eligibility criteria and are enrolled in this trial will be registered in Clinical Oncology Research e-Database (CORe) or other similar e-Database at the University of Texas MD Anderson Cancer Center at Houston. All protocol participants must be registered in the CORe. The date in the current informed consent document is displayed to ensure only the most current IRB approved version is used. Consent date, registration date, off study date, and evaluability data are required for all registrants.

Consent date, registration date, off study date, and evaluability data are required for all registrants. Consent date, registration date, off study date, and evaluability data are required for all registrants. Molecular and Clinical Data Integrated Platform (MOCLIA) will be used as the electronic case report form for this protocol and adverse events and protocol specific data will be entered into MOCLIA. Concurrent medications will be computed on the medical record of the patient in EPIC and not recorded on the case reporting form.

The principal investigator agrees to keep all information and results concerning the study confidential. The confidentiality obligation applies to all personnel involved with this clinical trial. The Investigator must ensure that each participant's anonymity will be maintained in accordance with applicable laws. The principal investigator should keep a separate log of ID numbers, names and medical record numbers. This information will be located in MOCLIA and EPIC. Documents that contain the names associated with these ID numbers (e.g., written consent/assent forms) should be maintained by the Investigator in strict confidence (MOCLIA and EPIC) except to the extent necessary to allow auditing by regulatory authorities, auditing or monitoring by the IRB.

The Principal Investigator shall obtain all such permissions and authorizations as may be necessary or desirable to allow the collection and use of information protected under federal privacy laws and state privacy laws, including permission/authorization for monitoring and analysis (including re-analysis in combination with results of other studies), for regulatory submission purposes and for applicable reporting (if any).

6.5 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements.

IND Annual Reports (DSUR)

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report.

TAIHO and/or partner shall be responsible for the preparation, content and submission of a Development Safety Update Report (DSUR). TAIHO may delegate the preparation of the DSUR to a third party. If requested, TAIHO shall provide the Investigator with the final version of this report within 15 calendar days after submission to health agencies and ethics committees.

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for “serious” and as defined above are present.

The Annual Report should be filed in the study's Regulatory Binder.

6.6 Adverse Event Updates/IND Safety Reports

The sponsor shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects. The Investigator must keep copies of all AE information, including correspondence with the sponsor and the IRB/EC, on file.

6.7 SAE Reconciliation

Reconciliation shall be performed quarterly as an exchange of Line Listings in English. At the end of the Clinical Trial a global reconciliation shall be performed.

7 STATISTICAL CONSIDERATIONS

7.1 Study Design

After patients have signed the informed consent, patients will be enrolled to receive therapy for toxicity and efficacy evaluation. One cycle of therapy is 21 days. No randomization is utilized to assign patients in this study.

The DLT window is 21 days after starting the treatment. The trial starts with safety lead-in:

- Six lead-in patients will be enrolled at dose level 1. If there is one or less DLT, the study will continue following a Bayesian optimal phase 2 (BOP2) design.
- If there are two or more DLTs, the study will enroll another six lead-in patients at dose level -1.
- If there are two or more DLTs at dose level -1, the study of that therapy will be terminated.
- If there is one or less DLT, the study will follow a BOP2 design at the dose level -1.
- The lead-in patients are allowed to be counted as the patients enrolled to stage I per a BOP2 design if they initiate the same dose.

The intent-to-treat (ITT) population includes all patients who have receive study agents. Efficacy will be analyzed based on the ITT population, following a BOP2 design [86,87] with p0 (historical response rate) = 15% and p1 (minimum desired experimental response rate) = 40%. The first stage will consist of 12 patients. Accrual will stop at the end of the first stage if fewer than 3 responses are seen. The second stage will consist of 12 patients. We will declare the experimental agent worthy of further study if 7 or more responses are seen in 24 patients. This design has a Type I error rate of 4.9% and an 86% power. The maximum number of patient enrollment is 6 + 24 = 30, noting that the lead-in patients will be counted as phase II patients.

Below are the operating characteristics of the design using the BOP2 web application,(Table 11), which is available at http://www.trialdesign.org.

Table 11: The Operating Characteristics Of The BOP2 Design For This Study

Scenario	Response Rate	Early Stopping (%)	Claim Promising (%)	Average Sample Size
1	0.15	73.58	4.87	15.2
2	0.30	25.28	55.61	21.0
3	0.40	8.34	86.20	23.0
4	0.50	1.93	97.38	23.8

During the phase II part, after 6 patients are treated, at any time > 30% of patients have DLTs, that dose level will be terminated.

7.2 Statistical Analyses

All patients will be evaluated for toxicity and efficacy from the time of their first treatment. All patients must be assessed for response to treatment to be assigned one of the following categories, even if there are major protocol treatment deviations or if they are ineligible.

1) Complete response
2) Partial response
3) Stable disease
4) Progressive disease
5) Early death from malignant disease
6) Early death from toxicity
7) Early death because of other cause
8) Unknown (not assessable, insufficient data)

Categorization of response will be based on RECIST 1.1. All of the patients who meet the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in response categories 4-8 as above should be considered as failing to respond to therapy (disease progression). A patient will be determined as having a response if he/she has CR or PR during the initial 6 months of therapy; a patient will be determined as a non-response if there is no evidence of response by 6 months during this study. Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. In computing PFS and OS, withdrawing patients will be censored at the time of withdrawal.

Wilcoxon's Signed-Rank Test and Fisher's exact test will be used for data analysis of continuous variables and categorical variables, respectively. A mixed model accounting for patient effects will be used to analyze longitudinal data (including biomarker data) over time. For the objective of describing the toxicity profile, descriptive statistics will be provided on the grade and type of toxicity by dose level. The Kaplan-Meier method will be used to estimate PFS and OS.

7.3 Stopping Rules

If during the phase II part, after 6 patients are treated, at any time > 30% of patients have DLTs at a dose level, that dose level will be terminated. Another cohort may be started at a lower dose level. In addition, if there are < 3 responses in the first 12 patients, the trial will also be terminated.

Patients may be removed from the study if they meet one of the following stop criteria. However, patients may remain on treatment only in their best medical interest.

- Any uncontrolled side effects affecting quality of life.
- Intercurrent illness that prevents further administration of treatment
- Patients demonstrate at least 20% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart (see below).
- Patients can stop participating at any time. However, if patients decide to stop participating in the study, we encourage them to talk to the researcher and their regular doctor first.
- The researcher may decide to take a patient off this study under several circumstances, such as in the participant's medical best interest, funding is stopped, agent supply is insufficient, patient's condition worsens, and new information becomes available.

- Lead-In Phase:

After the first 6 evaluable patients, complete 21 days of study treatment. IND Office approval must be obtained prior to expanding/changing dose levels.

- Phase II:

Toxicity summary will be submitted after 6 evaluable patients completing 21 days and every six evaluable patients thereafter. During every submission, toxicity data of the previously submitted patients will be updated.

Efficacy summary would be submitted after the first 12 evaluable patients complete 12 weeks of study. Final summary is due after the 24 patients complete 12 weeks of treatment. Responses can be updated till 6 months from the start of treatment.

A copy of the summary report should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

Note: Though modified RECIST 1.1 for immune-based therapeutics (iRECIST) criteria[87] are not utilized for efficacy assessment in this study, the investigator may decide to continue the treatment beyond tumor progression as defined by RECIST since antitumor response patterns seen with immunotherapeutic agents may extend beyond the typical time course of responses seen with cytotoxic agents. Once the specific criteria of RECIST defined disease progression are met, a repeat efficacy evaluation between 4 and 8 weeks after the initially documented disease progression should be performed in order to confirm disease progression. If the disease progression is confirmed, then the patient may be discontinued. Otherwise, the investigator may decide to continue treatment.

While awaiting confirmation of disease progression, patients may continue to receive study drug, if their clinical status is considered to be stable by the investigator, based on the following criteria (but are not limited to), to ensure that patients are not exposed to unreasonable risk:

- Absence of signs and symptoms indicating clinically significant progression
- Absence of symptomatic or rapid disease progression requiring urgent medical intervention
- No decline in ECOG performance status

The decision to continue study treatment after the first evidence of disease progression is at the discretion of the investigator and requires that the patient agrees to this treatment plan, and that the shared decision to treat beyond progression is documented in source documents. Beyond tumor progression, patients may remain on treatment only in their best medical interest.

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ATTACHMENT A: STUDY CALENDAR

Treatment with Futibatinib and Pembrolizumab									
Assessment Tool [a]	Screening [b]	Baseline [c]	Cycle 1 Day			Cycle 2, 3, 4, … Day			End of Therapy [d]
			1	8	15	1	8	15	
Futibatinib [e]			X	X	X	X	X	X	
Pembrolizumab [e]			X			X			
Medical history [f]	X			X		X			X
Physical exam [f]		X		X		X			X
ECOG performance status [f]		X		X		X			X
Ophthalmologic exam [g]	X							X	
CBC with differential [h]		X	X	X	X	X			X
Serum chemistries [h]		X	X	X	X	X			X
Serum Pregnancy test [i]		X				X			X
Urinalysis [i]		X				X			X
ECG, ECHO (or MUGA) [i]	X					X			X
TSH and free T4 [i]		X				X			X
Tumor markers, if applicable [i]	X					X			X
Radiological evaluations (CT, MRI or PET as appropriate) [j]	X				X			X	X
Pharmacodynamics (blood) [k]		X			X				X
Tumor specimens [l]	X								
Adverse event assessment [m]	X								
Concurrent medications	X								
DLT assessment [n]			X						
Patient survey [o]		X							

a) Dosing, laboratory tests, imaging studies and office visits/telemedicine will occur per protocol (within ± 4 days) unless patients' medical or logistical issues necessitate adjustment.
b) Screening to occur within 28 days prior to initiation of therapy (C1D1).
c) Baseline to occur within 7 days prior to initiation of therapy (C1D1).
d) End of therapy visit to occur within 30 days of the last dose of study agents, if feasible. Patients will be followed once every 3 months for up to 2 years after the end-of-dosing visit
e) Futibatinib is administered PO daily. Pembrolizumab is administered intravenously once every 21 days on day 1 of each cycle. One cycle is 21 days in length.
f) To be obtained at the start of treatment, after initial 21-day therapy for DLT evaluation, prior to initiating subsequent cycles of therapy, and more frequently as clinically indicated.
g) Perform a comprehensive ophthalmological examination, including optical coherence tomography (OCT) of the macula, prior to initiation of therapy, every 2 months for the first 6 months, and every 3 months thereafter. For onset of visual symptoms, refer patients for ophthalmologic evaluation urgently, with follow-up every 3 weeks until resolution or discontinuation of futibatinib.
.
h) Laboratory tests including CBC with leukocyte differential and platelet count and chemistries (sodium, potassium, chloride, carbon dioxide, BUN, creatinine, glucose, calcium, phosphate, magnesium, albumin, alkaline phosphatase, total bilirubin, AST, and ALT) to be obtained prior to initiation of therapy (C1D1), weekly for the initial 21 days, prior to initiation of each subsequent cycle of therapy, or more frequently as clinically indicated.
i) Pregnancy test in women of child-bearing potential, urinalysis, ECG, TSH, free T4 and tumor markers (CA125 and/or CA15.3, if elevated at screening) occur within 7 days prior to initiation of therapy (C1D1), and prior to initiation of each subsequent odd cycle of therapy; pregnancy test will continue monthly for at least 3 months after end of therapy; ECHO or MUGA occurs at screening, and then periodically as indicated clinically.
j) To be performed at screening, once every 6 weeks of therapy (± 7 days) for the initial 12 weeks after initiation of therapy, and then once every 9 weeks (± 7 days), or sooner as clinically indicated.
k) To collect peripheral blood samples prior to C1D1, C2D1, and end of therapy or prior to C13D1 if still on therapy.
l) To request tumor biopsy pre-study if archived tumor tissues (ten 5-μm thick slides) are not available; biopsy within 1 week prior to C2D1 (at stage II) and at time of relapse in patients with documented SD≥6months/CR/PR (optional).
m) Adverse events to be assessed at all study visits/telemedicine as clinically indicated.
n) DLT assessment to occur within the initial 21 days of therapy.
o) Assessments of PRO-CTCAE^T and/or EQ-5D-3L should occur at baseline, then weekly for the initial 6 weeks of therapy (cycle 1), and at the end of each subsequent cycle (subsequent cycles) (optional).

ATTACHMENT B: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX A: CYP3A AND TRANSPORTERS

CLASSIFICATION OF SUBSTRATES, INHIBITORS, AND INDUCERS OF CYP ENZYMES AND TRANSPORTERS

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

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

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

P-gp substrates and BCRP substrates: Futibatinib is a potential inhibitor of P-gp and BCRP. Futibatinib may alter the PK and activity of P-gp and BCRP substrates.

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

Example of CYP3A Inhibitors		
Cytochrome P450 (CYP) Enzymes	**Strong Inhibitors [a] ≥ 5-fold increase in AUC**	**Moderate inhibitors [b] ≥ 2 but < 5-fold increase in AUC**
CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice,[c] indinavir and ritonavir, idelalisib, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole	aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
a Strong inhibitors are drugs that increase the area under the concentration-time curve (AUC) of sensitive index substrates of a given metabolic pathway ≥5-fold. b Moderate inhibitors are drugs that increase the AUC of sensitive index substrates of a given metabolic pathway ≥2 to <5-fold. c The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).		

Example of CYP3A Inducers		
Cytochrome P450 (CYP) Enzymes	**Strong Inducers ≥ 80% decrease in AUC**	**Moderate Inducers 50-80% decrease in AUC**
CYP3A	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort [a]	bosentan, efavirenz, etravirine, modafinil
a The effect of St. John's wort varies widely and is preparation dependent.		

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

a Sensitive substrates are drugs that demonstrate an increase in AUC of ≥5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction studies.

b Moderate sensitive substrates are drugs that demonstrate an increase in AUC of ≥2 to <5-fold with strong index inhibitors of a given metabolic pathway in clinical drug-drug interaction studies.

c Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of MDR1 (P-gp), the observed increase in exposure could be due to inhibition of both CYP3A and MDR1 (P-gp).

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

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

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

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

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

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