A Phase 2 study of Savolitinib in Patients with *MET* Amplified Metastatic Colorectal CancerCancer Chemotherapy and Pharmacology

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Supplementary Table 1: Treatment-emergent adverse event summary

	N=5			
Adverse Event*	**Grade 1**	**Grade 2**	**Grade 3**	**All Grades**
Fatigue	3 (60%)	0 (0%)	0 (0%)	3 (60%)
Nausea	2 (40%)	1 (20%)	0 (0%)	3 (60%)
Constipation	2 (40%)	0 (0%)	0 (0%)	2 (40%)
Diarrhea	2 (40%)	0 (0%)	0 (0%)	2 (40%)
Hypertension	2 (40%)	0 (0%)	0 (0%)	2 (40%)
Muscle cramp	2 (40%)	0 (0%)	0 (0%)	2 (40%)
Noncardiac chest pain	2 (40%)	0 (0%)	0 (0%)	2 (40%)
White blood cell decreased	2 (40%)	0 (0%)	0 (0%)	2 (40%)
Anorexia	1 (20%)	1 (20%)	0 (0%)	2 (40%)
Edema limbs	1 (20%)	1 (20%)	0 (0%)	2 (40%)
Dyspnea	1 (20%)	1 (20%)	0 (0%)	2 (40%)
Alkaline phosphatase increased	1 (20%)	0 (0%)	1 (20%)	2 (40%)
AST increased	1 (20%)	0 (0%)	1 (20%)	2 (40%)
Anemia	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Blood bicarbonate decreased	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Blood lactate dehydrogenase increased	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Common Cold Symptoms	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Dizziness	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Dyspepsia	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Dysgeusia	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Headache	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Hoarseness	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Hot flashes	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Hyperglycemia	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Hypoalbuminemia	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Hyponatremia	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Indigestion	1 (20%)	0 (0%)	0 (0%)	1 (20%)
LDH Increased	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Pain	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Pruritus	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Serum amylase increased	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Sinus tachycardia	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Sore throat	1 (20%)	0 (0%)	0 (0%)	1 (20%)
Stubbed Toe	1 (20%)	0 (0%)	0 (0%)	1 (20%)

		N=5		
Adverse Event*	**Grade 1**	**Grade 2**	**Grade 3**	**All Grades**
Ascites	0 (0%)	1 (20%)	0 (0%)	1 (20%)
Back pain	0 (0%)	1 (20%)	0 (0%)	1 (20%)
Lymphocyte count decreased	0 (0%)	1 (20%)	0 (0%)	1 (20%)
ALT increased	0 (0%)	0 (0%)	1 (20%)	1 (20%)
Biliary Obstructions	0 (0%)	0 (0%)	1 (20%)	1 (20%)
Thromboembolic event	0 (0%)	0 (0%)	1 (20%)	1 (20%)
Vascular access complication	0 (0%)	0 (0%)	1 (20%)	1 (20%)
Summary				
Maximum Overall AE	2 (40%)	1 (20%)	2 (40%)	

* There were no Grade 4 or Grade 5 AEs.

Supplementary Appendix I: Complete list of inclusion and exclusion criteria.

1. INCLUSION CRITERIA

1.1 Histologically or cytologically confirmed adenocarcinoma of the colon or rectum that is metastatic and/or unresectable.

1.2 Documented wild-type in *KRAS* and *NRAS* (codons 12, 13, 59, 61, 117, and 146) and in BRAF codon 600, based on tumor tissue taken from primary or metastatic site prior to anti-EGFR antibody treatment.

1.3 At least one site of disease that is measurable by RECIST criteria as defined in Section **Error! Reference source not found.**.

1.4 *MET* amplification detected by the Guardant360 cfDNA screening assay (*MET* copy number ≥ 2.2).

1.5 Clinical or radiographic progression on treatments containing a fluoropyrimidine (e.g., 5- fluorouracil or capecitabine), oxaliplatin, irinotecan, an anti-VEGF monoclonal antibody (bevacizumab, ziv-aflibercept) or anti-VEGFR monoclonal antibody (ramucirumab), and an anti-PD1 monoclonal antibody (nivolumab or pembrolizumab) for patients with MSI-high/MMR deficient tumors, or the treatments were not tolerated or contraindicated.

1.6 Clinical or radiographic progression on prior anti-EGFR antibody therapy (either panitumumab or cetuximab).

1.7 Age ≥18 years.

1.8 ECOG performance status 0-1 (Karnofsky ≥80%, see Appendix A).

1.9 Adequate hematological function defined as:

- Absolute neutrophil count (ANC) ≥1,500/mcL
- Hemoglobin (Hgb) ≥9 g/dL (no transfusion in the past 2 weeks)
- Platelets ≥100,000/mcL (no transfusion in the past 10 days)

1.10 Adequate liver function defined as:

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 x the institutional upper limit of normal (ULN) with total bilirubin (TBL) ≤1 x ULN

OR

- Total bilirubin (TBL) >ULN ≤1.5 × ULN with ALT and AST ≤ 1x ULN

1.11 Adequate renal function defined as:
- GFR ≥60 mL/min/1.73m2 unless data exists supporting safe use at lower kidney function values, no lower than 30 mL/min/1.73m2

1.12 Adequate coagulation parameters, defined as:
- International Normalization Ratio (INR) <1.5 x ULN and activated partial thromboplastin time (aPTT) <1.5 x ULN unless patients are receiving therapeutic anticoagulation which affects these parameters

1.13 Females of childbearing potential should be willing to use adequate contraceptive measures (see Section 5.2.2), should not be breast feeding, and must have a negative pregnancy test if of childbearing potential or must have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:
- post-menopausal is defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments; women under the age of 50 years would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution; or women with documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.

1.14 Male patients with female partner of childbearing potential should be willing to use barrier contraception during the study and for 6 months following discontinuation of study drug.

1.15 Ability to swallow and retain oral medications.

1.16 Ability to understand and the willingness to sign a written informed consent document.

2. EXCLUSION CRITERIA

2.1 Cytotoxic chemotherapy (including investigational cytotoxic chemotherapy) or biologic agents (eg. Cytokines or antibodies) within 3 weeks of first dose of study treatment.

2.2 Not recovered to baseline or CTCAE ≤ Grade 1 from adverse events due to all prior anti-cancer therapies except alopecia, oxaliplatin-related neuropathy, and other non-clinically significant adverse events.

2.3 Any other investigational agents within 21 days before the first dose of study treatment.

2.4 Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days prior to starting study drug or has not recovered from side effects of such therapy.

2.5 Known brain metastases. (Radiated or resected lesions are permitted, provided the lesions are fully treated and inactive, patient is asymptomatic, and no steroids have been administered for at least 30 days).

2.6 History of allergic reactions attributed to compounds of similar chemical or biologic composition to savolitinib.

2.7 Prior treatment with a small molecule inhibitor of c-MET or monoclonal antibody against c-MET or HGF.

2.8 Any of the following concurrent medication use:

a. Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (dhea), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug (three weeks for St. John's wort).
b. Patients receiving or requiring strong inducers or strong inhibitors of CYP3A4, strong inhibitors of CYP1A2, or CYP3A4 substrates which have a narrow therapeutic range within 2 weeks of the first dose of study treatment (3 weeks for st john's wort) will be excluded.
c. Concomitant use of drugs that are known to be strong inhibitors of CYP3A4 or CYP1A2 is not permitted during the trial or must be stopped at least 2 weeks prior to receiving the first dose of savolitinib.

2.9 Any of the following cardiac disease currently or within the last 6 months:

a. Unstable angina pectoris
b. Congestive heart failure (New York Heart Association (NYHA) ≥ Grade II; See Appendix D for details of NYHA grading system)
c. Acute myocardial infarction
d. Stroke or transient ischemic attack

2.10 Known hypersensitivity to the active or inactive excipients of AZD6094.

2.11 Uncontrolled hypertension (BP ≥150/95 mmHg despite medical therapy)

2.12 Active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of oral therapy (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea Grade ≥2, and malabsorption syndrome).

2.13 Mean resting correct QT interval (QTcF) >470 msec for women and >450 msec for men on screening obtained from 3 electrocardiograms (ECGs).

2.14 Any factors that may increase the risk of QTc prolongation such as chronic hypokalaemia not correctable with supplements, congenital or familial long QT syndrome; or family history of unexplained sudden death under 40 years of age in first-degree relatives or any concomitant medications known to prolong QT interval and cause Torsade de Pointes (TdP).

2.15 Any clinically important abnormalities in rhythm, conduction or morphology of resting electrocardiograms (ECGs), e.g. complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250 msec.

2.16 Major surgical procedures ≤28 days of beginning study drug or minor surgical procedures ≤7 days. No waiting is required following port-a-cath placement.

2.17 Serious underlying medical condition at the time of treatment that would impair the ability of the patient to receive protocol treatment.

2.18 Active hepatitis B (positive HBV surface antigen (HBsAg) result) or hepatitis C (HCV) infection. Patients with positive HCV antibody are eligible only if the polymerase chain reaction is negative for HCV RNA. Patients with a past or resolved HBV infection are eligible if:

- negative for HBsAg and positive for hepatitis B core antibody [anti-HBc]
  OR
- positive for HBsAg, but for > 6 months have had normal transaminases and HBV DNA levels between 0 – 2000 IU/ml (inactive carrier state) and willing to start and maintain antiviral treatment for at least the duration of the study
  OR
- HBV DNA levels >2000 IU/ml but on prophylactic antiviral treatment for the past 3 months and will maintain the antiviral treatment during the study

2.19 Known serious active infection requiring antibiotic, antiviral or antifungal therapy. HIV-positive patients are eligible only if meeting ALL criteria below:

- No history of AIDS-defining conditions
- Has been on the current HARRT regimen for the past 3 months and will remain on the same regimen during the study
- Current HARRT regimen has a low potential for drug-drug interaction with the study drug
- HIV viral load consistently below detectable limit for the past 3 months
- CD4 count consistently >200 cells/mm3 for the past 3 months

2.20 Presence of other active cancers, or history of treatment for invasive cancer, within the last 5 years. Patients with Stage I cancer who have received definitive local treatment at least 3 years previously, and are considered unlikely (less than 5% probability) to recur are eligible. All patients with previously treated in situ carcinoma (i.e., non-invasive) are eligible, as are patients with history of non-melanoma skin cancer.

2.21 Psychiatric illness/social situations that would limit compliance with study requirements. Patients with impaired decision-making capacity who have a close caregiver or legal guardian are also eligible with the consent of the caregiver/guardian.

2.22 Judgment by the investigator that the patients should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements.