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TITLE: A Phase 2 Study of INC280 in NSCLC patients with MET exon 14 alterations or MET amplification who have received prior MET inhibitor.

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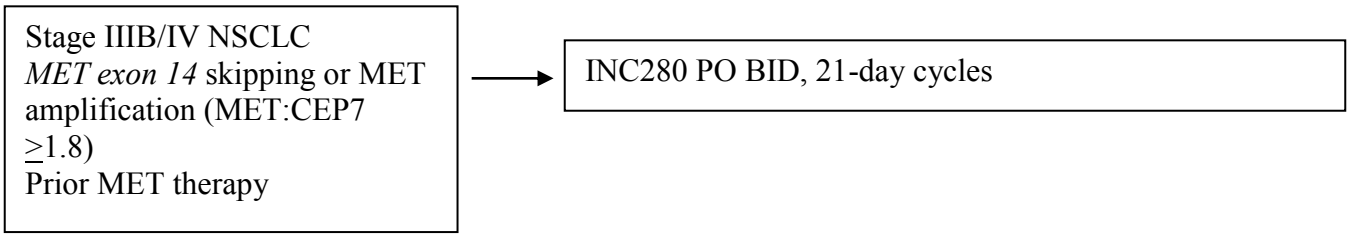
SCHEMA


Stage IIIB/IV NSCLC
MET exon 14 skipping or MET amplification (MET:CEP7 ≥1.8)
Prior MET therapy
INC280 PO BID, 21-day cycles

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1. OBJECTIVES

This is an open label phase II study of INC280 among patients with non-small cell lung cancer (NSCLC) with MET exon 14 skipping alterations (METex14) or MET amplification who have previously been on MET inhibitor therapy. The primary objective is to assess the objective response rate to INC280 among patients with METex14 or MET amplification who have previously been treated with a MET inhibitor. Secondary endpoints will include progression-free survival (PFS), disease control rate (DCR), intracranial response rate (IRR), duration of response (DOR), overall survival (OS), and safety and tolerability. In addition, exploratory analyses will be performed on archival tumor tissue as well as on tumor biopsies and circulating tumor DNA to analyze potential biomarkers of response and resistance to INC280.

1.1 Study Design

This is a phase II study with the primary objective of assessing objective response rate to INC280 among patients with non-small cell lung cancer with METex14 or MET amplification who have previously been on MET inhibitor therapy. Secondary endpoints will include PFS, DCR, IRR, DOR, OS, and safety and tolerability. In addition, exploratory analyses will analyze potential biomarkers of response and resistance to INC280.

1.2 Primary Objectives

Primary Objective: To assess the objective response rate in patients with lung cancer with METex14 or MET amplification with prior exposure to MET inhibitor therapy, when treated with INC280

1.3 Secondary Objectives

Secondary Objectives:

1. To assess progression-free survival (PFS), disease control rate (DCR), intracranial response rate (IRR), and duration of response (DOR) in patients with lung cancer with METex14 or MET amplification with prior exposure to MET inhibitor therapy, when treated with INC280
2. To assess overall survival (OS) in patients with lung cancer with METex14 or MET amplification with prior exposure to MET inhibitor therapy, when treated with INC280
3. To assess safety and tolerability of INC280 among patients with lung cancer with METex14 or MET amplification treated with INC280.

Exploratory Objectives:

1. To explore potential biomarkers of response and resistance to INC280
2. To explore co-occurrence of METex14 with *MET* amplification, *MDM2* amplification, and *CDK4* amplification, among others, and impact on response
3. To generate PDX and cell line models to explore the biology underlying sensitivity and

resistance

2. BACKGROUND

2.1 Non-small cell lung cancer

Lung cancer remains the leading cause of cancer related death in the United States [1]. Standard therapy for Stage IV non-small cell lung cancer (NSCLC) involves platinum-based chemotherapy regimens as first-line therapy, and incremental improvements in chemotherapies for lung cancer have led to a median overall survival of over a year [2-3]. However, the most dramatic successes in lung cancer have been seen with genotype-guided treatment. Driver genetic alterations such as *EGFR* activating mutations, and *ALK* and *ROS* translocations, among others, have been identified that are targets for therapy in lung cancer [4-7]. Targeted treatment of these oncogenic drivers has resulted in markedly higher response rates and survival compared to what is typically seen with conventional therapies [8-11]. Increasingly, lung cancer is becoming subdivided into molecular subsets with different treatment options depending on the molecular diagnostics of the cancer. Somatic mutations in *MET* that affect the splice sites of exon 14 (METex14) are emerging as a targetable alteration in lung cancer which is present in 3-4% of NSCLC [12-23] and are further discussed below in Section 2.3. In addition, MET amplification is another known targetable alteration reported in 2-4% of NSCLC [24]. This study investigates the activity of the MET inhibitor INC280 in patients with NSCLC with METex14 or MET amplification who have previously received another MET inhibitor therapy.

2.2 INC280

INC280 is a potent ATP competitive and reversible inhibitor of the c-MET kinase ($[IC]_{50}$ in a biochemical assay = 0.13 ± 0.05 nM). INC280 is highly specific for c-MET with a greater than 10,000-fold selectivity over a panel of 56 other human kinases tested. Potent activity has also been observed in cell-based biochemical and functional assays that measure c-MET-mediated signal transduction, as well as c-MET-dependent cell proliferation, survival, and migration. In c-MET/HGF-driven tumor models grown as xenografts in mice, oral dosing of INC280 demonstrated significant *in vivo* activity in blocking both c-MET phosphorylation and tumor growth.

After oral administration in humans, INC280 is rapidly absorbed. The apparent terminal half-life of INC280 is short to moderate, from 1.5 to 6 hours across studies. Steady state INC280 exposure is expected to be reached by the third day of consecutive dosing. Accumulation of INC280 following repeated administration is low with accumulation ratio of up to 3-fold. Median time to peak plasma concentrations is reached at approximately 2 hours (Tmax ranged from 0.5 to 8.1 h across studies). Solubility of INC280 is pH-dependent. Solubility of INC280 is high at pH 1.0 (>5 mg/mL) and low (~0.002 mg/mL) at pH 6.9 and pH 7.4.

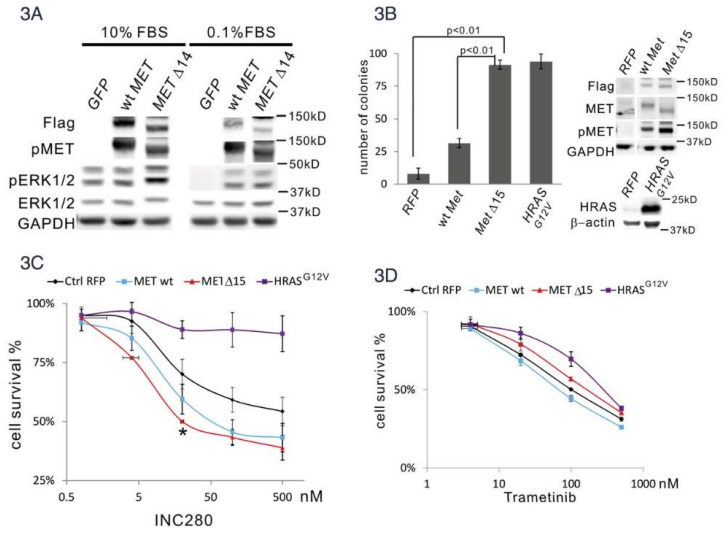
INC280 has been studied in multiple phase 1 and 2 trials, both as a single agent and in combination with other drugs. For detailed information please refer to the Investigator's Brochure. Of note in a phase 1 study in patients with c-MET dependent advanced solid tumors with an expansion part in HCC, gastric cancer, NSCLC, and PRCC and other solid tumors, INC280 showed preliminary signs of antitumor activity in the NSCLC expansion arm with three out of six patients having confirmed partial response; all patients were EGFR wildtype and had high MET status by immunohistochemistry or fluorescent *in-situ* hybridization [25].

2.3 Rationale for this study

Somatic mutations in *MET* that affect the splice sites of exon 14 (METex14) are a targetable alteration in lung cancer which is present in 3-4% of NSCLC [12-23]. These mutations are predominantly in the intronic segments and lead to an alternatively spliced transcript of MET in which deletion of the juxtamembrane domain results in the loss of the Cbl E3-ligase binding site [13]. The alternatively spliced MET receptor exhibits decreased ubiquitination and delayed downregulation, leading to prolonged activation of MET and MAPK/ERK pathway which is transforming [13,17]. In a retrospective study of 240 lung cancer cases at Massachusetts General Hospital, we found 11 cases of METex14 [19]. Similar to other reports, most of these occurred in the absence of other driver alterations, supporting the notion that this is a driver event. Although potentially enriched among never smokers who are wildtype for other driver mutations, METex14 is found in smokers as well, and appears to be present across all lung histologies [19].

Preclinical data have shown that METex14 is a transforming event that can respond well to MET inhibition [13, 17]. Kong-Beltran showed prolonged phosphorylation of MET and MAPK with stimulation by HGF in a cell line with METex14, and increased cell proliferation, which was inhibited by treatment with a MET inhibitor [13]. Frampton et al showed that human METex14 and the homologous mouse MET exon 15 skipping alteration is transforming in cell lines, at least partly through activation of the MEK/ERK pathway. A mouse model of the homologous exon 15 deletion in MET showed sensitivity to MET inhibition with INC280 [17] (see Figure 1).

Figure 1.



In line with these preclinical studies, recent reports have shown promising clinical activity among patients with METex14 treated with MET inhibitors including crizotinib, cabozantinib, and INC280 [17-23]. Paik et al reported on 4 patients with METex14 who were treated with MET inhibitors; three with crizotinib and one with cabozantinib. These patients all experienced significant regression of their tumor burden on the MET therapy [18]. Frampton et al reported on one patient who responded to crizotinib, and two pts who were treated on a phase 1 study of INC280 who also demonstrated a partial response to therapy [17]. Other case reports have shown similar marked responses [19-23]. Table 1 shows a summary of the reported cases in the literature which have shown response to MET therapy. Reported durations on therapy are preliminary in nature but range from approximately 3 months to 13 months.

Table 1. Summary of case reports of patients with METex14 and responses to MET Rx

METex14	MET amplification	Other alterations	Drug	Age	Sex	Smoking	Hist	Ref
c.3028G>C	MET amp	MDM2 amp and multiple others	cabozantinib	80	F	Never	Adeno	18
c.3024_3028delAGAA GGTATATT	No amp IHC H Score 300	multiple	crizotinib	78	M	Former	Adeno	18
c.3028+1G>T	MET amp IHC n/a	multiple	crizotinib	65	M	Former	Adeno	18
c.3028G>C	No amp IHC H score 300	CDK4 amp, MDM2 amp	crizotinib	90	F	Never	Adeno	18
c.2888-5_2944del62	n/a	TP53 ZMYM3	crizotinib	84	F	Never	Histiocytic sarcoma	17
c.3028G>C	FISH not done 3+IHC	TP53	INC280	82	F	Former	Large cell	17
c.3028+1G>T	copy number 4; MET:CEP7 2.3	None reported	INC280	66	F	Former	Squamous	17
c.3028 G>A	Borderline MET:CEP7 2.2	Snapshot wt	crizotinib	73	M	Former	Squamous	19
c.3028G>C	n/a (presume neg, Foundation)	MDM2 amp	crizotinib	76	F	Former	Squamous	20
Chr7:g.116412043G>C	No amp MET/CEP7 0.96	n/a	crizotinib	71	M	Former	Adeno	21
c.2887-18>2887-7del12	n/a	CDKN2A/B loss CDK4 amp MDM2 amp	crizotinib	86	M	Never	Adeno	22
Intron 14 +3 A>G	9 copies	n/a	crizotinib	74	F	Former	Sarcomatoid	23

In addition to MET exon 14 skipping, MET amplification is known to occur in NSCLC and may be targetable as well. Among 13 patients with MET amplified NSCLC enrolled in a clinical trial of crizotinib, 1 had low level amplification (MET/CEP7 ratio 1.8-2.2), 6 had intermediate level amplification (MET/CEP7 ratio 2.2 – 5), and 6 had high level amplification (MET/CEP7 ratio $\geq$5). Partial responses were observed in 4/13 patients (33%, 95% CI 10,65), with none (0/1) observed in the low amplification group, 1/6 (20%) in the intermediate amplification group, and 3/6 (50%) in the high amplification group. [26]

At Massachusetts General Hospital (MGH), we have been performing genotyping of tumors of patients with lung cancer as part of standard clinical care since 2009 [27]. Our current version of the SNaPshot genotyping panel tests for METex14, which previously was challenging to find due to their predominant location in the intronic segments of the gene. In addition, MET amplification is captured on our panel as well. Currently, all patients with lung cancer at MGH are tested reflexively for genetic mutations using the targeted next generation SNaPshot assay for point mutations and the targeted next generation translocation assay for rearrangements.

We propose a phase II study investigating the activity of INC280 in patients with METex14 or MET amplification who have previously received a MET inhibitor, to assess for activity in the setting of resistance. Other ongoing studies are already investigating the activity of INC280 in the first-line setting for METex14. The ability of ceritinib and alectinib to overcome resistance to crizotinib in ALK rearranged lung cancer [10, 28] points to the feasibility of a more potent drug being able to overcome acquired resistance. As there will be patients who have previously received other MET inhibitors such as crizotinib or cabozantinib, it will be important to know whether INC280 has activity in the setting of prior MET inhibitor therapy.

2.4 Correlative Studies Background

MGH has an active investigational program studying response and resistance to targeted therapies in lung cancer led by the Engelman lab [29-31]. Patients who respond to a targeted therapy and become resistant are routinely biopsied and investigations including repeat molecular testing as well as creation of cell line and xenograft models are utilized to interrogate the tumor for mechanisms of resistance. This collaborative framework will be utilized in this trial to study response and resistance mechanisms from biopsy samples of patients on this study. To date there is a dearth of cell line and PDX models for METex14; we will attempt to generate such model systems for study. In addition, *MET, MDM2*, and *CDK4* amplification have all been reported to co-exist with METex14 [17-18], but the relevance to response or resistance is not known. We will therefore explore the co-occurrence of these amplification events among the patients with METex14 enrolled in our study, and explore whether there is any preliminary signal of responsiveness or resistance depending on these co-alterations.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

1. Written informed consent must be obtained prior to any screening procedures.
2. Age $\geq$ 18 years
3. Histologically or cytologically confirmed non-small cell lung cancer, advanced, recurrent, or metastatic

4. MET exon 14 skipping alteration or MET amplification (MET:CEP7 ratio $\geq$ 1.8) by molecular testing (local testing is accepted for eligibility; all patients will have confirmation at MGH but this result is not necessary for eligibility; local molecular pathology result will suffice). This testing can be from any archival or fresh sample.
5. Must have received prior platinum containing chemotherapy for advanced/metastatic non-small cell lung cancer, or have refused or be ineligible for such therapy. Prior neoadjuvant/adjuvant platinum containing chemotherapy will count has having received prior platinum, provided that disease recurred within 6 months of completion of neoadjuvant/adjuvant therapy.
6. EGFR and ALK status must be known in all patients with adenocarcinoma histology. Patients with activating EGFR mutations or ALK translocations are excluded from this study, unless disease has progressed on all available, approved therapies targeting these alterations.
7. At least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation.
8. Must have received prior therapy with a MET inhibitor. Patients must have recovered from all toxicities related to prior anticancer therapies to grade $\leq$ 1 (CTCAE v 4.0). Patients with any grade of alopecia are allowed to enter the study.
9. Patients must have adequate organ function including the following laboratory values at the screening visit:
    - Absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L without growth factor support
    - Platelets $\geq$ 75 x 10^9/L
    - Hemoglobin (Hgb) > 9 g/dL
    - Serum creatinine $\leq$ 1.5 x ULN or calculated creatinine clearance (using Cockcroft-Gault formula) > 45 mL/min for patients with creatinine levels > 1.5 x ULN
    - Total bilirubin $\leq$ 1.5 x ULN, except for patients with Gilbert's syndrome, who may only be included if total bilirubin $\leq$ 3.0 x ULN or direct bilirubin $\leq$ 1.5 x ULN
    - Aspartate transaminase (AST) $\leq$ 3 x ULN, except for patients with liver metastasis, who are included if AST $\leq$ 5 x ULN
    - Alanine transaminase (ALT) $\leq$ 3 x ULN, except for patients with liver metastasis, who are only included if ALT $\leq$ 5 x ULN
    - Alkaline phosphatase (ALP) $\leq$ 5.0 x ULN
    - Asymptomatic serum amylase $\leq$ grade 2 and asymptomatic serum lipase $\leq$ grade 2. Patients with grade 1 or grade 2 serum amylase or lipase at the beginning of the study must be confirmed to have no signs and/or symptoms suggesting pancreatitis or pancreatic injury (e.g., elevated P-amylase, abnormal imaging findings of pancreas, etc.)
    - Patients must have the following laboratory values within the laboratory normal limits or corrected to within normal limits with supplements during screening:
        - Potassium
        - Magnesium
        - Phosphorus

- Total calcium (corrected for serum albumin)

10. ECOG performance status (PS) of 0 or 1
11. Willing and able to comply with scheduled visits, treatment plan and laboratory tests.

3.2 Exclusion Criteria

1. Patients with known hypersensitivity to any of the excipients of INC280 (crospovidone, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, magnesium stearate, colloidal silicon dioxide, and various coating premixes).
2. Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms
3. Presence or history of a malignant disease other than disease to be treated in current protocol that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, indolent malignancies that currently do not require treatment, and completely resected carcinoma in situ of any type
4. Presence or history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis
5. Clinically significant, uncontrolled heart diseases.
    - Unstable angina within 6 months prior to screening
    - Myocardial infarction within 6 months prior to screening
    - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
    - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication (s) is allowed prior to screening
    - Ventricular arrhythmias
    - Supraventricular and nodal arrhythmias not controlled with medication
    - Other cardiac arrhythmia not controlled with medication
    - QTcF > 480 msec
6. Thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting INC280 or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs), radiotherapy ≤ 2 weeks prior to starting INC280 or patients who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting INC280 is allowed

7. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting INC280 or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the study ≥ 1 week after the procedure
8. Patients receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to the start of treatment with INC280 and for the duration of the study:
   - Strong and moderate inhibitors of CYP3A4
   - Strong inducers of CYP3A4
   - Proton pump inhibitors (PPI)
9. Impairment of GI function or GI disease that may significantly alter the absorption of INC280 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome)
10. Unable or unwilling to swallow tablets as per dosing schedule
11. Patients receiving unstable or increasing doses of corticosteroids. If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms other than CNS related, dose must have been stabilized (or decreasing) for at least 5 days before first dose of INC280
12. Patients receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of INC280, and for the duration of the study. Patients on non-enzyme-inducing anticonvulsants are eligible
13. Previous anti-cancer and investigational agents within 2 weeks before first dose of INC280. If previous treatment is a small molecule TKI, last dose must be at least 7 days before first dose of INC280. A shorter washout period may be allowed after discussion with the Principal Investigator.
14. Other severe, acute, or chronic medical or psychiatric conditions or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results
15. Any other condition that would, in the Investigator's judgment, contraindicate patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures, e.g., infection/inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.
16. Pregnant or nursing women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test
17. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 30 days after stopping treatment. Highly effective contraception methods include:

- Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject
- Combination of any two of the following (a+b or a+c, or b+c):
  a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate ≤ 1%), for example hormone vaginal ring or transdermal hormone contraception
  b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential

18. Sexually active males unless they use a condom during intercourse while taking drug and for 7 days after stopping treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. For males with female partners of childbearing potential, couples must use highly effective means of contraception while taking the study drug.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

n/a

4.4 Registration Process for Other Investigative Sites

n/a

5. TREATMENT PLAN

5.1 Treatment Regimen

INC280 will be administered at 400 mg PO BID, with 21 consecutive days defined as a treatment cycle. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6.

Table 2. Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
INC280	Tablet for oral use	400 mg in case of single agent study	Twice Daily (BID)

5.2 Pre-Treatment Criteria

All toxicities must be grade 1 or less, or tolerable grade 2, or else deemed not clinically significant by the treating investigator, prior to starting any cycle of therapy. Results of day 1 labs must be reviewed prior to start of each cycle. Lab values on cycle 1 day 1 do not need to re-meet eligibility criteria if they were already met, but all adverse events must be grade 1 or less or else deemed not clinically significant by the treating investigator.

5.3 Agent Administration

INC280 tablet will be administered orally on a continuous twice daily (BID) dosing schedule, on a flat scale of 400 mg bid and not individually adjusted by weight or body surface area. A complete cycle of treatment is defined as a 21 day period. The investigator must instruct the patient to take the study drug exactly as prescribed.

Drugs are provided in the following strengths: 50 mg, 100 mg, and 200 mg. The tablets should be protected from moisture, and stored at ambient temperature (not above 25 degrees celsius or 77 degrees farenheit). The 50 mg and 100 mg tablets should be used within six week of opening, and the 200 mg tablet within 4 week of opening.

- Each dose of INC280 is to be taken with a glass of water (at least 8 ounces – approximately 250 mL) and consumed over as short a time as possible (i.e., not slower than 1 tablet every 2 minutes).
- Patients should be instructed to swallow the tablets whole and not to chew them.
- INC280 can be administered with or without food. The morning and the evening doses should be taken 12 (± 4) hours apart, although 12-hour interval is highly recommended. The morning dose should be taken the same time each morning. If a dose is not taken within 4 hours of the planned dosing time, the missed dose should not be replaced.
- Patients should be instructed not to make up for missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined as a case when the full dose is not taken within 4 hours of the scheduled twice daily dosing. If that occurs, then the dose (or part remaining dose) should not be taken and dosing should restart with the next scheduled dose. If vomiting occurs, no attempt should be made to replace the vomited dose before the next scheduled dose.
- During the whole duration of treatment with INC280 alone, the patient is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing, avoid sunbathing or using a solarium).

The investigator should instruct the patient to take INC280 exactly as prescribed.

5.4 General Concomitant Medication and Supportive Care Guidelines

Concomitant medications

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient (e.g. such as anti-emetics, anti-diarrhea) is permitted (see section below), except when

specifically prohibited (see section below). In selected cases after discussion with the PI longstanding medications may be allowed to continue with appropriate monitoring.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (excluding study treatment and prior antineoplastic treatments), blood transfusions, surgeries and procedures (including physical therapy) administered within 28 days prior to the first dose administration of INC280 through 30 days after the last dose of INC280 should be recorded. Medications include not only physician prescribed medications, but also all over-the counter medications, herbal medications, food supplements and vitamins.

The following restrictions apply during the entire duration of the study:
- No other investigational therapy should be given to patients
- No anticancer agents other than the study medication (INC280) should be given to patients.

Permitted concomitant therapy

Palliative radiation and/or palliative procedures may be allowed on study after discussion with the study PI. The duration of study drug hold around the palliative radiation or procedure will be determined on a case by case basis after discussion with the study PI.

Patients are permitted to use the following medications while taking INC280:
- Oral or topical antibiotics
- Medications to prevent or treat nausea, vomiting or diarrhea
- Growth factors (e.g. G-CSF, GM-CSF, erythropoietin, platelets growth factors, etc.) are allowed per the investigator's judgement and per local guidelines.
- Treatment with bisphosphonates for pre-existing bone metastases is permitted, if clinically indicated, and following existing local guidelines. Treatment with bisphosphonates should preferably begin before the study treatment is initiated, but can also be initiated during therapy only if absence of radiological bone disease progression is well documented (inthis case, the reason for its use must be clearly documented; i.e. "pre-existing, non-progressing bone metastases").
- Oxygen therapy and blood products or transfusions
- Nutritional support or appetite stimulants
- Pain medication

Permitted concomitant therapy requiring caution and/or action

INC280 is metabolized by CYP3A4. Medications that are moderate inducers of CYP3A4 are not prohibited but should be administered with caution. INC280 is a time-dependent inhibitor of CYP1A2 and CYP3A4. Sensitive substrates for CYP3A4 and CYP1A2 should be administered with caution. INC280 is a weak to moderate inhibitor of CYP2C8, CYP2C9 and CYP2C19. Sensitive substrates of CYP2C8, CYP2C9 and CYP2C19 and substrates with a narrow therapeutic window should be administered with caution. Sensitive substrates for Pgp and OATP trasnporters should also be administered with caution. Refer to Table 4 below

for a list of the medications that require caution when concomitantly used with INC280. Short acting gastric acid modulators containing aluminum hydroxide and magnesium hydroxide, or calcium carbonate can be taken. However, it is recommended to take these drugs at least 3 hours before or 3 hours after administration of INC280. H2 receptor antagonists should be avoided. If patients are using H2 receptor antagonists during the course of this study, patients should not take INC280 within 2 hours of taking H2 receptor antagonists. In addition, the next scheduled dose of INC280 should be administered at least 8 hours after taking H2 receptor antagonists.

Table 3. Drugs to be used with caution while on study

Mechanism of Interaction	Drug Name
Moderate CYP3A4 inducer	Bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, [talviraline], thioridazine
Sensitive CYP1A2, CYP2C8, CYP2C9 and CYP2C19 substrate	Caffeine, alosetron, duloxetine, melatonin, ramelteon, tacrine, repaglinide, celecoxib
Sensitive CYP3A4 substrate	Dronedarone, ebastine, brotizolam, midazolam, triazolam, felodipine, nisoldipine, brecanavir, capravirine, darunavir, atorvastatin, lovastatin, simvastatin, everolimus, lurasidone, perospirone, quetiapine, levomethadyl, budesonide, fluticasone, sildenafil, vardenafil, aprepitant, casopitant, alpha- dihydroergocryptine, aplaviroc, buspirone, darifenacin, eletriptan, eplerenone, lumefantrine, maraviroc, ridaforolimus, ticagrelor, tolvaptan, vicriviroc
CYP2C9 substrate with NTI	Phenytoin, warfarin
CYP2C19 substrate with NTI	s-Mephenytoin
P-gp substrates	Colchicine, digoxin, everolimus, fexofenadine, talinolol
OATP substrates	Atorvastatin, bosentan, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, valsartan, olmesartan, telmisartan
drug- drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.html), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies" Drugs between brackets are not marketed in US. Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor. NTI: narrow therapeutic index	

Prohibited concomitant therapy

INC280 is metabolized by CYP3A4 *in vitro*. Strong and moderate inhibitors or strong inducers of CYP3A4/5 shall be discontinued 7 days prior to the start of INC280 treatment and are prohibited. All agents that are metabolized mainly by CYP1A2 and/or CYP3A4/5 and have a narrow therapeutic index are prohibited.

In vitro solubility data indicated that INC280 may have decreased solubility and thus decreased oral absorption at pH > 4. Long-acting proton pump inhibitors are prohibited. Examples of this class of drugs include: omeprazole, pantoprazole, and lansoprazole. If patients are using proton pump inhibitors at the time of screening, these drugs must be discontinued at least 3 days prior to the first dose of INC280

Patients enrolled in this study are not permitted to participate in additional parallel investigational drug or device studies while on treatment.

Table 4 List of prohibited concomitant therapy

Mechanism of Interaction	Drug Name
Strong CYP3A4 inhibitor	Antibiotics: clarithromycin, telithromycin, troleandomycin Protease Inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole Antivirals: boceprevir, telaprevir Others: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Moderate CYP3A4 inhibitor	Antibiotics: ciprofloxacin, erythromycin Protease Inhibitors: amprenavir, atazanavir, darunavir, fosamprenavir Antifungals: fluconazole Calcium Channel Blockers: diltiazem, verapamil Others: aprepitant, casopitant, cimetidine, dronedarone, tofisopam, grapefruit juice, Seville (sour) oranges, pomegranate, star fruit, schisandra sphenanthera
Strong CYP3A4 inducer	Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin, St. John's wort
CYP1A2 substrate with NTI	Theophylline, tizanidine
CYP3A4 substrate with NTI	Quinidine, [terfenadine], astemizole, cyclosporine, sirolimus, tacrolimus, pimozide, alfentanil, fentanyl, diergotamine, ergotamine, cisapride
Long acting proton pump inhibitor	Omeprazole, pantoprazole, lansoprazole, esomeprazole, rabeprazole, dexlansoprazole
drug- drug interactions (DDI) database, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies" Drugs between brackets are not marketed in USA. NTI: narrow therapeutic index	

Table 5 Prohibited medications causing QTc prolongation

Class of medication	Drug Name
Antianginal	Bepridil
Antiarrhythmic	Amiodarone, disopyramide, dofetilide, flecainide, ibutilide, procainamide, quinidine*, sotalol
Antibiotic	Azithromycin, clarithromycin*, erythromycin*, moxifloxacin, sparfloxacin
Anticancer	Arsenic trioxide, vavdetanib
Antidepressant	Citalopram
Antihistamine	[Astemizole]*, [terfenadine]*
Anti-infective	Pentamidine
Antilipemic	Probucol
Antimalarial	Chloroquine, halofantrine
Antinausea	[Domperidone], droperidol

Antipsychotic	Chlorpromazine, [haloperidol]*, mesoridazine, pimozide, thioridazine
GI stimulant	[Cisapride]
Opiate agonist	[Levomethadyl], methadone
Please note: *CYP3A substrate; drugs between brackets are not marketed in USA. Source: Arizona Center for Education and Research on Therapeutics (CERT), Drugs that prolong the QT interval and/or induce Torsades de Pointes http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm	

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and/or lack of clinical benefit and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression (note that after discussion with the principal investigator, the decision can be made to continue on study past progression if the participant is having clinical benefit). The following criteria must be met if the decision is made to continue treatment past RECIST-defined progression, and written informed consent must be obtained for treatment beyond RECIST-defined disease progression.
    - absence of clinical symptoms or signs indicating clinically significant disease progression;
    - no decline in performance status that is thought due to disease progression
    - absence of rapid disease progression or threat to vital organs or critical anatomical sites requiring urgent alternative medical intervention;
    - no significant, unacceptable or irreversible toxicities related to study treatment

- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse event(s)

- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements

- Participant decides to withdraw from the protocol therapy

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Rebecca Heist MD at 617 724 4000.

5.6 Duration of Follow Up

Participants will be followed with periodic telephone follow up for two years after removal from protocol therapy or until death, whichever occurs first. Phone calls will be placed every three months and survival follow up obtained. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death
- Completion of required follow up

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A ODQ Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 4.0). Any changes must be recorded.

Dose reduction and re-escalation

An INC280 dose reduction will follow the dose reduction steps described in Table 6. For each patient, a maximum of 2 dose level modifications is allowed after which the patient must be discontinued from treatment with INC280.

Dose re-escalation of study treatment to the previous dose level is allowed only once, and if no AE leading to dose modification is observed after at least 1 cycle (3 weeks) of study treatment at the reduced dose.

Table 6 Dose reduction steps for INC280

INC280 dose levels*			
	Starting dose level - 0	Dose level - 1	Dose level – 2**
INC280	400 mg BID	300 mg BID	200 mg BID
*Dose reduction should be based on the worst toxicity demonstrated at the last dose.			
**Dose reduction below 200 mg is not allowed.			

General guidelines for dose modifications are presented in Table 7.

Unless otherwise indicated in Table 7, for grade 1 and tolerable grade 2 treatment-related toxicities, patients may continue full doses of study treatment. For intolerable grade 2 or any grade 3 treatment-related toxicities, dosing should be interrupted until at least resolution to grade 1 followed by either dose reduction or re-initiation at the same dose level, depending on the type of toxicity as described in Table 7. For any grade 4 toxicity, patients should interrupt study treatment until resolution to grade 1, followed by either dose reduction or treatment discontinuation (refer to Table 7).

A patient must discontinue treatment with INC280 if, after treatment is resumed at the lowest allowed dose (200 mg BID), the toxicity recurs with the same or worse severity despite use of maximal preventive measures as per the institution guidelines for toxicity prevention and management. All interruptions or change to study drug administration must be recorded.

Table 7 Criteria for interruption and re-initiation of INC280 treatment

Recommended dose modifications for INC280	
Worst toxicity CTCAE 4.0 Grade [a.] (value)	**During a cycle of therapy**
HEMATOLOGICAL	
Neutropenia (neutrophil count decreased, ANC)	
Grade 1 (ANC < LLN - 1500/mm3; < LLN - 1.5 x 109/L)	Maintain dose level

Recommended dose modifications for INC280	
Worst toxicity CTCAE 4.0 Grade [a.] (value)	**During a cycle of therapy**
Grade 2 (ANC < 1500 - 1000/mm3; < 1.5 - 1.0 x 109/L)	Maintain dose level
Grade 3 (ANC < 1000 - 500/mm3; < 1.0 - 0.5 x 109/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (ANC < 500/mm3; < 0.5 x 109/L)	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level
Febrile neutropenia (ANC < 1000/mm3 (< 1.0 x 109/L), fever > 38.3°C)	Omit dose, then: If resolved in ≤ 7 days, resume treatment at ↓ 1 dose level If resolved in > 7 days, discontinue patient from study treatment
Thrombocytopenia (platelet count decrease, PLT)	
Grade 1 (PLT < LLN - 75,000/mm3; < LLN - 75 x 109/L)	Maintain dose level
Grade 2 (PLT < 75,000 - 50,000/mm3; < 75 - 50 x 109/L)	Maintain dose level
Grade 3 (PLT < 50,000 - 25,000/mm3; < 50 - 25 x 109/L)	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25,000/mm3; < 25 x 109/L)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level

Recommended dose modifications for INC280	
Worst toxicity CTCAE 4.0 Grade [a.] (value)	**During a cycle of therapy**
Anemia (hemoglobin decrease)	
Grade 1 (Hgb < LLN - 10.0 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L)	Maintain dose level
Grade 2 (Hgb < 10.0 - 8.0 g/dL; < 6.2 – 4.9 mmol/L; < 100 - 80 g/L)	Maintain dose level
Grade 3 (Hgb < 8.0 g/dL; < 4.9 mmol/L; < 80 g/L)	Omit dose until resolved to ≤ grade 2, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4	Omit dose until resolved to ≤ grade 2 and then ↓ 1 dose level If toxicity recurs, discontinue study treatment permanently
RENAL	
Serum creatinine	
Grade 1 (>1 and ≤1.5 x baseline; > ULN and ≤ 1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 and ≤3.0 x baseline; > 1.5 and ≤ 3 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at the same dose level.
Grade 3 (> 3.0 x baseline; > 3.0 and ≤ 6.0 x ULN)	Omit dose until resolved to ≤ grade 1 or baseline, then resume treatment at ↓ 1 dose level. Patients will be instructed to increase their fluid intake until resolution to ≤ Grade 1 or baseline.
Grade 4 (> 6.0 x ULN)	Discontinue study treatment permanently
HEPATIC	
Total Bilirubin [b.]	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓1 dose level
Grade 3 (≥ 3.0 - 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then ↓ 1 dose level If resolved in > 7 days, then discontinue permanently
Grade 4 (> 10.0 x ULN)	Discontinue study treatment permanently

Recommended dose modifications for INC280	
Worst toxicity CTCAE 4.0 Grade [a.] (value)	**During a cycle of therapy**
AST or ALT	
Grade 1 (> ULN – 3.0 x ULN)	Maintain dose level with LFTs [c.] monitored per protocol
Grade 2 (> 3.0 - 5.0 x ULN) without total bilirubin elevation to > 2 x ULN	Maintain dose level with LFTs [c.] monitored per protocol
Grade 3 (> 5.0 - 20.0 x ULN) without total bilirubin elevation to > 2 x ULN	Omit dose until resolved to ≤ grade 1 (or ≤ grade 2 if liver metastases present), then If resolved in ≤ 7 days, then resume treatment at the same dose level If resolved in > 7 days, then resume treatment at ↓ 1 dose level
Grade 4 (> 20.0 x ULN) without total bilirubin elevation to > 2 x ULN	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
AST or ALT, and concurrent Total Bilirubin	
AST and/or ALT > 3.0 x ULN and total bilirubin > 2.0 x ULN and ALP < 2.0 x ULN	Discontinue study treatment permanently in the absence of signs of cholestasis, hemolysis, and alternative causes of the liver injury have been excluded (e.g., concomitant use of hepatotoxic drug(s), alcoholic hepatitis, etc.)
METABOLIC	
Asymptomatic amylase and/or lipase elevation	If symptomatic elevations of any grade, discontinue INC280
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2 (> 1.5 - 2.0 x ULN)	Maintain dose level
Grade 3 (> 2.0 - 5.0 x ULN)	Continue dosing and monitor laboratory values, if levels do not resolve to grade 2 or baseline by 14 days after the initial report, ↓ 1 dose level
Grade 4 (> 5.0 x ULN)	Continue dosing and monitor laboratory values, if levels do not resolve to grade 2 or baseline by 14 days after the initial report, ↓ 1 dose level

Recommended dose modifications for INC280	
Worst toxicity CTCAE 4.0 Grade [a.] (value)	**During a cycle of therapy**
PULMONARY	
Monitor patients for pulmonary symptoms indicative of ILD/Pneumonitis. In addition, withhold INC280 for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for ILD/Pneumonitis to exclude alternative causes such as, but not limited to infections, lymphangitic carcinomatosis, cardiogenic edema, or pulmonary hemorrhage.	
Interstitial lung disease/Pneumonitis	
Grade 1	Interrupt INC280 during diagnostic workup for ILD/Pneumonitis. Exclude infections and other etiologies. **In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue INC280.** Only in the absence of a diagnosis of ILD/Pneumonitis may study drug be restarted at the same dose. If it recurs after restarting of study drug, permanently discontinue INC280.
Grade 2	Mandatory: Interrupt INC280 dose during diagnostic workup for ILD until improvement to ≤ Grade 1. Exclude infections and other etiologies. **In presence of diagnosis of ILD/Pneumonitis after diagnostic workup, it is mandatory to permanently discontinue INC280.** Only in the absence of a diagnosis of ILD/Pneumonitis may study drug be restarted following these guidelines: • If resolves to ≤ Grade 1 in ≤ 7 days reduce study drug by 1 dose level • If fails to resolve to ≤ Grade 1 within 7 days or recurs after resumption of study drug at decreased dose, permanently discontinue INC280
Grade 3	Mandatory: Permanently discontinue study drug.
Grade 4	Mandatory: Permanently discontinue study drug.
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTc 450-480 ms) Grade 2 (QTc 481-500 ms)	Maintain dose level
Grade 3 (QTcF ≥ 501 ms on at least two separate ECGs)	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, resume treatment at the same dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (QTc ≥ 501 or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Discontinue study treatment permanently
GASTROINTESTINAL	
Pancreatitis	
Grade 2	Maintain dose level
Grade ≥ 3	Discontinue study treatment permanently
Diarrhea	At the first sign of abdominal cramping, loose stools, or onset of diarrhea, it is recommended that the patient be treated according to institutional standard of care.
Grade 1 (despite maximal anti-diarrheal medication)	Maintain dose level

Recommended dose modifications for INC280	
Worst toxicity CTCAE 4.0 Grade [a.] (value)	**During a cycle of therapy**
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then maintain dose level. If diarrhea returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Grade 3 or 4 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ grade 1, then resume treatment at ↓ 1 dose level
Vomiting	
Grade 1 (despite standard anti-emetics)	Maintain dose level
Grade 2 (despite standard anti-emetics)	Omit dose until resolved to ≤ grade 1, then maintain dose level. If vomiting returns as ≥ grade 2, then omit dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level
Grade 4 (despite standard anti-emetics)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level

Recommended dose modifications for INC280	
Worst toxicity CTCAE 4.0 Grade [a.] (value)	**During a cycle of therapy**
Nausea	
Grade 1 or 2 (despite standard anti-emetics)	Maintain dose level
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Rash/photosensitivity	
Grade 1	Maintain dose level.
Grade 2	Maintain dose level.
Grade 3 (despite skin toxicity therapy)	Omit dose until resolved to grade ≤ 1, then: If resolved in ≤ 7 days, then ↓ resume treatment at 1 dose level If resolved in > 7 days (despite appropriate skin toxicity therapy), then discontinue patient from study drug treatment
Grade 4 (despite skin toxicity therapy)	Discontinue study treatment permanently
Fatigue/ Asthenia (General disorders and administration site conditions)	
Grade 1 or 2	Maintain dose level
Grade 3	Omit dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, resume treatment at same dose level If resolved in > 7 days, resume treatment at ↓ 1 dose level
Other adverse events	
Grade 1 or 2	Maintain dose level,consider to initiate appropriate support medication. For any intolerable grade 2 (e.g.: limiting instrumental ADL), consider omitting the dose until resolved to ≤ grade 1, then ↓ 1 dose level.
Grade 3	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4	Discontinue study treatment permanently

All dose modifications should be based on the worst preceding toxicity.
[a.] Common Toxicity Criteria for Adverse Events (CTCAE version 4.0).
[b.] If grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level* and continue treatment at the discretion of the investigator.
[c.] LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin ≥ grade 2), alkaline phosphatase and GGT.

Treatment interruption and treatment discontinuation

If the administration of INC280 is temporarily interrupted for reasons other than toxicity, then treatment with INC280 may be resumed at the same dose. If the treatment with INC280 is withheld due to toxicity, the dose modification guidelines in Table 6 should be followed.

If the treatment with INC280 is withheld for more than 21 consecutive days (counting from the first day when a dose was interrupted), then INC280 should be permanently discontinued. When the treating physician believes that continuing treatment may still provide clinical benefit for the patient, study treatment may be resumed.

Patients who discontinue the study due to a study drug related AE or an abnormal laboratory value must be followed as described below.

Follow-up and management guidelines for toxicities

All patients will be followed for safety until 30 days after the last dose of INC280. Patients

whose treatment is temporarily interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event.

An assessment should be performed in all cases below where toxicity monitoring is needed according to the local standard of care and physician judgment.

All patients should receive best supportive care (BSC) as per standard local practice for the treatment of pre-existing medical conditions or adverse events that may arise during the study. BSC is defined as drug or non-drug therapies, nutritional support, physical therapy, or any other treatment alternative that the treating physician believes to be in the patient's best interest.

Table 8 outlines follow up evaluations and recommended management guidelines in the event of selected toxicities.

Table 8 Follow-up evaluations and management guidelines for selected toxicities

TOXICITY	FOLLOW-UP EVALUATION
HEMATOLOGICAL	
Febrile neutropenia, Neutropenia ≥ CTCAE grade 3 Thrombocytopenia ≥ CTCAE grade 3 Anemia ≥ CTCAE grade 3	Test weekly (or more frequently) until ≤ CTCAE grade 2. Perform physical exam for check on bruising in case of major thrombocytopenia.
RENAL	
Serum creatinine ≥ CTCAE grade 2	Test weekly (or more frequently) until ≤ CTCAE grade 1 or baseline. Patients will be instructed to increase hydration until resolution to ≤ CTCAE grade 1 or baseline.
HEPATIC	
Total bilirubin ≥ CTCAE grade 2	Test weekly (or more frequently) until ≤ CTCAE grade 1 Patients with total bilirubin > 1.5 ULN (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional work-up as clinically indicated by these results. Follow-up of hyperbilirubinemia should proceed as per the guidelines in table 2, irrespective of the results of fractionation.
AST/ALT ≥ CTCAE grade 2 and 3	Test weekly (or more frequently) until ≤ CTCAE grade 1 or ≤ CTCAE grade 2 (if patient is Grade 2 at baseline). In particular, test for all the following liver function tests (LFTs): albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 1.5 x ULN), alkaline phosphatase and GGT. Note: for patients with Gilbert Syndrome, total and direct bilirubin must be monitored, but intensified monitoring applies to changes in direct bilirubin only.

TOXICITY	FOLLOW-UP EVALUATION
METABOLIC	
Asymptomatic amylase or lipase ≥ CTCAE grade 3	Test weekly (or more frequently) until ≤ CTCAE grade 2 A CT scan or equivalent imaging procedure to assess the pancreas, liver, and gallbladder is recommended within 7 days of the first occurrence of any ≥ CTCAE grade 3 result, to exclude disease progression or potential other liver or pancreatic disease.
CARDIAC	
≥ CTCAE grade 3	Test weekly (or more frequently) until ≤ CTCAE grade 2.
QTcF ≥ 501 ms (CTCAE grade 3)	When QTcF ≥ 501 ms (CTCAE grade 3), perform the following: ● Call the study's central ECG review laboratory immediately and request an immediate manual read of the ECG. ● Perform an analysis of serum potassium, calcium, phosphorus, and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. ● Review concomitant medication usage for the potential to inhibit CYP3A4/5 (table 4) and/or to prolong the QT-interval (Table 6). ● Check compliance with correct dose and administration of study treatment Perform a repeat ECG within one hour of the first QTcF of ≥501 ms. ● If QTcF remains ≥ 501 ms, repeat ECG as clinically indicated, but at least once daily until the QTcF returns to < 501 ms. Repeat ECGs 7 days and 14 days (and then every 21 days) after dose resumption for all patients who had therapy interrupted due to QTcF ≥ 501 ms. ● If QTcF of ≥ 501 ms recurs, repeat ECGs as described above. Notes: ● The investigator should contact the Novartis Medical Lead or designee regarding any questions that arise if a patient with QTcF prolongation should be maintained on study. ● If the central ECG report shows a QTcF ≥ 501 msec (not previously documented on the site machine), contact the patient and instruct him/her to suspend study treatment and return for a repeat ECG as soon as possible. The central ECG reader should be called for a manual read of the repeat ECG immediately, and the above guidance followed.
GASTROINTESTINAL	
Diarrhea	Initiate anti-diarrhea treatment after first signs of abdominal cramping, loose stools or overt diarrhea. Consider/Investigate potential concomitant medication, food or comorbidity driven causes of diarrhea (including infectious causes) and remedy these causes, if possible (e.g., discontinuation of concomitant medication, dietary modification, treatment of comorbidity). The patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Antidiarrheal medication must be initiated at the first sign of abdominal cramping, loose stools or overt diarrhea. Concomitant medication for the treatment of diarrhea should follow local practice and the investigator's best judgment and may follow "the recommended guidelines for the treatment of cancer treatment-induced diarrhea"For example: ● For uncomplicated diarrhea (grade 1 or 2 without complicating signs or symptoms), loperamide given at a standard dose (e.g. initial administration of 4 mg, then 2 mg every 2-4 hours, maximum of 16 mg/day), along with oral hydration and dietetic measures should be considered. Note: complicating signs or symptoms include: moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration. ● For complicated diarrhea (all grade 3 or 4, grade 1-2 with complicating signs or symptoms), management should involve intravenous (IV) fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg sub-cutaneous tid or 25 to 50 µg IV) and antibiotics (e.g. fluoroquinolone) should be given.

TOXICITY	FOLLOW-UP EVALUATION
Nausea and Vomiting	The investigator should consider/investigate potential concomitant medication, food or comorbidity driven causes of nausea and/or vomiting and remedy these causes if possible (e.g. discontinuation of concomitant medication, dietary modification, treatment of comorbidity). Individualized supportive and anti-emetic treatment should be initiated, as appropriate, at the first signs and/or symptoms of these AEs. In patients with vomiting, the patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration. Concomitant medication for the treatment of nausea and/or vomiting should follow local practice and the investigator's best judgment.
NERVOUS SYSTEM DISORDERS	
Any Neurological Toxicity	
≥ Grade 2	Neurological assessments must be repeated at least twice a week until resolution to < CTCAE grade 1. Unscheduled MRI and gadolinium enhanced T1 imaging may also be conducted to evaluate patients for intramyelinic edema like lesions, brain metastases and other unanticipated CNS occurrences. An EEG may be performed to monitor for physiological changes in brain activity.
SKIN TOXICITY (rash and photosensitivity)	
Prevention/Prophylaxis	Avoid unnecessary exposure to sunlight Apply broad-spectrum sunscreen with SPF≥15 at least twice daily
CTCAE grade 1	Use alcohol-free emollient cream (e.g. glycerine and cetomacrogol cream) for management of itching related to dry skin Consider to initiate institute appropriate skin toxicity therapy (such as antihistamines, topical antibiotics and/or corticosteroids and short course low-dose systemic corticosteroids)
CTCAE grade 2	Initiate/intensify appropriate skin toxicity therapy (such as antihistamines, topical antibiotics and/or corticosteroids and short course low-dose systemic corticosteroids).
≥ CTCAE grade 3	Intensify appropriate skin toxicity therapy and monitor weekly or more frequently until resolved to grade ≤ 2

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Adverse Events

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

For a detailed discussion of toxicities seen to date please see the Investigator's Brochure.

In brief, a total of 622 patients have been treated with INC280 as a single agent at different doses, and 487 patients have been treated with INC280 in combination therapies: with gefitinib (161 patients), with buparlisib (43 patients), with erlotinib (55 patients), with

cetuximab (13 patients), with LGX818/MEK162 (12 patients), with EGF816 (130 patients), with nivolumab (18 patients), with sonidegib (one patient), with PDR001 (20 patients), and with bevacizumab (34 patients). Twenty-one clinical trials are currently ongoing with INC280.

A total of nineteen patients have experienced 25 DLTs: one Grade 3 AST and ALKP increase (50 mg QD), one Grade 2 suicidal ideation (600 mg BID), one Grade 3 depression (400 mg BID), two Grade 3 fatigue (200 mg BID and 450 mg BID respectively), one Grade 3 ALT increased, AST increased, and rash (400 mg BID, in combination with erlotinib), one Grade 3 rash pustular (400 mg BID, in combination with erlotinib), one Grade 3 total bilirubin increase (250 mg BID), one Grade 4 cough and dyspnea (600 mg BID, combination with gefitinib), one Grade 3 dizziness (800 mg QD, combination with gefitinib), one Grade 3 personality change (400 mg BID, in combination with buparlisib), one Grade 3 nausea (300 mg BID, in combination with buparlisib), two Grade 3 ALT increased and AST increased (400 mg BID, in combination with buparlisib), one Grade 3 ALT increased (INC280 200mg with 50 mg QD EGF816), one Grade 3 anaphylactic reaction (INC280 400mg with 100mg QD EGF816), one Grade 3 rash maculo-papular and Grade 1 pyrexia (INC280 400 mg BID with 150 mg QD EGF816), one Grade 3 rash maculopapular and dermatitis allergic (INC280 400mg BID with 150 mg QD EGF816), and one Grade 3 diarrhea (400mg BID, in combination with PDR001).

The majority of the reported AEs were mild or moderate (CTCAE Grade 1 or 2). CTCAE Grade 3/4AEs suspected to be related to INC280 included- ALT increased, AST increased, GGT increased, neutrophil count decreased, white blood cell count decreased, hypophosphatemia, hyponatremia, depression, colitis ulcerative and lung infection (each in one patient [2.3%]) (in [CINC280X1101]); AST increased, hypophosphatemia, and peripheral edema (each in one patient [2.2%])(in [CINC280X2101]); edema peripheral and lipase increased (each in nine patients [4.1%]), nausea, ALT increased (7 patients [3.2%]), AST increased, hypophosphatemia, nausea, and vomiting (each in three patients [1.4%])(in [CINC280A2201]); fatigue (three patients [7.9%]), =ALT increased, hypophagia (two patients [5.3%]), decreased appetite, amylase increased, AST increased, blood bilirubin increased, edema peripheral, hypoalbuminemia, anemia, lipase increased, and neutropenia (each in one patient [2.6%]) (in [CINC280X2102]); ALT increased (4 patients [4.3%], nausea, fatigue, lipase increased, hypophosphatemia (each in three patients [3.2%]), peripheral edema, rash maculo-papular, amylase increased, AST increased, asthenia, dehydration (each in two patients [2.2%]) (in Dose Expansion Group, [CINC280X2102]); vomiting (2 patients [13.2%]), nausea, ALT increased, AST increased, amylase increased and blood bilirubin increased (each in one patient [2.6%] (in combination with erlotinib, [CINC280X2201]); ALT increased, edema peripheral, amylase increased, gamma-glutamyl transferase increased, interstitial lung disease, and neutropenia (each in one patient [6.3%]) (in [CINC280X2205]); fatigue and amylase increased (each in two patients [15.4%]), ALT increased and lipase increased (each in one patient [7.7%]) (in combination with cetuximab, [CINC280X2104]); rash maculopapular (17 patients, [14.9%]), ALT increased and amylase increased (each in 8 patients [4.4%]), fatigue (4 patients [3.5%]), asthenia, AST increased, and vomiting (each in 3 patients [2.6%]) (in combination with EGF816, [CINC280X2105C]); nausea (2 patients [10%]), edema peripheral, ALT increased, diarrhea, stomatitis, hypotension, platelet count decreased, acute myocardial infarction, unstable angina, blood bilirubin increased, dehydration, and neutropenia (each in one

patient [5%]) (in combination with PDR001, [CINC280X2108]); amylase increased and lipase increased (each in 10 patients [6.2%]), edema peripheral (6 patients [3.7%]), vomiting and fatigue (each in four patients [2.5%]), ALT increased (3 patients [2.1%]),rash, pulmonary embolism, hyponatremia, asthenia, AST increased, dizziness (each in 2 patients [1.2%]), and, with single incidences of paronychia, vomiting, blood bilirubin increased, and hemoptysis [0.6%] (in combination with gefitinib, [CINC280X2202]); hyperlipasaemia (2 patients [5.4%]), asthenia, blood alkaline phosphatase increased, lipase increased (each in one patient [2.7%]) (in DDI-study, [CINC280A2103]); and vomiting (2 patients [6.3%]), anemia, abdominal pain, ALT increased, AST increased, asthenia, blood albumin decreased, lipase increased, lymphocyte count decreased, malaise, quality of life decreased and vitamin k decreased (each in one patient [3.1%]) (in DDI-study, [CINC280A2105]).

Adverse Drug Reactions considered to be expected for reporting purposes

System Organ Class	**Adverse Reaction**	**Nature[1]**	**Serious[2]**	AE frequency regardless of causality from single agent study-CINC280A2201		AE frequency, suspected to be INC280 related from single agent study-CINC280A2201		**Number of observed suspected SARs[5] and frequency**
				CINC280A2201 (N=220)[3] n (%)	**Category**	**CINC280A2201 (N=220)[4] n (%)**	**Category**	**N =1109 cancer patients[6]**
Gastrointestinal disorders	Vomiting	Hospitalization and antiemetic were required in most of serious cases	Yes	59 (26.8)	Very common	40 (18.2)	Very common	12 (1.0)
	Nausea	Nausea often associated with vomiting, Hospitalization and antiemetic were required in most of serious cases.	Yes	94 (42.7)	Very common	69 (31.4)	Very common	8 (0.7)

System Organ Class	**Adverse Reaction**	**Nature[1]**	**Serious[2]**	AE frequency regardless of causality from single agent study-CINC280A2201		AE frequency, suspected to be INC280 related from single agent study-CINC280A2201		**Number of observed suspected SARs[5] and frequency**
				CINC280A2201 (N=220)[3] n (%)	**Category**	**CINC280A2201 (N=220)[4] n (%)**	**Category**	**N =1109 cancer patients[6]**
	Diarrhea	Diarrhea associated with vomiting and nausea; Interruption of study medication; Hospitalization was required in most of serious cases.	Yes	35 (15.9)	Very common	22 (10.0)	Very common	9 (0.8)
	Abdominal pain; Abdominal pain upper	Hospitalization and study medication dose adjustment or interruption /discontinuation was required in most serious cases	Yes	27 (12.3)	Very common	12 (5.5)	Common	5 (0.4)
General disorders and administration site conditions	Fatigue	Hospitalization and study medication dose adjustment or interruption /discontinuation was required in most serious cases	Yes	52 (23.6)	Very common	34 (15.5)	Very common	5 (0.4)

System Organ Class	**Adverse Reaction**	**Nature[1]**	**Serious[2]**	AE frequency regardless of causality from single agent study-CINC280A2201		AE frequency, suspected to be INC280 related from single agent study-CINC280A2201		**Number of observed suspected SARs[5] and frequency**
				CINC280A2201 (N=220)[3] n (%)	**Category**	**CINC280A2201 (N=220)[4] n (%)**	**Category**	**N =1109 cancer patients[6]**
	Edema peripheral	Hospitalization and study medication dose adjustment or interruption. Treatment with diuretics.	Yes	98 (44.5)	Very common	77 (35.0)	Very common	4 (0.3)
	Asthenia	Hospitalization and study medication dose adjustment or interruption /discontinuation was required in most serious cases	Yes	27 (12.3)	Very common	12 (5.5)	Common	4 (0.3)
Investigations	Alanine aminotransferase increased	Hospitalization and study medication interruption was required in some of the serious cases	Yes	18 (8.2)	Common	12 (5.5)	Common	9 (0.8)
	Aspartate aminotransferase increased	Hospitalization and study medication interruption was required in some of the serious cases	Yes	15 (6.8)	Common	11 (5.0)	Common	5 (0.4)
	Gamma-glutamyltransferase increased	n/a	No	12 (5.5)	Common	3 (1.4)	Common	n/a

System Organ Class	**Adverse Reaction**	**Nature[1]**	**Serious[2]**	AE frequency regardless of causality from single agent study-CINC280A2201		AE frequency, suspected to be INC280 related from single agent study-CINC280A2201		**Number of observed suspected SARs[5] and frequency**
				CINC280A2201 (N=220)[3] n (%)	**Category**	**CINC280A2201 (N=220)[4] n (%)**	**Category**	**N =1109 cancer patients[6]**
	Blood bilirubin increased	Hospitalization and study medication interruption was required in some of the serious cases	Yes	7 (3.2)	Common	6 (2.7)	Common	2 (0.2)
	Amylase increased	n/a	No	12 (5.5)	Common	11 (5.0)	Common	n/a
	Lipase increased	n/a	No	14 (6.4)	Common	13 (5.9)	Common	n/a
	Blood creatinine increase	Hospitalization, study medication interruption and treatment with fluids and electrolytes	Yes	54 (24.5)	Very common	39 (17.7)	Very common	2 (0.2)
Metabolism and nutrition disorders	Decreased appetite	Hospitalization and study medication dose adjustment or interruption /discontinuation was required in most serious cases	Yes	46 (20.9)	Very common	31 (14.1)	Very common	3 (0.3)
	Hyponatremia	Hospitalization and study medication dose adjustment or interruption /discontinuation was required in most serious cases	Yes	7 (3.2)	Common	1 (0.5)	Uncommon	3 (0.3)

System Organ Class	**Adverse Reaction**	**Nature[1]**	**Serious[2]**	AE frequency regardless of causality from single agent study-CINC280A2201		AE frequency, suspected to be INC280 related from single agent study-CINC280A2201		**Number of observed suspected SARs[5] and frequency**
				CINC280A2201 (N=220)[3] n (%)	**Category**	**CINC280A2201 (N=220)[4] n (%)**	**Category**	**N =1109 cancer patients[6]**
Nervous system disorders	Dizziness	n/a	No	17 (7.7)	Common	8 (3.6)	Common	n/a
Renal and urinary disorders	Renal impairment; Acute kidney injury	Hospitalization, study medication interruption and treatment with fluids and electrolytes	Yes	4 (1.9)	Common	2 (0.9)	Uncommon	2 (0.2)
Respiratory, thoracic and mediastinal disorders	Pneumonitis / interstitial lung disease	Hospitalization, study medication interruption and steroid treatment is required	Yes	7 (3.2)	Common	2 (0.9)	Uncommon	10 (0.9)

n/a: not applicable

1 Additional description of serious ADRs

2 For the purpose of individual case safety reporting in clinical trials, serious forms of adverse reactions indicated as non-serious in this table will always be considered unexpected.

3 Frequency is calculated based on all events regardless of grades and causality assessment in study CINC280A2201 clinical trial database (N=220) with the data cut-off of 09-Aug-2017. The category is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)

4 Frequency is calculated based on all events (all grades) which are assessed as suspected by the investigators in study CINC280A2201 clinical trial database (N=220) with the data cut-off of 09-Aug-2017. The category is based on the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000)

5 Number of subjects who have experienced the suspected SAR and frequency of suspected SAR as of the cut-off date of 28-Sep-2017

6 As of the cut-off date of 28-Sep-2017, a total of 1109 cancer patients received INC280.

7.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Serious Adverse Events

A serious adverse event (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening. Life-threatening means that the person was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires or prolongs inpatient hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the person was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly or birth defect; or
- Is an important medical event when, based upon appropriate medical judgment, it may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. 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.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- Abnormal lab values that do not require treatment
- treatment planned before signing informed consent for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

Expected Adverse Events

Adverse events can be 'Expected' or 'Unexpected'. Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the Investigator's Brochure

Unexpected Adverse Events

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the Investigator's Brochure.

Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely - The AE is doubtfully related to the study treatment.
- Unrelated - The AE is clearly NOT related to the study treatment.

7.3 Procedures for AE and SAE Recording and Reporting

Reporting or participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study.

All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms. Each recorded AE or SAE will be described by its duration (i.e., start and end dates), intensity treatment required, grade, suspected relationship to the investigational product (causality), outcome and actions taken with investigational product.

The descriptions and grading scales found in the CTEP NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. The CTCAE version 4.0 is located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

- **YES**

There is a plausible temporal relationship between the onset of the AE and administration of the investigational product, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational product; and/or the AE abates or resolves upon discontinuation of the investigational product or dose reduction and, if applicable, reappears upon re-challenge.

- **NO**

Evidence exists that the AE has an etiology other than the investigational product (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational product (e.g., cancer diagnosed 2 days after first dose of study drug).

Each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator. Specific reporting requirements are detailed below.

Reporting to Novartis

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided the main informed consent and until at least 30 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department - Fax: (877-778-9739).

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment and pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving study treatment and up to 7 days after INC280 treatment has been stopped. If a pregnancy occurs while on study treatment, the newborn will be followed for at least 3 months.

Serious Adverse Event Reporting

Reporting to the Institutional Review Board

All serious adverse events that occur, during treatment, or within 28 days of the last dose of treatment must be reported to the DFCI Office for Human Research Studies (OHRS). This includes events meeting the criteria outlined in Section 6.2.2, as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.

- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.

- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 28 days of the last study intervention.

  Note: If the participant is in long term follow up, report the death at the time of continuing review.

Participating investigators must report each serious adverse event within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.
Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Events that occur after consent but before study enrollment/registration and receiving study treatment do not need to be reported.

7.4 Expedited Adverse Event Reporting

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.

7.4.1 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.5 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 INC280

8.1.1 Description

The chemical name of INC280 drug substance is 2-fluoro-N-methyl-4-(7-(quinolin-6-ylmethyl)imidazo[1,2-b][1,2,4]triazin-2-yl)benzamide dihydrochloride monohydrate. INC280 has a molecular formula of $C_{23}H_{21}Cl_2FN_6O_2$ and a molecular weight of 503.35 (salt form on monohydrate basis).

INC280 dihydrochloride monohydrate is a slightly hygroscopic light yellow to yellow powder. The solubility of INC280 dihydrochloride at 25°C is approximately 3.47 mg/mL in water; 0.08 mg/mL in pH 6.8 and 0.72 mg/mL in pH 3.0 buffer.

8.1.2 Form

INC280 is presently formulated as an orally administered capsule dosage form or as a film-coated tablet. The tablet form will be used in this study. Drug request order forms are sent directly to Novartis.

The orally administered film-coated tablets contain the active drug INC280, along with the following commonly used excipients: colloidal silicon dioxide, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, povidone, sodium lauryl sulfate, and various coating premixes.

8.1.3 Storage and Stability

The stability data of clinical batches for INC280 film-coated tablets shows acceptable physical and chemical stability under designated storage conditions. Refer to the clinical

label for storage condition requirements.

8.1.4 **Compatibility**

INC280 will be administered as a single agent in this study.

8.1.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6 **Availability**

INC280 will be provided by Novartis for this study.

8.1.7 **Preparation**

INC280 is presently formulated as an orally administered capsule dosage form or as a film-coated tablet. The tablet form will be used in this study.

8.1.8 **Administration**

INC280 tablet will be administered orally on a continuous twice daily (BID) dosing schedule, on a flat scale of mg/day and not individually adjusted by weight or body surface area. A complete cycle of treatment is defined as 21 days of twice daily treatment with INC280. The investigator must instruct the patient to take the study drug exactly as prescribed. Patients will record their daily dosing in a drug diary.

- Each dose of INC280 is to be taken with a glass of water (at least 8 ounces – approximately 250 mL) and consumed over as short a time as possible (i.e., not slower than 1 tablet every 2 minutes).
- Patients should be instructed to swallow the tablets whole and not to chew them.
- INC280 can be administered with or without food. The morning and the evening doses should be taken 12 (± 4) hours apart, although 12-hour interval is highly recommended. The morning dose should be taken the same time each morning. If a dose is not taken within 4 hours of the planned dosing time, the missed dose should not be replaced.
- Patients should be instructed not to make up for missed doses or partial doses (i.e., when the entire dose is not taken as instructed). A missed or partial dose will be defined as a case when the full dose is not taken within 4 hours of the scheduled twice daily dosing. If that occurs, then the dose (or part remaining dose) should not be taken and dosing should restart with the

next scheduled dose. If vomiting occurs, no attempt should be made to replace the vomited dose before the next scheduled dose.

During the whole duration of treatment with INC280 alone, the patient is recommended to use precautionary measures against ultraviolet exposure (e.g., use of sunscreen, protective clothing, avoid sunbathing or using a solarium).

8.1.9 Ordering

INC280 will be provided by Novartis.

8.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 Destruction and Return

Drug will be returned and destroyed per DF/HCC SOP pharmacy policy (INV-100 and INV-102)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

Archival tumor tissue will be collected at baseline for all patients where this is available. At least 10 unstained slides will be obtained from the archival tissue if possible. An optional biopsy at study entry may be used to provide this tissue. Tumors will be tested for biomarkers that may predict response, including baseline mutational status as assessed by a next generation sequencing panel, as well as *MET, CDK4*, and *MDM2* amplification, among others. Circulating tumor DNA will be collected at study entry and during study and assessed for mutational status as well. Biomarker testing will be done at MGH in collaboration with Dr. Engelman's lab.

Optional tumor biopsy at time of progression

Patients will be asked to undergo an optional biopsy at time of progression for correlative studies investigating mechanisms of resistance to INC280. For any patient undergoing an optional biopsy, tumor will be collected and assessed for mutational testing and for development

into cell lines or patient-derived xenograft models for further study. This will be done at MGH in collaboration with Dr. Engelman's lab.

Sample Type	Proposed Studies
Archival FFPE tumor tissue or optional tumor biopsy at study entry	**Baseline mutational status** **MET, CDK4, MDM2 amplification, among others** **Cell lines and PDX models, if optional fresh biopsy**
Optional tumor biopsy at progression	**Mutational status at progression** **MET, CDK4, MDM2 amplification, among others** **Cell lines and PDX models**

10. STUDY CALENDAR

Screening evaluations are to be conducted ≤ 4 weeks prior to start of protocol therapy. Scans must be done $\leq$4 weeks prior to the start of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

Follow-up data will be collected every 3 months until participant withdrawal, death, or removal from study.

				+/- 3 day window around visits			
Visit Name	**Screen**	**Cycle 1 (21days)**		**Cycle 2 -18 (Up to Month 13)**	**Cycles > 18 (Months > 13)**	**EOT**	**Follow up phone calls**
Day of cycle	**-28 to -1**	**C1 D1**	**C1 D8**	**Day 1**	**Day 1 of Every Other Cycle**		**Every three months from end of treatment**
Obtain study informed consent	x						
Collection of archival tumor tissue (paraffin blocks/slides) [a]	x						
Confirm METex14 (locally confirmed by investigator)	x						
Inclusion/exclusion criteria	x						
Relevant medical and oncologic history [b]	x						
Physical examination	x	x	x	x	x	x	
Vital signs	x	x	x	x	x	x	
Performance status	x	x	x	x	x	x	
ECG	x	x		x	x	x	
Pregnancy test (serum test)	x						
Hematology[c]	x	x	x	x	x	x	
Chemistry[d]	x	x	x	x	x	x	
Tumor evaluation by RECIST (CT/MRI)[e]	x			Every two cycles			
INC280 PO BID		x	x	x	x		
Adverse events		x	x	x	x	x	
Optional tumor biopsy	x					x	
Circulating tumor DNA	x			Every two cycles			
Survival follow up							x

[a] Collection of archival tumor tissue is highly encouraged but not mandatory for study entry if archival tissue is not available
[b]Relevant medical and oncologic history should include prior cancer treatment history
[c]Hematology includes: a complete blood count (CBC) consisting of red blood cells (RBCs), hemoglobin, a complete white blood cell count with differential (total neutrophils (bands and segs), lymphocytes, monocytes, eosinophils, and basophils), and platelet count
[d] Chemistry includes: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total and fractionated (e.g., direct and/or indirect) bilirubin, calcium, creatinine, glucose, magnesium, phosphate (inorganic phosphorus), potassium, protein (total), sodium, urea or blood urea nitrogen (BUN), amylase, lipase.
[e]Tumor evaluations, repeating the type of scan which was originally performed at screening, will be performed every two cycles and evaluated by RECIST by TIMC. At the discretion of the treating investigator, non-scheduled scans can be performed if clinically indicated.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every two cycles.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions

(longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. 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 baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). 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.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches

may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine).The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 μCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used

as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

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 participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of

20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

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

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best

response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

Duration of overall response: 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 progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease 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, including the baseline measurements.

11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.7 Response Review

N/a

11.2 Antitumor Effect – Hematologic Tumors

N/a

11.3 Other Response Parameters

N/a

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The ODQ will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Multicenter Guidelines

n/a

12.4 Collaborative Agreements Language

n/a

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is an open label Phase II study enrolling patients with MET exon 14 skipping or MET amplification who have previously been treated with a MET inhibitor.

The primary endpoint is response rate (RR) as measured by RECIST 1.1 criteria.

Secondary endpoints are:

Progression-Free Survival (PFS): PFS will be defined as the time from the start of study drug to the date of first documented progression or death.

Disease control rate (DCR): Disease control rate will be defined as the sum of complete response, partial response, and stable disease at 12 weeks by RECIST 1.1.

Intracranial response rate (IRR): Intracranial response rate will be calculated based on response assessments in the brain for patients with measurable CNS disease at baseline by RECIST v 1.1 criteria.

Duration of response (DOR): Duration of response will be calculated from the time of first assessment of CR or PR until the first occurrence of progressive disease or death.

Overall survival (OS): Overall survival will be defined as the time from the start of study drug to the date of death due to any cause. OS time for patients who are alive at the end of hte study or are lost to follow up will be censored at the time of last contact. OS will be estimated using the Kaplan-Meier method.

Safety and tolerability: Toxicity will be assessed using the CTCAE v4.0 criteria.

Exploratory studies will assess biomarkers of response and resistance as well as attempt to establish cell lines and PDX models from optional tumor biopsies.

All patients who begin study drug on protocol will be considered evaluable. Any patient who does not begin study drug on protocol will be considered not evaluable and will be replaced.

13.2 Sample Size, Accrual Rate and Study Duration

The planned sample size is n = 20. Patients who never begin protocol therapy after signing consent or who are not evaluable will be replaced. With n =20 patients, the study will have an 80% power to detect an improvement in the overall response rate of 21.3% from the null of 10% using a one-sided binomial test with alpha of 0.05; i.e. a comparison of response rate of 10% versus 31.3%.

13.3 Stratification Factors

No stratification planned

13.4 Interim Monitoring Plan

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual from this study.

13.5 Analysis of Primary Endpoints

As described in section 13.1.

13.6 Analysis of Secondary Endpoints

As described in section 13.1.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.7.2 Evaluation of the Primary Efficacy Endpoint

All participants will be evaluable for response from the time of their first treatment. Participants who never start protocol therapy will be considered inevaluable.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A 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.