Abbreviated Title: INC280 in RCC

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Title: A Phase 2 Study of the MET Kinase Inhibitor INC280 in Papillary Renal Cell Cancer

Principal Investigator: Ramaprasad Srinivasan, M.D., Ph.D.
Urology Oncology Branch, CCR, NCI
10 Center Drive, Building 10/CRC 2W-5940
Bethesda, MD 20892
Phone: 240-760-6251
Email: ramasrin@mail.nih.gov

Investigational Agents:

Drug Name:	INC 280
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Sponsor:	Center for Cancer Research
Manufacturer:	Novartis
Supplier:	

Commercial Agents: None

PRÉCIS

Background:

- Papillary RCC is the second most common histologic subtype of kidney cancer, accounting for approximately 10-15% of cases
- Type 1 papillary RCC occurs in both sporadic and hereditary forms, which are histologically identical. Non familial type 1 papillary RCC can present as both solitary renal tumors and as bilateral, multifocal disease
- There are no standard agents of proven efficacy for patients with advanced papillary RCC.
- Patients with disease localized to the kidney are managed surgically while patients with advanced/unresectable disease are usually managed in the community with VEGF pathway antagonists or mTOR inhibitors.
- Activating mutations of MET were identified in the germline of affected HPRC patients, who have a predilection for the development of bilateral, multifocal type 1 papillary RCC. Somatic MET mutations have been found in a subset of patients with non-inherited, sporadic papillary renal carcinoma
- The investigational agent INC280 is a selective MET inhibitor lacking activity against the VEGF pathway
- This is a proof-of-concept study using INC280 in patients with papillary RCC to test the idea that effectively blocking the HGF/MET pathway will lead to clinical activity in patients with papillary renal cell cancer

Objectives:

Primary Objective:

- To determine the overall response rate (RECIST 1.1) in patients with papillary renal cell carcinoma treated with single agent INC280

Eligibility:

- Diagnosis of hereditary papillary renal carcinoma (HPRC) or sporadic papillary renal cell carcinoma (RCC)
    - Patients with bilateral multifocal disease can have tumors localized to the kidney or have metastatic disease
    - Patients with sporadic papillary RCC (but without multifocal disease) should have advanced disease that is considered unresectable
- ECOG 0-2
- Measurable disease
- Adequate organ function
- No active brain metastases
- Prior therapy
    - No more than 3 prior lines of systemic therapy
    - Prior therapy with a MET inhibitor is allowed as long as the patient has not had progressive disease while receiving the agent

Design:

- This is a phase 2 single center non-randomized trial.
- The study will be conducted using a Simon 2 stage minimax design. Initially 13 evaluable subjects will be recruited. If there are no responses to therapy, the study will be terminated. If there is at least 1 response an additional 7 evaluable subjects will be accrued.
- The two-stage minimax design is based on assuming an ineffective response rate of 5% and a targeted effective response rate of 25%. We also assume that the probability of accepting an ineffective treatment and the probability of rejecting an effective treatment are each 10%.
- Subjects will be dosed orally at a starting dose of 400 mg twice daily.
- The overall response rate (complete response + partial response) will be determined.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase/serum glutamic pyruvic transaminase/SGPT
AST	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase/SGOT
AUC	Area under the plasma concentration-time curve
AUC0-24	Area under the plasma concentration-time curve from 0 to 24 hours
b.i.d.	bis in diem/twice a day
Cmax	Maximum (peak) concentration of drug
CNS	Central nervous system
DLT	Dose limiting toxicity
DMPK	Drug metabolism and pharmacokinetics
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
EEG	Electroencephalogram
HGF	Hepatocyte growth factor
Hr	Hour
i.v.	intravenous(ly)
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
IHC	Immunohistochemical
IRB	Institutional Review Board
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NOAEL	No observable adverse event level
PK	Pharmacokinetics
pRCC	Papillary renal cell carcinoma
QD	Once daily
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
VEGFR	Vascular endothelial growth factor receptor

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

To determine the overall response rate (RECIST 1.1) in patients with papillary RCC treated with single agent INC280

1.1.2 Secondary Objective(s)

To assess progression-free survival, overall survival, disease control rate (partial and complete response plus stable disease ≥ 6 months) and duration of response

To evaluate tolerability of INC280 in patients with papillary RCC

Pharmacodynamic Endpoints

Evaluate modulation of the HGF/MET pathway using paired pre- and on-therapy tumor biopsies (when available)

Evaluate modulation of plasma HGF and sMET

1.1.3 Exploratory objective

To evaluate the impact of MET mutation (germline or somatic) or MET amplification/trisomy 7 and/or prior MET therapy on overall response rate, PFS and other outcome measures

1.2 BACKGROUND AND RATIONALE

1.2.1 Overview of disease pathogenesis, epidemiology and current treatments

In 2012, RCC was the sixth and eighth most common malignancy among men and women, respectively, with an estimated new 64,770 cases and 13,570 deaths in the United States[1]. While

surgical treatment for localized disease can be curative, the outlook for patients with metastatic disease remains poor[2]. With increased understanding of the molecular pathways involved in the pathogenesis of RCC, several new systemic agents are available for use in metastatic disease, largely for patients with clear cell RCC, the most common subtype.

Papillary RCC is the second most common histologic subtype of kidney cancer, accounting for approximately 10-15% of cases of all tumors arising in the kidney, with a significantly higher incidence in African Americans[3-5]. Papillary RCC can be further separated histologically into papillary type I and II subtypes[6]. Although our understanding of the molecular underpinnings of papillary RCC are still evolving, emerging data suggests that there may be significant differences in the genetics and molecular pathways underlying different types of papillary RCC as well as disparate outcomes associated with these entities[7-9].

Type 1 papillary tumors are characterized histologically by the presence of papillary or tubulo/papillary architecture with slender short papillae containing delicate fibrovascular cores lined by small cells with low grade basophilic nuclei and scant amphophilic cytoplasm. Type 1 papillary RCC occurs in both sporadic and hereditary forms, which are histologically identical. Hereditary Papillary Renal Carcinoma (HPRC) is a hereditary cancer syndrome in which affected individuals are at risk for the development of bilateral, multifocal type 1 papillary renal carcinoma[8,10]. HPRC is inherited in an autosomal, dominant fashion. It has been estimated that affected patients with HPRC may develop up to 3,000 tumors per kidney (Figure 1). Activating mutations of MET were identified in the germline of affected HPRC patients (Figure 2) and have been found in tumors in a subset of patients with non-inherited, sporadic papillary renal carcinoma[10-14].

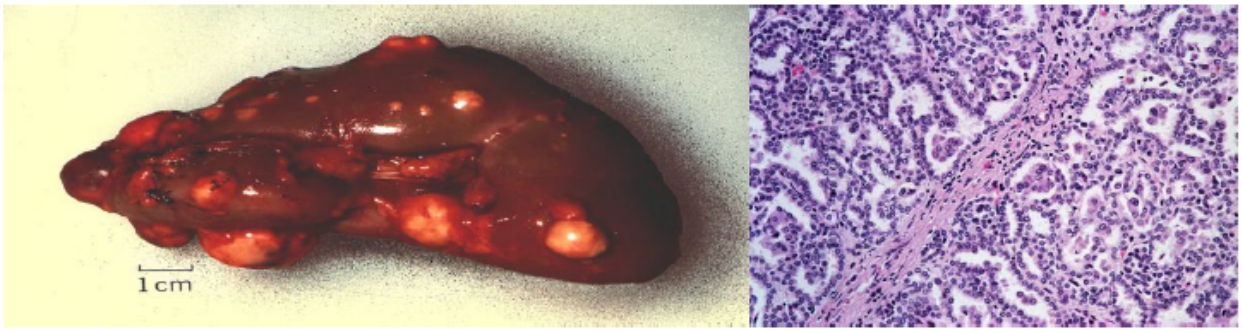


Figure 1: Multiple renal tumors in a resected kidney from an HPRC patient. Histopathologic evaluation reveals Type 1 papillary RCC.

The proto-oncogene MET (hepatocyte growth factor receptor) was identified as the gene for hereditary papillary renal carcinoma by genetic linkage analysis in families with this inherited renal cancer syndrome[12-15]. MET encodes the cell surface receptor for hepatocyte growth factor (HGF), and the HGF/MET pathway plays a key role in several biological processes including mitogenesis, morphogenesis and motogenesis[16,17]. Activating mutations in the tyrosine kinase domain of MET have been detected in the germline of affected patients and in a subset of sporadic papillary kidney cancers. Nonrandom duplication of the chromosome 7 bearing the mutant MET allele, which was demonstrated in HPRC kidney tumors, may afford a growth advantage to these tumor cells, providing an important second step in HPRC tumor progression[18,19] (Figure 2).

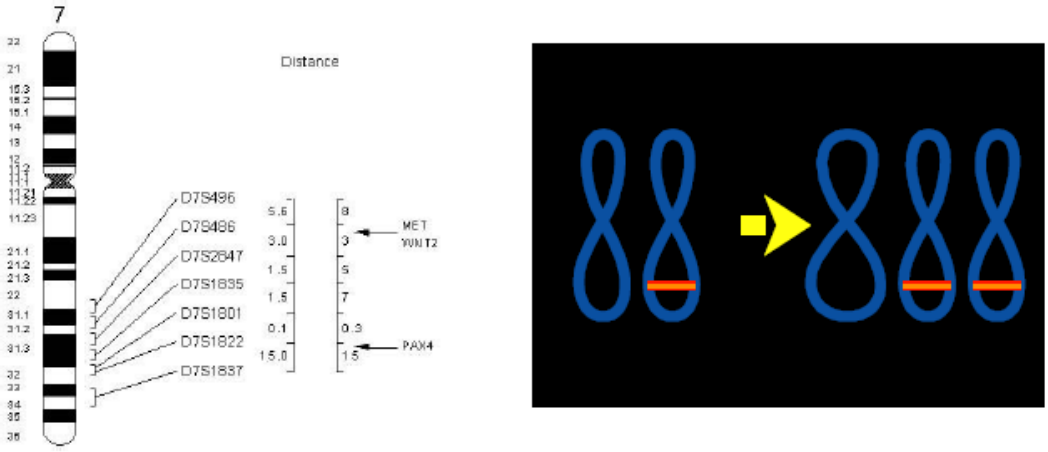


Figure 2: The MET proto-oncogene is located on the long arm of chromosome 7 and is mutated in patients with HPRC. Tumors from HPRC patients demonstrate non-random duplication of the chromosome bearing the mutated MET allele.

Sporadic type 1 papillary RCC accounts for approximately 5% and type 2 papillary RCC for approximately 10% of all kidney tumors diagnosed. While sporadic type 1 papillary RCC can present with solitary renal tumors, patients with bilateral multifocal tumors with no family history of RCC have also been described. There has been no systematic attempt at evaluating the role of MET activation in sporadic type 1 papillary RCC. One study identified mutations in 13% of patients with all subtypes of papillary RCC and no family history of renal tumors, although the prevalence of this genetic alteration in sporadic type I papillary RCC has not been adequately defined[11]. Furthermore, polysomy of chromosome 7, on which both MET and the gene for its ligand HGF are located, is seen in over two-thirds of patients with papillary RCC (both subtypes included in most studies), suggesting an alternative means of activation of the HGF/MET pathway is some papillary tumors[20,21].

Both sporadic and hereditary forms of papillary RCC have metastatic potential. Patients with tumors localized to the kidney are managed surgically. For patients with bilateral, multifocal papillary RCC, surgical management is geared toward preservation of renal function. These patients are usually followed radiologically until 1 or more tumors reach a size of approximately 3 cm, at which point nephron-sparing surgical excision of these tumors is performed. Partial nephrectomies in these patients are not curative, but are aimed at reducing the risk of metastatic spread. Repeated surgical intervention may be needed because of multifocality, leading to compromise of renal function and other morbidity associated with multiple partial nephrectomies.

There are no standard therapies of proven benefit for patients with metastatic papillary RCC. While several agents targeting the VEGF- and mTOR-pathways are approved by the US FDA for the treatment of metastatic RCC, their activity has been best studied in patients with clear cell RCC, in whom these agents appear to offer clinically meaningful improvements in progression free or overall survival. Papillary RCC patients with unresectable disease requiring systemic therapy usually receive either an mTOR inhibitor or a VEGF pathway antagonist, based on demonstration of modest activity in several retrospective analyses, small single arm phase 2 studies, and at least one subgroup analysis of a large randomized phase 3 study. In most studies, objective response

rates following therapy with mTOR or VEGFR-targeted TKIs were low (0-36%), with a median progression free survival (PFS) of less than 6 months[22-28]. Inhibitors of the epidermal growth factor receptor (EGFR) have also been evaluated in papillary RCC; in a phase 2 trial of the EGFR inhibitor erlotinib, the overall response rate in 52 patients with metastatic papillary RCC was 11%, with a 6 month PFS of only 29%[29]. Several phase 2 trials evaluating the efficacy of everolimus, pazopanib or combined VEGF- and mTOR-pathway blockade in non clear cell RCC are currently underway.

The identification of oncogenic MET mutations in patients with HPRC as well as in a subset of patients with sporadic papillary RCC has led to considerable interest in targeting the HGF/MET pathway in these malignancies. Foretinib (formerly XL880), an inhibitor of Met, VEGFR2, RON and AXL tyrosine kinases was one of the earliest agents targeting the Met pathway available for clinical investigation. In a recently concluded multicenter phase 2 study, two dosing schedules of foretinib were evaluated in patients with papillary RCC[30]. A total of seventy-four patients were enrolled sequentially into one of two independent cohorts to receive either: A) an intermittent dosing regimen (240mg/d PO days 1-5 of every 14-day cycle, N=37) or B) a daily dosing regimen (80mg/d PO, N=37). The overall response rate in the entire cohort was 13.5%, with 10/75 patients experiencing a partial response. The median PFS was 9.3 months, considerably higher than that seen in historical controls treated with agents targeting VEGFR or mTOR pathways. The clinical activity of foretinib was most pronounced in patients with germline mutations in MET; in a preplanned subgroup analysis, 5/10 (50%) of patients with germline MET mutations experienced a PR, while only 5/57 (9%) of patients without this alteration had an objective response[30,31]. Patients with papillary type 1 as well as those with type 2 tumors were enrolled on this study. Although central pathology review of all tumors was conducted to confirm papillary histology, sufficient tumor was not available in several instances to render an accurate subclassification; it was, therefore, not possible to determine if type 1 and type 2 papillary tumors included in this trial exhibited differential sensitivity to foretinib. The adverse event profile associated with this agent was reminiscent of that seen with other inhibitors of the VEGF axis. However, a higher than anticipated incidence of pulmonary thromboembolism (11%) was noted, as were alterations in dark adaptation in several patients treated on this trial. These data suggest that Met pathway antagonists are worthy of further study at least in some subgroups of papillary RCC. At least one other Met inhibitor, tivantinib (ARQ197), is currently undergoing evaluation with or without erlotinib in a randomized phase 2 trial in patients with advanced papillary RCC. (NCT01688973)

1.2.2 Overview of INC280

The chemical name for INC280 is 2-fluoro-N-methyl-4-(7-(quinolin-6-ylmethyl)imidazo[1,2 b][1,2,4]triazin-2-yl) benzamide dihydrochloride; dihydrochloride. INC280 is a light yellow to yellow powder as confirmed by visual inspection against a white background. INC280 dihydrochloride is a nonhygroscopic solid. INC280 presents good solubility in water (4.7 mg/mL) at an acidic pH (2.1 mg/mL) but has poor solubility characteristics in the pH range of 7.4 to 8 (0.002 mg/mL). INC280 drug product is provided as 50 mg, 100 mg, and 200 mg tablets. The formulations contain the active ingredient along with commonly used excipients that are of compendial grade.

INC280 possesses potent inhibitory activity against the MET kinase in vitro (IC50 = 0.13 ± 0.05 nM). INC280 has been shown to be both ATP competitive and reversible in its mode of action. INC280 is also active against MET kinases from different species including murine and canine.

INC280 has been shown to be highly specific for MET with > 10,000-fold selectivity over 56 other human kinases.

INC280 demonstrates very potent activity in cells; cell-based biochemical assays that measure MET phosphorylation in response to constitutive or HGF mediated activation have yielded IC50 values ranging from 0.2- 1.1 nM. INC280 also has been shown to inhibit MET mediated signal transduction with similar potency. In agreement with the biochemical assay, INC280 has shown potent activity, with IC50 values ranging from 0.2 – 2 nM, in functional cell assays of MET-dependent cell proliferation, colony formation, cell survival and cell migration. Finally, the effect of INC280 on the activation of the EGFR family members EGFR and HER-3 by MET in relevant model cancer cells has also been demonstrated. To assess the effect of human serum protein binding on the cellular potency of INC280, a phospho-MET assay using human whole blood was developed. Using this assay, INC280 exhibits potent activity, with an IC50 value of 13.5 ± 3.9 nM and an IC90 value of 71 ± 25.1 nM.

The pharmacokinetic/pharmacodynamic relationship of INC280 was characterized in tumor-bearing mice. These experiments probed the potential of INC280 to inhibit phosphorylation of MET, as assessed by phospho-MET levels in tumors using immunohistochemical or ELISA-based methods. In MET/HGF-driven xenograft mouse tumor models, oral dosing of INC280 demonstrated significant in vivo activity in blocking MET phosphorylation. Oral administration of INC280 at a dose of 3 mg/kg suppressed > 90% MET phosphorylation for at least 7 hours in a mouse xenograft tumor model and this correlated with plasma INC280 levels greater than or equivalent to the human whole blood IC90 of 71 nM.

These studies were extended to determine the effect of INC280 on tumor cell proliferation and apoptosis in vivo. INC280 suppressed phosphorylation of MET nearly completely in these tumors and this was associated with a decrease in the percentage of cells within tumor samples staining positively for Ki67, a marker of proliferation and was associated with an increase in the number of cells staining positively for apoptosis as measured by fragmentation of DNA (TUNEL). Oral dosing of INC280 at dose level of 10 mg/kg and above resulted in > 90% tumor growth inhibition in the U-87MG glioblastoma xenograft model. Further efficacy experiments demonstrated the activity of INC280 as a single agent in tumor models expressing MET and its ligand HGF.

Plasma levels of INC280 correlated with both the dose administered and the extent of tumor growth inhibition.

Collectively, the data suggest that INC280 possesses potent in vivo biological and pharmacological activities, and supports its clinical development as a potentially effective oral treatment for human cancers.

1.2.2.1 Non-clinical experience

Nonclinical drug metabolism and pharmacokinetics (DMPK)

INC280 was absorbed rapidly in rats, dogs and monkeys. The absolute oral bioavailability following a single low dose was low in dogs (28%), and moderate to complete in rats and monkeys (>66%). Single and multiple dose toxicokinetic studies in rats and monkeys showed increase in plasma maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) values of INC280 with increased dose, but the increases were not always dose-proportional.

INC280 plasma protein binding was moderate to high across species, and was 96% in humans with no concentration dependency. The in vitro blood-to-plasma ratio in humans was 1.5 (concentration

range of 10-1000 ng/mL). After oral dose of [14C]-INC280 in male pigmented and albino rats, INC280 and/or its metabolites were widely and rapidly distributed to all tissues. Melanin-containing structures such as eye (choroid) and eye (ciliary body) appeared to show specific uptake and prolonged retention of drug related material. The presence of total radiolabeled components in those tissues was at least partly reversible. INC280 can penetrate across the blood-brain barrier.

Systemic clearance (CL) was low- to-moderate in mice, rats, dogs and monkeys. The estimated terminal half-life (T1/2) was short in mice, rats and dogs but long in monkeys. Metabolism is the predominant mechanism of elimination of INC280 in rats and monkeys after oral administration. The hydroxylated metabolite M8 and the imidazo-triazinone (lactam) M16 were main metabolites observed in plasma and excreta of rats and monkeys. After single oral administration of [14C]INC280 to rats and monkeys, the majority of the radioactivity was excreted at the end of the observation period. The major portion of administered radioactivity was recovered in feces and only a minor fraction in urine. Direct renal excretion of INC280 was negligible and biliary excretion/intestinal secretion contributed only to a minor extent to the overall elimination of INC280.

1.2.2.1.1 MET kinase domain mutations causing resistance to INC280

Biochemical and cellular assays indicate that mutations of tyrosine 1230 (Y1230) and aspartic acid 1228 (D1228) in the activation loop of the MET kinase domain strongly interfere with INC280 activity. Based on several published co-crystal structures with chemically related compounds, these residues can be assumed to play a key role in binding of INC280 to MET.

More details can be found in the [Investigator's Brochure]. Y1230 and D1228 mutations also promote MET kinase activity and have been described in rare cases of papillary RCC. It is unknown if the predicted inability of some mutant forms of MET to bind INC280 will lead to resistance of tumors carrying these mutations.

1.2.2.2 Preclinical safety

Safety pharmacology studies with INC280 indicated that INC280 had no significant effects on central nervous system (CNS) and respiratory functions in rats, and no effects on cardiovascular function in monkeys. In vitro, INC280 inhibited human Ether-à-go-go-related gene (hERG) potassium current by 50% at 18.7 M.

Oral administration studies in mice, rats, and Cynomolgus monkeys were conducted in order to assess the potential systemic toxicity of INC280. In single dose studies, the no adverse effect level (NOAEL) doses were defined as 600 mg/kg both in mice and in monkeys. Repeat dose toxicity studies conducted in mice, rats, and Cynomolgus monkeys revealed the kidneys, pancreas, CNS, and potentially liver as target organs or organ systems.

In vitro genetic toxicology studies indicated that INC280 did not induce mutations or cause chromosome aberrations. The in vivo bone marrow micronucleus test in rats indicated that INC280 did not induce micronuclei in the polychromatic erythrocytes of the bone marrow at doses up to the maximum tolerated dose (MTD).

Studies on embryofetal development in rats and rabbits indicated that INC280 is teratogenic to both species, and the teratogenicity is consistent with the mechanism of action by c-MET inhibition. INC280 should be considered potentially teratogenic to humans.

Additionally, INC280 has shown photosensitization potential in in vitro and in vivo assays.

1.2.2.3 Clinical experience

As of 28-Sep-2015, a total of 500 cancer patients and 90 non-cancer subjects have received INC280.

A total of 271 patients have been treated with INC280 as a single agent at different doses (198 patients received the capsule formulation only, 66 patients received tablet formulation only, and 7 patients switched from capsule to tablet formulation during treatment with INC280), and 229 patients have been treated with INC280 in combination therapies: with gefitinib (143 patients of which 98 patients received the capsule formulation and 45 patients received the tablet formulation), with buparlisib (33 patients of which 21 patients received the capsule formulation and 12 patients received the tablet formulation), with erlotinib (23 patients of which 15 patients received the capsule formulation and 8 patients received the tablet formulation), with cetuximab (7 patients, all treated with tablet formulation),with LGX818/MEK162 (4 patients, all treated with capsule formulation), with EGF816 (15 patients, all treated with tablet formulation), with nivolumab (3 patients, all treated with tablet formulation) and with sonidegib (1 patient, treated with capsule formulation). In addition, 90 non-cancer subjects have received INC280 (6 subjects received the capsule formulation only, 60 subjects received the tablet formulation and 24 subjects received both capsule and tablet formulations). Fourteen clinical studies are currently ongoing with INC280.

A total of fourteen patients have experienced 14 DLTs: 6 in single agent studies (1 in [CINC280X2101T] study, 2 in [CINC280X1101] study and 3 in [CINC280X2102] study) and 8 in combination studies (2 in combination with gefitinib ([CINC280X2202] study), 4 in combination with buparlisib ([CINC280X2204] study), and 2 in combination with EGF816 ([CINC280X2105C] study).

The DLTs in single agent studies were: one Grade 3 AST and ALKP increase (50 mg QD capsules) (in [CINC280X2101T] study); one Grade 2 malaise, Grade 2 intake difficulty and Grade 2 suicidal ideation (600 mg BID capsules) (due to the size and number of capsules) (in [CINC280X1101] study); one Grade 3 depression (400 mg BID tablets) (in [CINC280X1101] study); two Grade 3 fatigue (200 mg BID and 450 mg BID capsules respectively) (in [CINC280X2102] study); one Grade 3 total bilirubin increase (250 mg BID capsules) (in [CINC280X2102] study).

The DLTs in combination with gefitinib were: one Grade 4 cough and dyspnea (600 mg BID capsules); and one Grade 3 dizziness (800 mg QD capsules).

The DLTs in combination with buparlisib were: one Grade 3 personality change (400 mg BID capsules); one Grade 3 abdominal pain and nausea (300 mg BID tablets); one Grade 3 ALT increased and AST increased (400 mg BID tablets); and one Grade 3 ALT increased (400 mg BID tablets).

The DLTs in combination EGF816 were: one Grade 3 ALT increased (200 mg BID tablets); and one Grade 3 anaphylactic reaction (400 mg BID tablets).

Overall, the majority of the reported adverse events (AEs) are of mild or moderate severity.

The most frequent AEs suspected to be related to INC280 of any grade reported in the

[CINC280X2102] study, which is considered as the reference study for the safety profile of

INC280 as a single agent, were nausea (38 patients, [32.2%]), vomiting (31 patients, [26.3%]), fatigue (29 patients, [24.6%]), edema peripheral (27 patients, [22.9%]), and decreased appetite (22 patients, [18.6%]), and the majority were Grade 1/2. The most frequently occurring Grade 3/4 AEs suspected to be related to INC280 included fatigue (6 patients, [5.1%]), lipase increased (4 patients [3.4%]), ALT increased (4 patients [3.4%]), AST increased (3 patients, [2.5%]), anemia, nausea, neutropenia, dehydration and hypophagia (each in 2 patients, [1.7%]), thrombocytopenia, vomiting, diarrhea, edema peripheral, blood bilirubin increased, amylase increased, lymphocyte count decreased, decreased appetite, hypoalbuminemia, hypophosphatemia, hyperlipasemia, hyperlipidemia, cerebral venous thrombosis, and rash maculopapular (each in 1 patient, [0.8%]). In addition, recent reports of interstitial lung disease/ pneumonitis have been reported as possibly related to single agent INC280 therapy.

The MTD for INC280 capsules as single agent was not reached. The RP2D for INC280 as a single agent has been determined to be 600 mg BID in capsule formulation and 400 mg BID in tablet formulation.

Table 1-1: Summary of human study

Study	**Population (No. of enrolled subjects /patients)**	**No of subjects exposed to INC280**	**Study Title**	**Dose / Frequency / Formulation**
CINCB28060-101 (Novartis code [CINC280X2101T])	N=45/45 patients	45	A Phase 1, open-label, dose escalation study to determine the safety, tolerability, pharmacokinetics and pharmacodynamics of INC280 in subjects with advanced malignancies	Single agent study Dose escalation arm: INC280 QD regimen with capsule: 10 mg, 20 mg, 50 mg, 70 mg, 150 mg, 200 mg, 300 mg, 400 mg INC280 BID regimen with capsule: 50 mg, 200 mg, 300 mg
[CINC280X1101]	N=44 patients	44	A Phase I study of INC280 in Japanese patients with advanced solid tumors	Single agent study Dose escalation arm: INC280 QD regimen with capsule: 100 mg, 200 mg, 400 mg, 500 mg, 600 mg, 800 mg INC280 BID regimen with capsule: 400 mg, 600 mg INC280 BID regimen with tablet: 200 mg , 400 mg

Study	Population (No. of enrolled subjects /patients)	No of subjects exposed to INC280	Study Title	Dose / Frequency / Formulation
[CINC280X2102]	N=118 patients	118	A Phase I open-label dose escalation study with expansion to assess the safety and tolerability of INC280 in patients with cMET dependent advanced solid tumors	Single agent study Dose escalation arm: INC280 BID regimen with capsule: 100 mg, 200 mg, 250 mg, 350 mg, 450 mg, 600 mg Dose expansion part: INC280 600 mg BID regimen with capsule Safety cohort with tablet: INC280 400 mg BID with tablet Current dose expansion arm: INC280 400 mg BID regimen with tablet
[CINC280X2201]	N=36 patients	36	A Phase II open-label, single arm, multicenter study of INC280 administered orally in adult patients with advanced hepatocellular carcinoma	Single agent study Dose determining part: INC280 300 mg BID with capsule Dose expansion part: INC280 600 mg BID with capsule
[CINC280X2205]	N=26 patients	3	A Phase II, open-label, multiple arm study of single agents AUY922, BYL719, INC280, LDK378 and MEK162 in Chinese patients with advanced NSCLC	Single agent study INC280 600 mg BID with capsule INC280 400 mg BID with tablet
[CINC280A2201]	N=18 patients	18	A Phase II, multicenter, four cohort study of oral cMET inhibitor INC280 in adult patients with EGFR wild-type (wt), advanced NSCLC who have received one or two prior lines of systemic therapy for advanced/metastatic disease	Single agent study INC280 400 mg BID with tablet
[CINC280XUS04T]	N=7 patients	7	A Phase II open-label Investigator-led study of INC280 in adults patients with papillary renal cell cancer	Single agent study INC280 600 mg BID with capsule INC280 400 mg BID with tablet

Study	Population (No. of enrolled subjects /patients)	No of subjects exposed to INC280	Study Title	Dose / Frequency / Formulation
[CINC280X2104]	N=7 patients	7	A Phase Ib, open-label, multicenter, dose escalation and expansion study, to evaluate the safety, pharmacokinetics and activity of INC280 in combination with cetuximab in cMET positive CRC and HNSCC patients who have progressed after anti-EGFR monoclonal antibody therapy	Combination study First dose level: INC280150 mg BID with tablet plus cetuximab 400mg/m2 initial infusion followed by 250mg/m2 infusions weekly Second dose level: INC280 300 mg BID with tablet plus cetuximab 400mg/m2 initial infusion followed by 250mg/m2 infusions weekly
[CINC280X2105 C]	N=15 patients	15	A Phase Ib/II, multicenter, open-label study of EGF816 in combination with INC280 in adult patients with EGFR mutated NSCLC	Combination study Cohort 1: INC280 200 mg BID with tablet plus EGF816 50 mg QD Cohort 2: INC280 200 mg BID with tablet plus EGF816 100 mg QD Cohort 3: INC280 400 mg BID with tablet plus EGF816 100 mg QD Cohort 4: INC280 400 mg BID with tablet plus EGF816 150 mg QD
[CINC280X2202]	N=143 patients	143	A Phase Ib/II, open-label, multicenter study of INC280 administered orally in combination with gefitinib in adult patients with EGFR mutated, cMET-amplified NSCLC who have progressed after EGFR inhibitor treatment cancer who have progressed after EGFR inhibitor treatment	Combination study Dose escalation arm: INC280 QD regimen with capsule: 100 mg, 200 mg, 400 mg, 800 mg in combination with gefitinib 250 mg QD INC280 BID regimen with capsule: 200 mg, 400 mg, 600 mg in combination with gefitinib 250 mg QD INC280 BID regimen with tablet: 200 mg in combination with gefitinib 250 mg QD Dose expansion part and Phase II: INC280 BID regimen with capsule: 400 mg in combination with gefitinib 250 mg QD INC280 BID regimen with tablet: 400 mg in combination with gefitinib 250 mg QD

Study	Population (No. of enrolled subjects /patients)	No of subjects exposed to INC280	Study Title	Dose / Frequency / Formulation
[CINC280X2204]	N=33 patients	33	A Phase Ib/II, open-label, multicenter study of INC280 in combination with buparlisib in adult patients with recurrent glioblastoma	Combination study Dose escalation arm: INC280 BID regimen with capsule: 200 mg, 400 mg, 500 mg in combination with buparlisib 50 mg QD, 500 mg in combination with buparlisib 80 mg QD INC280 BID regimen with tablet: 300 mg, 400 mg in combination with buparlisib 80 mg QD Phase II: INC280 400 mg BID with tablet, single agent only
[CINC280XUS02T]	N=23 patients	23	A Phase Ib/II open-label investigator-led study of INC280 in combination with EGFR TKI erlotinib including dose escalation and expansion in adult patients with cMET expressing NSCLC	Combination study Dose escalation INC280 mg BID regimen with capsule: First dose level: INC280 100 mg plus erlotinib 100 mg QD Subsequent dose levels: INC280 mg BID regimen with capsule: 100 mg, 200 mg, 400 mg, 600 mg plus erlotinib 150mg QD INC280 mg BID regimen with tablet: 400 mg plus erlotinib 150 mg QD
[CEGF816X2201]	N=17 patients	3	A Phase II, multicenter, open label study of EGF816 in combination with Nivolumab in adult patients with EGFR mutated NSCLC and of INC280 in combination with Nivolumab in adult patients with cMET positive NSCLC	Combination study INC280 400 mg BID with tablet in combination with nivolumab (3 mg/kg administered every 2 weeks)

Study	Population (No. of enrolled subjects /patients)	No of subjects exposed to INC280	Study Title	Dose / Frequency / Formulation
[CLGX818X2109]	N=130 patients	4	A Phase II, multi-center, open label study of sequential LGX818/MEK162 combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma	Combination study Cohort 1: INC280 200 mg BID with capsule in combination with 200 mg LGX818 QD & 45 mg MEK162 BID
[CINC280XUS05I]	N=1/1 patient	1	A Phase II open-label investigator-led study of INC280 in combination with LDE225 in an adult patient with cMET-amplified and 12- span transmembrane receptor protein Patched1 (PTCHI)- truncated glioblastoma	Combination study INC280 600 mg BID with capsule monotherapy for 4 months, then in combination with 200 mg sonidegib QD
[CINC280X2103]	N=24/24 healthy subjects	24	A randomized, open-label, two sequence, two-period crossover study evaluating the relative bioavailability of INC280 between capsule and tablet following a single oral dose of INC280 in healthy subjects	Treatment A: single dose of INC280 600 mg given as 12 x 50 mg with capsule Treatment B: single dose of INC280 600 mg given as 3 x 200 mg with tablet
[CINC280X2106]	N=6/6 healthy subjects	6	A single-center, open-label study to investigate the absorption, distribution, metabolism and excretion (ADME) of INC280 after a single oral dose of 600 mg [14C] INC280 (5.55 MBq) in healthy male subjects	Single dose of INC280 600 mg with radiolabeled with capsule (14C)INC280
[CINC280X2107]	N=24/24 healthy subjects	24	A randomized, single-center, open-label, three-period, six sequence, crossover study to investigate the effect of food on the pharmacokinetics of INC280 following a single oral dose of 3 x 200 mg film-coated tablets in healthy subjects	INC280 600 mg given as 3 x 200 mg with tablet administered 3 times (fasting/low-fat meal/high-fat meal) separated by a 7-day washout between each treatment

Study	Population (No. of enrolled subjects /patients)	No of subjects exposed to INC280	Study Title	Dose / Frequency / Formulation
[CINC280A2101]	N=20/20 healthy subjects	20	A single center, open-label, two-period, single-sequence study to assess the effect of rabeprazole on the pharmacokinetics of a single dose of INC280 in healthy subjects	Single dose of INC280 600 mg with tablet
[CINC280A2106]	N=16 non-cancer subjects	16	An open-label, single-dose, multi-center, parallel-group, two-staged study to evaluate the pharmacokinetics of the oral cMET inhibitor INC280 in non-cancer subjects with impaired hepatic function and non-cancer subjects with normal hepatic function	Single dose of INC280 200 mg with tablet

The cut-off date for the safety data updates is 28-Sep-2015. As of the cut-off date, a total of 500 cancer patients and 90 non-cancer subjects have received INC280. A total of 271 patients with solid tumors have been treated with INC280 as a single agent (198 patients received the capsule formulation only, 66 patients received the tablet formulation only, and 7 patients switched from capsule to tablet formulation during treatment with INC280), and a further 229 patients have been treated with INC280 in combination therapies (139 patients received the capsule formulation and 90 patients received the tablet formulation). In addition, 90 non-cancer subjects have received INC280 (6 subjects received the capsule formulation only, 60 subjects received the tablet formulation only, and 24 subjects received both capsule and tablet formulations).

The most common AEs summarized in Table 1-2 through Table 1-7 below.

Table 1-2: Adverse events (greater than or equal to 5%) suspected to be related to study treatment in study

MedDRA Preferred Term	**10 mg QD (n=3)**	**20 mg QD (n=4)**	**50 mg QD (n=6)**	**70 mg QD (n=4)**	**50 mg BID (n=3)**	**150 mg QD (n=3)**	**200 mg QD (n=4)**	**300 mg QD (n=4)**	**400 mg QD (n=6)**	**200 mg BID (n=4)**	**300 mg BID (n=4)**	**Total (N=45)**
Subjects with any AEs, n (%)	1 (33.3)	3 (75.0)	5 (83.3)	4 (100.0)	2 (66.7)	3 (100.0)	3 (75.0)	4 (100.0)	5 (83.3)	4 (100.0)	3 (75.0)	37 (82.2)
Nausea	0	0	3 (50.0)	2 (50.0)	0	1 (33.3)	0	0	2 (33.3)	3 (75.0)	1 (25.0)	12 (26.7)
Tremor	1 (33.3)	1 (25.0)	2 (33.3)	1 (25.0)	1 (33.3)	1 (33.3)	0	0	3 (50.0)	0	1 (25.0)	11 (24.4)
Peripheral edema	0	0	1 (16.7)	0	0	1 (33.3)	0	2 (50.0)	1 (16.7)	3 (75.0)	2 (50.0)	10 (22.2)
Fatigue	1 (33.3)	1 (25.0)	1 (16.7)	3 (75.0)	0	0	1 (25.0)	1 (25.0)	0	1 (25.0)	0	9 (20.0)
Headache	0	0	0	2 (50.0)	0	1 (33.3)	1 (25.0)	0	1 (16.7)	2 (50.0)	0	7 (15.6)
Dysgeusia	0	0	0	0	0	0	1 (25.0)	2 (50.0)	0	3 (75.0)	0	6 (13.3)
Vomiting	0	0	0	0	0	0	0	1 (25.0)	2 (33.3)	2 (50.0)	1 (25.0)	6 (13.3)
Diarrhea	0	0	1 (16.7)	0	0	1 (33.3)	1 (25.0)	0	0	0	1 (25.0)	4 (8.9)
Asthenia	0	0	1 (16.7)	0	0	0	0	0	1 (16.7)	0	1 (25.0)	3 (6.7)
Decreased appetite	0	0	0	0	0	1 (33.3)	0	0	1 (16.7)	1 (25.0)	0	3 (6.7)

Table 1-3: Adverse events (greater than or equal to 5%) suspected to be related to study treatment in study [CINC280X1101]

	INC280											
	100 mg QD Cap N=3		**200 mg QD Cap N=4**		**400 mg QD Cap N=3**		**500 mg QD Cap N=4**		**600 mg QD Cap N=4**		**800 mg QD Cap N=4**	
Preferred Term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
-Total	2 (66.7)	0	2 (50.0)	0	2 (66.7)	0	3 (75.0)	1 (25.0)	4 (100)	2 (50.0)	3 (75.0)	0
Blood creatinine increased	1 (33.3)	0	0	0	1 (33.3)	0	2 (75.0)	0	2 (75.0)	0	1 (25.0)	0
Nausea	0	0	1 (25.0)	0	0	0	0	0	3 (75.0)	0	1 (25.0)	0
Vomiting	0	0	2 (50.0)	0	0	0	0	0	2 (50.0)	0	1 (25.0)	0
Decreased appetite	0	0	1 (25.0)	0	0	0	0	0	3 (75.0)	0	1 (25.0)	0
Diarrhea	0	0	0	0	1 (33.3)	0	3 (75.0)	0	0	0	0	0
Fatigue	0	0	0	0	0	0	1 (25.0)	0	1 (25.0)	0	0	0
Malaise	0	0	0	0	0	0	0	0	1 (25.0)	0	0	0
Edema peripheral	0	0	0	0	0	0	0	0	1 (25.0)	0	0	0
Hypoalbuminemia	0	0	1 (25.0)	0	0	0	0	0	0	0	1 (25.0)	0
Constipation	0	0	1 (25.0)	0	0	0	0	0	0	0	1 (25.0)	0
Dry skin	1 (33.3)	0	0	0	0	0	0	0	0	0	0	0
Alanine aminotransferase increased	0	0	0	0	0	0	1 (25.0)	1 (25.0)	1 (25.0)	0	0	0
Amylase increased	0	0	0	0	0	0	0	0	0	0	0	0
Anemia	0	0	0	0	0	0	0	0	1 (25.0)	0	1 (25.0)	0

	INC280											
	100 mg QD Cap		**200 mg QD Cap**		**400 mg QD Cap**		**500 mg QD Cap**		**600 mg QD Cap**		**800 mg QD Cap**	
	N=3		**N=4**		**N=3**		**N=4**		**N=4**		**N=4**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Aspartate aminotransferase increased	0	0	0	0	0	0	1 (25.0)	1 (25.0)	1 (25.0)	0	0	0
Hypophosphatemia	0	0	0	0	0	0	0	0	0	0	0	0
Hypotension	0	0	0	0	0	0	2 (50.0)	0	0	0	0	0
Weight decreased	0	0	1 (25.0)	0	0	0	0	0	0	0	0	0
Hypoalbuminemia	0	0	1 (25.0)	0	0	0	0	0	0	0	1 (25.0)	0
Constipation	0	0	1 (25.0)	0	0	0	0	0	0	0	1 (25.0)	0
Dry skin	1 (33.3)	0	0	0	0	0	0	0	0	0	0	0
Alanine aminotransferase increased	0	0	0	0	0	0	1 (25.0)	1 (25.0)	1 (25.0)	0	0	0
Amylase increased	0	0	0	0	0	0	0	0	0	0	0	0
Anemia	0	0	0	0	0	0	0	0	1 (25.0)	0	1 (25.0)	0
Aspartate aminotransferase increased	0	0	0	0	0	0	1 (25.0)	1 (25.0)	1 (25.0)	0	0	0
Hypophosphatemia	0	0	0	0	0	0	0	0	0	0	0	0
Hypotension	0	0	0	0	0	0	2 (50.0)	0	0	0	0	0
Weight decreased	0	0	1 (25.0)	0	0	0	0	0	0	0	0	0

Table 1-4: Adverse events (greater than or equal to 5%) suspected to be related to study treatment in study [CINC280X2102]

	INC280 100 mg BID Capsules N=4		**INC280 200 mg BID Capsules N=5**		**INC280 250 mg BID Capsules N=4**		**INC280 350 mg BID Capsules N=3**		**INC280 450 mg BID Capsules N=9**	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**	**All grades n (%)**	**Grade 3/4 n (%)**
-Total	3 (75.0)	1 (25.0)	5 (100.0)	3 (60.0)	3 (75.0)	2 (50.0)	2 (66.7)	0	8 (88.9)	3 (33.3)
Nausea	1 (25.0)	0	2 (40.0)	0	0	0	0	0	4 (44.4)	0
Vomiting	2 (50.0)	0	1 (20.0)	0	1 (25.0)	0	0	0	3 (33.3)	0
Fatigue	0	0	2 (40.0)	1 (20.0)	1 (25.0)	1 (25.0)	0	0	3 (33.3)	1 (11.1)
Edema Peripheral	0	0	1 (20.0)	1 (20.0)	1 (25.0)	0	1 (33.3)	0	2 (22.2)	0
Decreased Appetite	1 (25.0)	0	2 (40.0)	0	1 (25.0)	1 (25.0)	1 (33.3)	0	3 (33.3)	0
Diarrhea	1 (25.0)	0	0	0	0	0	1 (33.3)	0	0	0
Aspartate Aminotransferase Increased	0	0	0	0	1 (25.0)	0	0	0	1 (11.1)	1 (11.1)
Asthenia	2 (50.0)	0	1 (20.0)	0	0	0	1 (33.3)	0	1 (11.1)	0
Hypoalbuminemia	0	0	2 (40.0)	1 (20.0)	0	0	1 (33.3)	0	0	0
Blood Creatinine Increased	0	0	1 (20.0)	0	0	0	1 (33.3)	0	0	0
Alanine Aminotransferase Increased	0	0	0	0	0	0	0	0	1 (11.1)	0
Lipase Increased	0	0	0	0	1 (25.0)	1 (25.0)	0	0	0	0

	INC280 600 mg BID Capsules – All N=63				**INC280 400 mg BID Capsules – All N=30**				**All patients N-118**			
Preferred term	**All grades n (%)**		**Grade 3/4 n (%)**		**All grades n (%)**		**Grade 3/4 n (%)**		**All grades n (%)**		**Grade 3/4 n (%)**	
-Total	54 (85.7)		17 (27.0)		23 (76.7)		3 (10.0)		98 (83.1)		29 (24.6)	
Nausea	24	(38.1)	2	(3.2)	7	(23.3)	0		38	(32.2)	2	(1.7)
Vomiting	17	(27.0)	1	(1.6)	7	(23.3)	0		31	(26.3)	1	(0.8)
Fatigue	18	(28.6)	2	(3.2)	5	(16.7)	1	(3.3)	29	(24.6)	6	(5.1)
Edema Peripheral	16	(25.4)	0		6	(20.0)	0		27	(22.9)	1	(0.8)
Decreased Appetite	13	(20.6)	0		1	(3.3)	0		22	(18.6)	1	(0.8)
Diarrhea	14	(22.2)	0		3	(10.0)	1	(3.3)	19	(16.1)	1	(0.8)
Aspartate Aminotransferase Increased	6	(9.5)	1	(1.6)	3	(10.0)	1	(3.3)	11	(9.3)	3	(2.5)
Asthenia	5	(7.9)	0		1	(3.3)	0		11	(9.3)	0	
Hypoalbuminemia	4	(6.3)	0		3	(10.0)	0		10	(8.5)	1	(0.8)
Blood Creatinine Increased	5	(7.9)	0		2	(6.7)	0		9	(7.6)	0	
Alanine Aminotransferase Increased	4	(6.3)	3	(4.8)	3	(10.0)	1	(3.3)	8	(6.8)	4	(3.4)
Lipase Increased	6	(9.5)	3	(4.8)	0		0		7	(5.9)	4	(3.4)

Table 1-5: Adverse events (greater than or equal to 5%) suspected to be study treatment related in study [CINC280X2202]

	Dose of INC280 in combination with 250 mg QD gefitinib									
QD 100 mg Cap N=5			**QD 200 mg Cap N=7**		**QD 400 mg Cap N=6**		**QD 800 mg Cap N=7**		**BID 200 mg Cap N=4**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
-Total	4 (80.0)	1 (20.0)	7 (100)	2 (28.6)	6 (100)	0	6 (85.7)	1 (14.3)	4 (100)	2 (50.0)
Nausea	1 (20.0)	0	0	0	3 (50.0)	0	5 (71.4)	0	1 (25.0)	0
Decreased Appetite	0	0	0	0	0	0	3 (42.9)	0	1 (25.0)	0
Edema Peripheral	0	0	0	0	0	0	0	0	1 (25.0)	1 (25.0)
Paronychia	1 (20.0)	0	1 (14.3)	0	1 (16.7)	0	0	0	2 (50.0)	0
Diarrhea	1 (20.0)	0	1 (14.3)	0	0	0	2 (28.6)	0	3 (75.0)	0
Rash	1 (20.0)	0	3 (42.9)	0	0	0	2 (28.6)	0	2 (50.0)	0
Vomiting	0	0	1 (14.3)	0	1 (16.7)	0	5 (71.4)	1 (14.3)	1 (25.0)	0
Amylase Increased	1 (20.0)	1 (20.0)	1 (14.3)	0	0	0	0	0	0	0
Fatigue	0	0	1 (14.3)	0	1 (16.7)	0	1 (14.3)	0	0	0
Alanine Aminotransferase Increased	0	0	0	0	1 (16.7)	0	1 (14.3)	0	1 (25.0)	0
Blood Bilirubin Increased	0	0	0	0	0	0	0	0	0	0
Aspartate Aminotransferase Increased	0	0	0	0	1 (16.7)	0	1 (14.3)	0	0	0
Blood Creatinine Increased	0	0	0	0	0	0	0	0	0	0
Lipase Increased	1 (20.0)	1 (20.0)	1 (14.3)	1 (14.3)	0	0	0	0	0	0
Dermatitis Acneiform	1 (20.0)	0	2 (28.6)	0	0	0	1 (14.3)	0	0	0
Pruritus	1 (20.0)	0	1 (14.3)	0	0	0	1 (14.3)	0	1 (25.0)	0

	Dose of INC280 in combination with 250 mg QD gefitinib													
BID 400 mg Cap - P1b			**BID 400 mg Cap - P2**		**BID 600 mg Cap**		**BID 200 mg Tab**		**BID 400 mg Tab - P1b**		**BID 400 mg Tab - P2**		**All patients**	
N=12			**N=52**		**N=5**		**N=7**		**N=8**		**N=30**		**N=143**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
-Total	11 (91.7)	3 (25.0)	43 (82.7)	7 (13.5)	4 (80.0)	1 (20.0)	6 (85.7)	3 (42.9)	6 (75.0)	1 (12.5)	23 (76.7)	9 (30.0)	120 (83.9)	30 (21.0)
Nausea	0	0	5 (9.6)	0	1 (20.0)	0	4 (57.1)	0	3 (37.5)	1 (12.5)	9 (30.0)	0	32 (22.4)	1 (0.7)
Decreased Appetite	1 (8.3)	0	11 (21.2)	0	3 (60.0)	0	1 (14.3)	0	2 (25.0)	0	5 (16.7)	0	27 (18.9)	0
Edema Peripheral	4 (33.3)	0	10 (19.2)	0	2 (40.0)	0	2 (28.6)	0	1 (12.5)	0	6 (20.0)	1 (3.3)	26 (18.2)	2 (1.4)
Paronychia	3 (25.0)	0	7 (13.5)	0	0	0	2 (28.6)	0	3 (37.5)	0	6 (20.0)	1 (3.3)	26 (18.2)	1 (0.7)
Diarrhea	3 (25.0)	0	7 (13.5)	0	1 (20.0)	0	1 (14.3)	0	1 (12.5)	0	5 (16.7)	1 (3.3)	25 (17.5)	1 (0.7)
Rash	3 (25.0)	0	5 (9.6)	1 (1.9)	0	0	1 (14.3)	0	2 (25.0)	0	4 (13.3)	0	23 (16.1)	1 (0.7)
Vomiting	1 (8.3)	0	7 (13.5)	0	1 (20.0)	0	2 (28.6)	1 (14.3)	2 (25.0)	0	1 (3.3)	0	22 (15.4)	2 (1.4)
Amylase Increased	4 (33.3)	2 (16.7)	5 (9.6)	1 (1.9)	0	0	1 (14.3)	1 (14.3)	1 (12.5)	0	5 (16.7)	4 (13.3)	18 (12.6)	9 (6.3)
Fatigue	1 (8.3)	0	5 (9.6)	0	1 (20.0)	0	1 (14.3)	0	2 (25.0)	0	4 (13.3)	1 (3.3)	17 (11.9)	1 (0.7)
Alanine Aminotransferase Increased	2 (16.7)	1 (8.3)	8 (15.4)	2 (3.8)	1 (20.0)	0	0	0	0	0	0	0	14 (9.8)	3 (2.1)
Blood Bilirubin Increased	4 (33.3)	0	8 (15.4)	1 (1.9)	0	0	0	0	0	0	1 (3.3)	0	13 (9.1)	1 (0.7)
Aspartate Aminotransferase Increased	1 (8.3)	0	8 (15.4)	2 (3.8)	0	0	0	0	0	0	0	0	11 (7.7)	2 (1.4)
Blood Creatinine Increased	2 (16.7)	0	5 (9.6)	0	0	0	1 (14.3)	0	0	0	2 (6.7)	0	10 (7.0)	0

BID 400 mg Cap - P1b			**BID 400 mg Cap - P2**		**BID 600 mg Cap**		**BID 200 mg Tab**		**BID 400 mg Tab - P1b**		**BID 400 mg Tab - P2**		**All patients**	
N=12			**N=52**		**N=5**		**N=7**		**N=8**		**N=30**		**N=143**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Lipase Increased	2 (16.7)	2 (16.7)	3 (5.8)	0	0	0	0	0	0	0	3 (10.0)	3 (10.0)	10 (7.0)	7 (4.9)
Dermatitis Acneiform	1 (8.3)	0	0	0	0	0	2 (28.6)	0	0	0	2 (6.7)	0	9 (6.3)	0
Pruritus	1 (8.3)	0	2 (3.8)	0	0	0	0	0	0	0	2 (6.7)	0	9 (6.3)	0

Table 1-6: Adverse events suspected to be related to study treatment in study [CINC280X2201]

	INC280 capsules BID 300 mg N=9		**BID 600 mg N=27**		**All patients N=36**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
-Total	7 (77.8)	1 (11.1)	17 (63.0)	4 (14.8)	24 (66.7)	5 (13.9)
Nausea	5 (55.6)	0	9 (33.3)	1 (3.7)	14 (38.9)	1 (2.8)
Vomiting	3 (33.3)	1 (11.1)	8 (29.6)	1 (3.7)	11 (30.6)	2 (5.6)
Fatigue	1 (11.1)	0	6 (22.2)	0	7 (19.4)	0
Diarrhea	1 (11.1)	0	3 (11.1)	0	4 (11.1)	0
Blood Creatinine Increased	0	0	3 (11.1)	0	3 (8.3)	0
Decreased Appetite	1 (11.1)	0	2 (7.4)	0	3 (8.3)	0
Leukopenia	0	0	3 (11.1)	0	3 (8.3)	0
Alanine Aminotransferase Increased	0	0	2 (7.4)	1 (3.7)	2 (5.6)	1 (2.8)
Aspartate Aminotransferase Increased	0	0	2 (7.4)	1 (3.7)	2 (5.6)	1 (2.8)
Thrombocytopenia	0	0	2 (7.4)	0	2 (5.6)	0
Abdominal Pain	0	0	1 (3.7)	0	1 (2.8)	0
Amylase Increased	0	0	1 (3.7)	1 (3.7)	1 (2.8)	1 (2.8)
Blood Alkaline Phosphatase Increased	0	0	1 (3.7)	0	1 (2.8)	0
Blood Bilirubin Increased	0	0	1 (3.7)	1 (3.7)	1 (2.8)	1 (2.8)
Cholecystitis	0	0	1 (3.7)	0	1 (2.8)	0
Constipation	1 (11.1)	0	0	0	1 (2.8)	0
Dehydration	1 (11.1)	0	0	0	1 (2.8)	0
Dizziness	0	0	1 (3.7)	0	1 (2.8)	0
Dyspepsia	1 (11.1)	0	0	0	1 (2.8)	0

	INC280 capsules BID 300 mg N=9		**BID 600 mg N=27**		**All patients N=36**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hypoalbuminemia	0	0	1 (3.7)	0	1 (2.8)	0
Hypocalcemia	0	0	1 (3.7)	0	1 (2.8)	0
Insomnia	0	0	1 (3.7)	0	1 (2.8)	0
International Normalized Ratio Increased	0	0	1 (3.7)	0	1 (2.8)	0
Leukocytosis	0	0	1 (3.7)	0	1 (2.8)	0
Myalgia	0	0	1 (3.7)	0	1 (2.8)	0
Neutropenia	0	0	1 (3.7)	0	1 (2.8)	0
Oral Candidiasis	1 (11.1)	0	0	0	1 (2.8)	0
Peptic Ulcer	0	0	1 (3.7)	0	1 (2.8)	0
Protein Urine	0	0	1 (3.7)	0	1 (2.8)	0

Table 1-7: Adverse events (greater than or equal to 5%) suspected to be related to study treatment in study [CINC280X2204]

	All patients													
	INC280 200 mg BID Cap + Buparlisib 50 mg QD N=5		**INC280 400 mg BID Cap + Buparlisib 50 mg QD N=6**		**INC280 500 mg BID Cap + Buparlisib 50 mg QD N=4**		**INC280 500 mg BID Cap + Buparlisib 80 mg QD N=6**		**INC280 300 mg BID Cap + Buparlisib 80 mg QD N=7**		**INC280 400 mg BID Cap + Buparlisib 80 mg QD N=5**		**N=33**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
-Total	4 (80.0)	1 (20.0)	4 (66.7)	2 (33.3)	4 (100)	2 (50.0)	4 (66.7)	0	7 (100)	4 (57.1)	5 (100)	3 (60.0)	28 (84.8)	12 (36.4)
Fatigue	2 (40.0)	0	2 (33.3)	0	0	0	2 (33.3)	0	2 (28.6)	1 (14.3)	2 (40.0)	0	10 (30.3)	1 (3.0)
Alanine Aminotransferase Increased	1 (20.0)	0	1 (16.7)	1 (16.7)	1 (25.0)	1 (25.0)	0	0	2 (28.6)	1 (14.3)	4 (80.0)	3 (60.0)	9 (27.3)	6 (18.2)
Nausea	1 (20.0)	0	1 (16.7)	0	1 (25.0)	0	1 (16.7)	0	3 (42.9)	1 (14.3)	2 (40.0)	0	9 (27.3)	1 (3.0)
Aspartate Aminotransferase Increased	1 (20.0)	0	1 (16.7)	1 (16.7)	1 (25.0)	1 (25.0)	0	0	2 (28.6)	1 (14.3)	3 (60.0)	3 (60.0)	8 (24.2)	6 (18.2)
Depression	1 (20.0)	0	0	0	1 (25.0)	0	0	0	3 (42.9)	0	2 (40.0)	0	7 (21.2)	0
Hyperglycemia	2 (40.0)	0	0	0	2 (50.0)	0	1 (16.7)	0	2 (28.6)	0	0	0	7 (21.2)	0
Blood Bilirubin Increased	1 (20.0)	0	0	0	2 (50.0)	0	0	0	1 (14.3)	0	1 (20.0)	0	5 (15.2)	0

All patients

	INC280 200 mg BID Cap + Buparlisib 50 mg QD N=5		**INC280 400 mg BID Cap + Buparlisib 50 mg QD N=6**		**INC280 500 mg BID Cap + Buparlisib 50 mg QD N=4**		**INC280 500 mg BID Cap + Buparlisib 80 mg QD N=6**		**INC280 300 mg BID Cap + Buparlisib 80 mg QD N=7**		**INC280 400 mg BID Cap + Buparlisib 80 mg QD N=5**		**N=33**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Blood Creatinine Increased	2 (40.0)	0	0	0	1 (25.0)	0	0	0	0	0	2 (40.0)	0	5 (15.2)	0
Diarrhea	1 (20.0)	0	1 (16.7)	0	0	0	1 (16.7)	0	2 (28.6)	0	0	0	5 (15.2)	0
Insulin C-Peptide Increased	2 (40.0)	0	0	0	1 (25.0)	0	0	0	2 (28.6)	0	0	0	5 (15.2)	0
Anxiety	1 (20.0)	0	0	0	0	0	0	0	2 (28.6)	1 (14.3)	1 (20.0)	0	4 (12.1)	1 (3.0)
Dyspepsia	0	0	0	0	0	0	1 (16.7)	0	1 (14.3)	0	1 (20.0)	0	3 (9.1)	0
Glomerular Filtration Rate Decreased	2 (40.0)	0	0	0	1 (25.0)	0	0	0	0	0	0	0	3 (9.1)	0
Hypophosphatemia	0	0	0	0	1 (25.0)	0	0	0	2 (28.6)	1 (14.3)	0	0	3 (9.1)	1 (3.0)
Lipase Increased	1 (20.0)	0	0	0	1 (25.0)	1 (25.0)	0	0	0	0	1 (20.0)	0	3 (9.1)	1 (3.0)
Platelet Count Decreased	0	0	0	0	0	0	0	0	1 (14.3)	0	2 (40.0)	0	3 (9.1)	0

All patients

	INC280 200 mg BID Cap + Buparlisib 50 mg QD N=5		**INC280 400 mg BID Cap + Buparlisib 50 mg QD N=6**		**INC280 500 mg BID Cap + Buparlisib 50 mg QD N=4**		**INC280 500 mg BID Cap + Buparlisib 80 mg QD N=6**		**INC280 300 mg BID Cap + Buparlisib 80 mg QD N=7**		**INC280 400 mg BID Cap + Buparlisib 80 mg QD N=5**		**N=33**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Vomiting	1 (20.0)	0	0	0	0	0	0	0	1 (14.3)	0	1 (20.0)	0	3 (9.1)	0
Amylase Increased	1 (20.0)	0	0	0	1 (25.0)	0	0	0	0	0	0	0	2 (6.1)	0
Constipation	0	0	1 (16.7)	0	1 (25.0)	0	0	0	0	0	0	0	2 (6.1)	0
Cough	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (20.0)	0	2 (6.1)	0
Decreased Appetite	0	0	1 (16.7)	0	1 (25.0)	0	0	0	0	0	0	0	2 (6.1)	0
Leukopenia	1 (20.0)	0	1 (16.7)	0	0	0	0	0	0	0	0	0	2 (6.1)	0
Pruritus	1 (20.0)	0	0	0	0	0	0	0	0	0	1 (20.0)	0	2 (6.1)	0
Rash	0	0	0	0	0	0	0	0	0	0	2 (40.0)	0	2 (6.1)	0
Rash Maculopapular	0	0	0	0	0	0	0	0	1 (14.3)	0	1 (20.0)	0	2 (6.1)	0

All patients

	INC280 200 mg BID Cap + Buparlisib 50 mg QD N=5		**INC280 400 mg BID Cap + Buparlisib 50 mg QD N=6**		**INC280 500 mg BID Cap + Buparlisib 50 mg QD N=4**		**INC280 500 mg BID Cap + Buparlisib 80 mg QD N=6**		**INC280 300 mg BID Cap + Buparlisib 80 mg QD N=7**		**INC280 400 mg BID Cap + Buparlisib 80 mg QD N=5**		**N=33**	
	All grades	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Somnolence	1 (20.0)	0	0	0	0	0	0	0	1 (14.3)	0	0	0	2 (6.1)	0
Stomatitis	0	0	0	0	0	0	1 (16.7)	0	0	0	1 (20.0)	0	2 (6.1)	0

1.2.2.4 Pharmacokinetics

As of 28-Sep-2015, INC280 single agent steady state PK data are evaluable in four studies with tablet and/or capsule formulations ([CINC280X2101T], [CINC280X1101], [CINC280X2102] and [CINC280X2201]). The mean plasma exposures (Cmax and AUC) of INC280 capsules were increased with dose following QD administration up to 600 mg/day in studies [CINC280X2101T] and [CINC280X1101], no further increase in the mean exposure was observed at 800 mg QD in [CINC280X1101]). Following twice daily dosing the mean plasma exposures (Cmax and AUC) of INC280 capsules increased with dose up to 600 mg twice per day (1200 mg/day). INC280 tablet provided higher exposures than the capsule at the same doses tested, with generally lower inter-subject variability. The mean plasma exposures of INC280 tablet appeared to increase dose proportionally from 200 to 400 mg twice per day ([CINC280X1101] and [CINC280X2102]). In the study [CINC280X2102], compared with the INC280 capsule at 600 mg BID (RP2D, N=21), the INC280 tablet at 400 mg BID (N=4) provided comparable mean AUC0-12h,ss (1.03-fold) and slightly higher Cmax,ss (1.22-fold) in the limited subjects tested. The apparent terminal half-life T1/2 of INC280 estimated from [CINC280X1101] QD treatment is 4.4 h, ranging, from 2.8 to 9.0 across the cohorts. Steady state INC280 exposure is expected to be reached by the third day of consecutive dosing. Accumulation of INC280 tablet following repeated administration at 400 mg BID is low with an accumulation ratio of up to 2-fold in [CINC280X1101] and [CINC280X2102]; however, some subjects had higher accumulation ratios up to 10-fold in [CINC280X1101].

1.2.2.5 Dose Rationale

INC280 600 mg bid is the highest safe dose being evaluated based on the clinical experience from ongoing studies. INC280 exposure increases by dose up to 600 mg bid. At this dose level, INC280 is expected to achieve target inhibition. In preclinical S114 xenograft model, plasma concentration of 71 nM was associated with 90% inhibition of p-MET. To predict the drug exposure of INC280 and its tumor growth inhibition effect, a PK/PD-tumor growth model has been built based on the data from preclinical xenograft models. The model suggested that average INC280 drug exposure at total daily doses of 400 mg (400 mg qd or 200 mg bid) and above will lead to tumor shrinkage in MET addicted tumors. BID dosing regimen is potentially more appropriate in fast growing tumors than a QD regimen (Georgieva et al, 2012). Concentration leading to tumor stasis (Cstasis) calculated from the GTL-16 xenograft model was close to five folds of in vivo IC90 for p-c-MET inhibition. Observed mean Ctrough concentration on Day 15 at 600 bid was about 2648 nM (preliminary PK result from ongoing study INC280X2102), equaling to 37 folds of in vivo IC90 and 7 folds of Cstasis. Therefore, minimal average steady state concentration of INC280 600 mg bid in tumor patients could well above Cstasis. Allowing for interpatient PK variability, given at 600 mg bid, more than 90% patient population could achieve concentration above Cstasis throughout the dosing interval. Novartis plans to use 600mg BID as the RP2D for all their single agent studies.

Taken together, the clinical safety and PK data as well as PKPD information from preclinical xenograft models suggest that 600 mg bid is a reasonable dose for this phase II study.

1.2.3 INC 280 Tablet Formulation

The Recommended Phase 2 Dose (RP2D) for INC280 single agent therapy has been determined in study CINC280X2102. CINC280X2102 study is a Phase I dose-escalation study conducted by

Novartis with expansion in patients with solid tumors and MET dysregulation. The dose of INC280 at 600 mg BID was selected as the RP2D (in capsules) based on safety, PD parameters, and PK profiles as outlined above.

INC280 was originally formulated as hard gelatin capsules (HGC) at 10 mg and 50 mg strengths. Consequently, a large number of capsules are required to be taken by the patients e.g., twelve 50 mg size 0 capsules twice a day for a 600 mg BID dosing (RP2D), amounting to a total of 24 capsules per day. For technical reasons capsules with strengths higher than 50 mg cannot be manufactured. To improve convenience for patients and consequently patient compliance, INC280 film coated tablets (FCT) at 50 mg, 100 mg, and 200 mg strengths were developed. A relative bioavailability study (CINC280X2103) compared the tablet and the capsule formulations in healthy volunteers (N=24). The study results showed that the tablet formulation provided higher systemic exposure with geometric mean ratios (tablet vs. capsule) of 2.4 and 3 for AUC and Cmax, respectively.

The tablet formulation was subsequently tested in patients first at 200 mg BID (N=3) and then at 400 mg BID (N=3) as a single agent (study CINC280X1101), and at 200 mg BID (N=7) in combination with gefitinib (study CINC280X2202). Based on the tablet PK and safety data from these studies, the dosage of 400 mg BID tablets was then introduced initially with a tablet safety cohort in study CINC280X2102 (Protocol Amendment #5; IND 116,691/S-0026/12-Feb-2014).

The INC280 tablet formulation at 400 mg BID showed good tolerability, comparable/favorable safety profile and exposure within the range of exposure of the capsule formulation at 600 mg BID with a 41% increase in mean steady state Cmax. Prior to the Dose Determination Meeting on 23-Oct-2014, no DLT has been observed with the tablet formulation. The preliminary PK data also suggest that 400 mg tablet BID may achieve and maintain the drug concentration needed for tumor inhibition throughout the treatment (e.g., unbound Ctrough greater than IC50 and IC90 for the inhibition of proliferation of the S114 cell line in vitro; Investigator's Brochure edition 5.1). As the exposure of the 600 mg capsule BID was reached by the 400 mg tablet BID, and the targeted unbound Ctrough was achieved and maintained throughout the treatment with the 400 mg tablet BID dose, further dose escalations were deemed unnecessary and 400 mg BID was declared the tablet RP2D for single agent INC280 in study CINC280X2102. During the Dose Determination Meeting on 23-Oct-2014, all study investigators agreed to 400 mg BID as the RP2D for the tablet formulation in study CINC280X2102. With no DLTs being observed, an expansion cohort with INC280 tablets at 400 mg BID was opened, as well as allowing patients to switch from 600 mg BID capsules to 400 mg BID tablets n study CINC280X2102.

Based on the clinical safety and pharmacokinetic data with INC280 tablet and as supported by the risk assessment (EWOC) within the BLRM derived from current single-agent dose-DLT data and predicted interaction, Novartis considers 400 mg BID is the RP2D for the INC280 single agent tablet formulation.

INC280 single agent at the dose of 400 mg BID in tablet formulation has been administered to patients enrolled in study CINC280X1101 and study CINC280X2102. Study CINC280X1101 is a Phase I, open-label, multi-center dose-escalation study with an expansion part of INC280 conducted in Japanese patients with MET-dependent advanced solid tumors. Study CINC280X2102 is a global Phase I, open-label, multi-center, dose-escalation study with a dose expansion part of INC280 in patients with MET-dependent advanced solid tumors.

As of a data cut-off date of 31-Dec-2014, a total of twenty-four patients have been treated with INC280 single agent at 400 mg BID in tablet formulation: six patients in study CINC280X1101 and eighteen patients in study CINC280X2102 (five of these patients received 400 mg BID INC280 tablets after switching from 600 mg BID INC280 capsules).

As of 31-Dec-2014, no DLTs have been observed for patients treated with the INC280 tablet formulation. Safety data from these patients are outlined in Table 1-4, Table 1-5 and Table 1-6. As per preliminary safety data, fatigue grade 3 and hypophosphatemia grade 3 suspected to be related to investigational treatment have been observed in patients treated with 400 mg BID tablet in the CINC280X2102 study and hypophosphatemia grade 3 and hyponatremia grade 3 suspected to be related to INC280 have been reported in patients treated at 400 mg BID in tablet in the Japanese study CINC280X1101. The PK and safety profiles of INC280 tablet formulation (at 400 mg BID) continues to be further evaluated in the ongoing INC280 studies.

PK data from studies CINC280X1101 and CINC280X2202 are summarized in Table 1-11 and Table 1-12, and Figure 3 and include preliminary PK data with the tablet formulation at 400mg PO BID tablets (Table 1-12).

Table 1-8: Patients (N=6) treated at 400 mg BID INC280 tablets in study CINC280X1101 as of 31-Dec-2014

Patient ID	**Treatment start**	**Treatment end**	**Treatment duration days (number of cycles*)**	**Dose interruption**	**G1/2 AEs suspected to be related to study drug**	**G3/4 AEs suspected to be related to study drug**	**SAE**	**Treatment d/c (reason for EOT/ study completion)**
1001_022	13-Nov-2014	9-Dec-2014	27 days (0.96 cycles)	yes	peripheral edema G1, decreased appetite G1, nausea G1, vomiting G1	hypophosphatemia G3 started on C1D22 and lasted 2 days; study drug temporarily interrupted; hypophosphatemia started after drug d/c (11-Dec-2014) and lasted 12 days	worsening of tumor pain G3 not suspected to be related to study drug, started on C2D9 and lasted 7 days; no action taken on the study drug;	yes (PD)
1001_023	18-Nov-2014	20-Nov-2014	3 days (0.1 cycles)	yes	increased serum creatinine G2	no	no	yes (PD)
1002_022	15-Jul-2014	5-Sep-2014	53 days (1.89 cycles)	no	increased serum creatinine G1, pruritus G1, peripheral edema G1, hypoalbuminemia G2	no	no	yes (PD)
1002_023	29-Jul-2014	6-Nov-2014	101 days (3.6 cycles)	no	increased serum creatinine G1, vomiting G1, malaise G1, erythema multiforme G1, weight loss G1, peripheral edema G1; anemia G2, hypoalbuminemia G2, increased lipase G2	no	no	yes (PD)
1002_024	19-Aug-2014	ongoing	134 days (4.8 cycles)	no	increased AST G1, increased ALT G1, peripheral edema G1, vomiting G1, maculopapular rash G1, gastroesophageal reflux G1	no	no	N/A (ongoing)
1002_025	22-Dec-2014	ongoing	10 days (0.3 cycles)	yes	nausea G1, vomiting G1, diarrhea G1	hyponatremia G3 started on C1D8 and lasted 2 days; study drug temporarily interrupted; AE resolved	no	N/A (ongoing)

* Cycle duration = 28 days; AEs = adverse events; SAE = serious adverse event; d/c = discontinuation; EOT = End of Trial; PD = disease progression; N/A = not applicable

Table 1-9: Patients (N=13) treated at 400 mg BID INC280 tablets in study CINC280X2102 as of 31-Dec-2014

Patient ID	**Treatment start**	**Treatment end**	**Treatment duration days (number of cycles*)**	**Dose interruption**	**G1/2 AEs suspected to be related to study drug**	**G3/4 AEs suspected to be related to study drug**	**SAE**	**Treatment d/c (reason for EOT/ study completion)**
1351_31001	19-Aug-2014	1-Sep- 2014	14 days (0.5 cycles)	no	no	no	death on 15-Sep-2014 due to PD	yes (PD)
1201_31002	22-Aug-2014	17-Oct-2014	57 days (2 cycles)	no	dizziness G1, oral mucositis G1, fatigue G1, constipation G1, hearing impairing G1	no	no	yes (PD)
1452_31003	26-Aug-2014	ongoing	127 days (4.5 cycles)	no	diarrhea G1, nausea G1, hypoalbuminemia, G1, peripheral edema G1, hypoalbuminemia G2, peripheral edema G2	no	no	N/A (ongoing)
1501_31005	21-Aug-2014	11-Dec-2014	113 days (4 cycles)	no	peripheral edema G1	no	no	yes (PD)
1351_31007	28-Aug-2014	22-Oct-2014	56 days (2 cycles)	yes	epigastralgia G1, vomiting G1, nausea G1, AST increase G1, ALT increase G1, gastroesophageal reflux G1, odynophagia G1, cholestasis G1, anxious depressive syndrome G1; hypoalbuminemia G2, asthenia G2	no	no	yes (PD)
1301_22031	14-Nov-2014	15-Dec-2014	32 days (1.1 cycles)	no	nausea G1, vomiting G1, AST increase G1, ALT increase G2, nausea G2, fatigue G2	fatigue G3, started on C2D3, ongoing 30 days after treatment discontinuation; no action taken on study drug	malaise G2 suspected to be related with study drug, started on C2D4, lasted 4 days	yes (PD)

1600_22032	4-Nov- 2014	ongoing	58 days (2 cycles)	no	lipase increase G1, loss of appetite G1, AST increase G1, lymphopenia G1	no	no	N/A (ongoing)
1501_22033	11-Dec-2014	ongoing	21 days (0.7 cycles)	yes	no	no	no	N/A (ongoing)
1600_22034	17-Nov-2014	ongoing	45 days (1.6 cycles)	no	leukopenia G1, peripheral edema G1; lymphopenia G2	hypophosphatemia G3, started on C1D8, lasted 14 days, no action taken on study drug C1D4	no	N/A (ongoing)
1501_23016	6-Nov- 2014	ongoing	56 days (1.9 cycles)	no	fatigue G1, peripheral edema G1	no	no	N/A (ongoing)
1152_24026	27-Oct-2014	16-Nov-2014	21 days (0.8 cycles)	no	vomiting G1	no	no	yes (PD)
1501_24027	21-Nov-2014	30-Nov-2014	10 days (0.4 cycles)	no	Fatigue G2, nausea G2, vomiting G2	no	no	yes (withdrawn consent)

* Cycle duration = 28 days; AEs = adverse events; SAE = serious adverse event; d/c = discontinuation; EOT = End of Trial; PD = disease progression; N/A = not applicable

Table 1-10: Patients (N=5) who switched from 600 mg BID INC280 capsules to 400 mg BID INC280 tablets in study CINC280X2102 as of 31-Dec-2014

Patient ID	Treatment start with capsule	Date of switch to tablet	Treatment duration[a] days capsule + tablet (number of cycles[b])	Treatment duration[a] days tablet only (number of cycles[b])	Dose interruption	G1/2 AEs suspected to be related to study drug	G3/4 AEs suspected to be related to study drug	SAE
1600_21017	15-May-2014	28-Oct-2014	231 days (8.3 cycles)	65 days (2.3 cycles)	no	cough G1, pruritus G1, dyspnea G1, fatigue G1, thrombocytopenia, G1, peripheral edema G1, pruritus G2, fatigue G2	no	no
1600_22016	6-Jun- 2014	24-Oct-2014	209 days (7.5 cycles)	69 days (2.4 cycles)	no	ALT increase G1, hypophosphatemia G1, hypocalcemia, G1, peripheral edema G1; peripheral edema G2	no	pulmonary haemorrhage G2, not suspected to be related to study drug, started on 13-Dec- 2014 and lasted 4 days
1151_22024	30-Jul-2014	19-Nov-2014	155 days (5.5 cycles)	43 days (1.5 cycles)	no	edema G1, vomiting G1, nausea G1; lipase increase G2	no	pneumonia G2, not suspected to be related to study drug; started on C1D12, lasted 11 days
1201_22027	15-Sep-2014	27-Oct-2014	108 days (3.9 cycles)	66 days (2.3 cycles)	no	fatigue G1, weight loss G1, anorexia G1, nausea G1, vomiting G1, odynophagia G1, insomnia G1; fatigue G2, vomiting G2	no	no
1600_24023	26-Jun-2014	13-Nov-2014	189 days (6.8 cycles)	49 days (1.7 cycles)	no	nausea G1, edema G1, lipase increase G1, leukopenia G1; edema G2, leukopenia G2	no	no

[a] all patients are ongoing at the time of data cut-off date (31-Dec-2014); [b] Cycle duration = 28 days; AEs = adverse events; SAE = serious adverse event;

Table 1-11: Summary of PK parameters after INC280 administration as a single agent (mean ([SD]) on Cycle 1, Day 15 (as of Sept 28, 2015)

Study	Regimen	Tmax (range) (h) [a]	Cmax,ss (ng/mL)	AUC0-t,ss (h*ng/mL) [b]
[CINC280X2101T]				
(n = 3)	10 mg QD	2.0 (0.5; 2. 0)	38 (15)	214 (77)
(n = 3)	20 mg QD	2.0 (1.0; 2. 0)	63 (12.5)	393 (53)
(n = 5)	mg QD	2.0 (1.0; 5. 0)	240 (115)	1184 (395)
(n = 4)	70 mg QD	1.1 (1.0; 1. 1)	394 (241)	1720 (742)
(n = 3)	150 mg QD	2.0 (1.0; 2. 0)	1159 (656)	5444 (2318)
(n = 4)	200 mg QD	1.5 (1.0; 2. 0)	895 (381)	5114 (1897)
(n = 4)	300 mg QD	2.0 (1.0; 2. 0)	866 (213)	4248 (1262)
(n = 5)	400 mg QD	2.0 (1.0; 4. 0)	1712 (1250)	9445 (8207)
(n = 3)	50 mg BID	1.1 (1.0; 4. 1)	181 (92)	957 (292)
(n = 4)	200 mg BID	1.0 (1.0; 1. 1)	2070 (1081)	7754 (2598)
(n = 4)	300 mg BID	1.6 (1.1; 4. 0)	4124 (1105)	15713 (3411)
[CINC280X1101]				
(n = 3)	100 mg QD	4.0 (1.0; 4. 1)	395 (53.1)	2770 (1040)
(n = 3)	200 mg QD	1.0 (1.0; 2. 0)	2160 (760)	9910 (1960)
(n = 3)	400 mg QD	2.0 (2.0; 2. 1)	5060 (4010)	26400 (18400)
(n = 3)	500 mg QD	2.0 (1.0; 2. 0)	7960 (952)	43700 (7680)
(n = 4)	600 mg QD	1.5 (1.0; 2. 0)	7180 (897)	39000 (7140)
(n = 4)	800 mg QD	3.0 (2.0; 4. 1)	6450 (3550)	39400 (7700)
(n = 3)	400 mg BID	4.0 (2.0; 4. 0)	1980 (1740)	11000 (8750)
(n = 2)	600 mg BID	2.0 (2.0; 2. 0)	16500 (2190)	62500 (645)
(n = 3)	200 mg BID (tablet)	1.0 (1.0; 2. 0)	3140 (1620)	12000 (6150)
(n = 12)	400 mg BID (tablet)	1.0 (0.45; 2.0)	7110 (4440)	29300 (20100)

Study		Regimen	Tmax (range) (h) [a]	Cmax,ss (ng/mL)	AUC0-t,ss (h*ng/mL) [b]
[CINC280X2102]					
(n = 4)	100 mg BID		2.9 (1.9; 4. 0)	660 (550)	2910 (2090)[h]
(n = 5)	200 mg BID		1.9 (1.9; 8. 0)	2500 (856)	9700 (4040)[c]
(n = 3)	250 mg BID		1.0 (0.5; 2. 0)	1580 (1010)	6140[d]
(n = 3)	350 mg BID		3.9 (1.0; 4. 0)	4410 (3800)	25500[d]
(n = 7)	450 mg BID		2.0 (1.8; 7. 9)	3200 (1280)	19600[d]
(n = 45)	600 mg BID		2.0 (0.0; 8. 4)	4790 (3440)	24700 (13500)[e]
(n = 8)	400 mg BID (tablet)		1.6 (0.5; 4. 3)	5860 (2780)	25500 (14400)[g]
[CINC280X2201]					
(n = 8)	300 mg QD		2.0 (1.0; 2.0)[f]	3060 (1703)[f]	10276 (6208)[g]

n: number of subjects with non-missing values and evaluable PK

[a] median value

[b] AUC0-12h for BID regimen and AUC0-24h for QD regimen

[c] n=3

[d] n=1

[e] n=21

[f] n=6

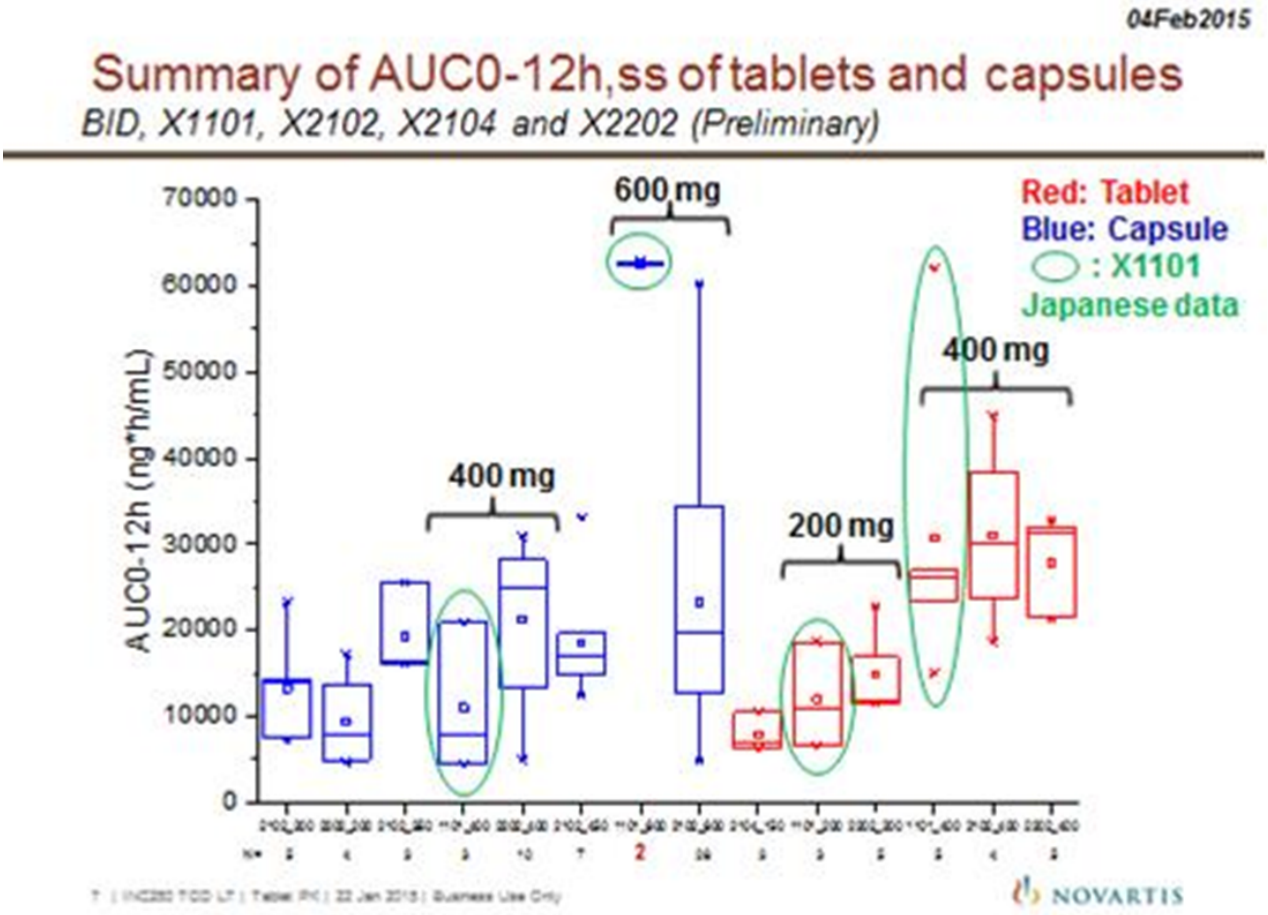
[g] n=4

[h] AUC0-8h

Table 1-12: Summary of PK parameters after INC280 administration (400mg BID Tablet formulation) as a single agent (mean ([SD]) on Cycle 1, Day1 and C1D 15 (as of Dec 31, 2014)

Study	Dose (mg)	Formulation	C1D1 (Mean (CV%))				C1D15 (Mean (CV%))			
			N	Tmax (h)	Cmax (ng/mL)	AUC_{0-12} (ng*h/mL)	N	Tmax (h)	Cmax (ng/mL)	AUC_{0-12} (ng*h/mL)
X2102	400	Tablet	4	2.0	5385 (44)	20214 (26)	4	1.5	7425 (30)	30988 (35)
X2202	400	Tablet	NA	NA	NA	NA	5	1	6600 (29)	27800 (21)

Figure 3: Summary of AUC)-12 of single agent INC 280 capsules and tablets (preliminary)



1.2.4 Study purpose/rationale

While several treatment options are available for patients with metastatic clear-cell RCC, systemic therapies for patients with unresectable papillary RCC are limited. Multikinase inhibitors recommended for advanced clear-cell RCC generally do not target the MET receptor, and appear to have limited activity in papillary RCC 9. Similarly, the role of mTOR inhibitors, another class of agents with activity in RCC, remains poorly defined in papillary RCC. A recently concluded clinical trial sought to determine the efficacy of foretinib, a kinase inhibitor of both MET and VEGF receptors, in patients with papillary kidney cancer (both hereditary and sporadic). Results from this study have suggested efficacy of this agent in patients with papillary RCC[31,32]. However, it would be difficult to determine if activity associated with this agent is attributable to its VEGF pathway or MET inhibitory properties. Furthermore, most of the adverse events reported with this agent appear to be related to VEGF pathway inhibition, dictating tolerability and drug dosing, and potentially compromising the ability to optimally target the MET pathway with this and similar agents.

We propose to conduct a phase 2, proof-of-concept study using a selective MET antagonist lacking activity against the VEGF pathway in patients with papillary RCC to test the hypothesis that

effective pharmacologic blockade of the HGF/MET pathway will translate to clinical activity in patients with papillary renal cell cancer. In addition to advancing research in an area of unmet need in a rare patient population, this trial would offer critical scientific insight into the role of the MET pathway in papillary RCC.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically or cytologically confirmed papillary RCC.

a. Patients with bilateral multifocal disease can have tumors localized to the kidney or have metastatic disease
b. Patients with sporadic papillary RCC (but without multifocal disease) should have advanced disease that is considered unresectable

2.1.1.2 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions). Nodal lesions must be ≥ 15mm by CT scan or MRI. Non nodal lesions must be >10 mm with CT scan or MRI. See Section 6.2 for the evaluation of measurable disease.

2.1.1.3 Patients must have normal organ and marrow function as defined below:

- Hemoglobin > 9 g/dL (SI Units: 90 g/L)
- Platelet count ≥ 75 x 109/L
- Absolute neutrophil count (ANC) ≥ 1.5 x 109/L without growth factor support
- Total bilirubin ≤ 2 x upper limit of normal (ULN)
- AST/SGOT and/or ALT/SGPT ≤ 2.5 x upper limit of normal (ULN)
- Serum creatinine ≤ 1.5 x ULN
- Asymptomatic serum amylase ≤ 2 x ULN; patients with > ULN but ≤ 2 x ULN serum amylase at study start must be confirmed to have no signs and/or symptoms suggestion pancreatitis or pancreatic injury (e.g. elevated P-amylase, abnormal imaging findings of pancreas, etc.)
- Serum lipase ≤ ULN
- Fasting serum triglyceride level ≤500 mg/dL

2.1.1.4 Patients may have had no more than 3 prior lines of systemic therapy. Prior therapy with a MET inhibitor is allowed as long as the patient has not had progressive disease while receiving the agent

2.1.1.5 Patient must be able to swallow and retain oral medication

2.1.1.6 Age >18 years.

2.1.1.7 ECOG performance status 0 - 2 (see Appendix A).

2.1.1.8 Patients must provide written informed consent prior to any study procedures.

2.1.1.9 Patients must be willing and able to comply with scheduled visits, treatment plan and laboratory tests

2.1.2 Exclusion Criteria

2.1.2.1 Patients who are receiving any other investigational agents for treatment of their kidney cancer.

2.1.2.2 History of allergic reactions attributed to compounds of similar chemical or biologic composition to INC280. Excipients in the current formulation include microcrystalline cellulose, mannitol, sodium starch glycolate, magnesium stearate and colloidal silicon dioxide

2.1.2.3 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring intravenous antibiotics, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements or potentially affect the interpretation of study data.

2.1.2.4 Subjects with significant or uncontrolled cardiovascular disease (e.g., uncontrolled hypertension, peripheral vascular disease, congestive heart failure, cardiac arrhythmia, or acute coronary syndrome) within 6 months prior to starting study treatment or heart attack within 12 months prior to starting study treatment

2.1.2.5 Patients receiving any medications that are known to be strong inducers or inhibitors of CYP3A4, or sensitive substrates of CYP3A4, CYP1A2, CYP2C9, CYP2C9, CYP2C19 or P-gp with a narrow therapeutic index. Lists including medications and substances known or with the potential to interact with the relevant CYP isoenzymes and P-gp transporter are provided in Table 4-1.

2.1.2.6 Symptomatic CNS metastases that are neurologically unstable or requiring > 5 mg/day of dexamethasone (or equivalent) to control CNS disease.

Note: Patients with controlled CNS metastases are allowed. Radiotherapy or surgery for CNS metastases must have been completed >2 weeks prior to study entry. Patients must be neurologically stable, having no new neurologic deficits on clinical examination, and no new findings on CNS imaging. Steroid use for management of CNS metastases must be at a stable dose for two weeks preceding study entry.

2.1.2.7 Patients with ≥ Grade 2 neuropathy.

2.1.2.8 Treatment with proton pump inhibitors within 3 days prior to study entry. If continued use of GI prophylaxis is required, the patient will be switched to an appropriate H2 antagonist with appropriate counsel and caution as detailed in Section 4.2.

2.1.2.9 Currently receiving any prohibited medications including vitamins and herbal supplements found in section 4.

2.1.2.10 Major surgery within 4 weeks prior to initiating treatment, excluding the placement of vascular access.

2.1.2.11 The subject has not recovered to baseline, CTCAE ≤ Grade 1 from toxicity due to all prior therapies for RCC or to a level permitted under other sections of the eligibility criteria except alopecia and other non-clinically significant AEs.

2.1.2.12 Any other condition that would, in the Investigator's judgment, contraindicate 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.

2.1.2.13 Pregnant or nursing (lactating) 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 (> 30 mIU/mL). Laboratory values >5 mIU/mL, but <30 mIU/mL should be repeated in 48 hours.

2.1.2.14 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 3 month days after stopping study drug. Highly effective contraception methods include:

- Total abstinence or
- Male or female sterilization or
- 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
  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

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.

2.1.2.15 Sexually active males must use a condom during intercourse while taking the drug and for 3 months after stopping study drug 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.

2.1.2.16 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with INC280.

2.1.2.17 Prior invasive malignancy of other histology currently requiring treatment.

2.2 SCREENING EVALUATION

Screening evaluations must be performed within the timeframes indicated below. Screening procedures may be performed on an NIH screening protocol or the Urology Branch 89-C-0086 and/or 97-C-0149. Imaging studies may also be performed at an outside institution for expedience. If procedures are performed on this treatment protocol, the screening examination must start with the Informed Consent procedure. The investigator is obliged to give the patient thorough information about the study and the study related assessments, and the patient should be given ample time to consider his or her participation. The investigator must not start any study related

procedure before ICF is signed and dated by both patient (and impartial witness, if applicable) and investigator.

- To be performed within 4 weeks prior to subject receiving study drug
  - History and physical evaluation
  - Performance status
  - Bone scan (performed on all patients with known or suspected metastatic disease)
  - Brain MRI or Brain CT (studies are to be performed with contrast unless renal impairment or allergy prohibits the use of contrast)
  - FDG-PET in patients with known or suspected metastatic disease
- To be performed within 2 weeks prior to subject receiving the study drug
  - CBC with differential
  - Serum β hCG (in female patients of childbearing potential)
  - Total and direct bilirubin, acute care panel, albumin, AST/SGOT, ALT/SGPT, serum creatinine, calcium, magnesium, LDH, amylase, lipase, lipid panel T3, free thyroxine, TSH PT, PTT, Creatine Kinase, Uric Acid, Total Protein, Urinalysis, Urine Creatinine.
  - CT chest/abdomen/pelvis or CT chest plus MRI abdomen for organ confined disease; MRI of the pelvis only if indicated.

For baseline evaluations, please see section 2.4.

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site () must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.4 TREATMENT ASSIGNMENT PROCEDURE

Cohort

Number	Name	Description
1	Single cohort	Patients with hereditary papillary renal carcinoma (HPRC) or sporadic papillary renal cell carcinoma (RCC)

Arm

Number	Name	Description
1	Single arm	INC280 400 mg twice every day by mouth, continuously

Patients enrolled to cohort 1 will be directly assigned to arm 1.

2.5 BASELINE EVALUATION

Baseline procedures need not be repeated if they have been performed within the appropriate screening timeframe (See section 2.2).

- Serum β hCG (in female patients of childbearing potential)
- CBC with differential
- Total and direct bilirubin, AST/SGOT, ALT/SGPT, acute care panel, albumin, calcium, magnesium, LDH, amylase, lipase, lipid panel, T3, free thyroxine, TSH
- Ocular Monitoring (as needed):
  - Dilated Eye Examination
  - Electroretinogram and Dark Adaptation Testing
  - Optical Coherence Tomography
  - Humphrey Visual Field 30-2 Sita Fast
  - Optos color and fundus autofluorescence photos
- CT chest/abdomen/pelvis or CT chest and MRI abdomen for organ confined disease; MRI of the pelvis only if indicated.
- Bone scan (if metastases are suspected)
- Brain MRI or Brain CT
- ECG
- FDG-PET in patients with known or suspected metastatic disease
- Biopsies (optional) and blood for correlative studies (see section 5)
- Obtain archival tumor tissue when available (tissue block and/or up to 30 unstained slides)

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is an open-label single arm phase 2 study. Up to 20 evaluable patients with bilateral multifocal papillary RCC (metastatic or localized to the kidney) or patients with advanced papillary RCC will be enrolled on study to be treated with 400 mg of INC280 taken orally twice per day until disease progression or unacceptable toxicity. Treatment may also be discontinued permanently if the manufacturer (Novartis) is unable to provide the agent for ongoing use (in accordance with the terms outlined in the clinical M-CRADA under which this trial will be conducted). Each treatment cycle will consist of 28 days and drug dosing will be continuous (i.e., there will be no break between cycles in the absence of toxicity). Patients will be assessed for overall response rate with restaging studies performed approximately every 8 weeks for the first 32 weeks and approximately every 12 weeks thereafter while on study. Patients will also be assessed for progression free survival, duration of response, safety and pharmacodynamic endpoints. Patients will be counseled on evaluation for the presence of germline MET mutations when clinically indicated (bilateral multifocal disease and/or family history suggestive of HPRC). These patients will be counseled by the PI or qualified genetic counselor on the risks of genetic testing and the implications should the subject be found to have a germline alteration; patients who agree to pursue germline testing at the Clinical Center will typically be enrolled on another IRB approved protocol designed for this purpose, such as 89-C-0086. When feasible, patients without germline mutations will have their tumors evaluated for the presence of: a) Somatic MET mutations by full length sequencing, b) Polysomy 7/ amplification of the MET and/or HGF locus

by CGH. These data will be used in an exploratory analysis to determine if alterations in MET impact response to therapy. Please see section 8.5, the statistical section, for further details.

Patients will also undergo optional biopsies of accessible tumors before initiation of therapy and following 2 cycles of therapy. These paired tumor samples will be used to assess target modulation (of MET and related pathways).

3.2 DRUG ADMINISTRATION

Patients should be instructed to take the study drug as per protocol and instructed to complete the medication diary found in Appendix B. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded appropriately.

Table 3-1: Treatment and Treatment Schedule

Study treatments	**Pharmaceutical form and route of administration**	**Dose**	**Frequency and/or regimen**
INC280	Tablet for oral use	400 mg	twice every day, continuously

The orally administered film coated tablet formulation is provided in two strengths of 100mg and 200mg. The 100 mg strength is formulated as a light red ovaloid, curved tablet with beveled edges, without score, imprinted with 'OU' on one side and 'NVR' on the back side. The 200 mg strength is formulated as a dark brown, ovaloid, curved tablet, without score, imprinted with 'NVR' on both sides. The 200 mg strength can also be formulated as a yellow ovaloid, curved tablet with beveled edges, without score, imprinted with 'LO' on one side and 'NVR' on the back side.

INC280 will be dosed on a flat scale and not individually adjusted by weight or body surface area.

Patients will self-administer the study medication with at least 8 ounces of water and consume at least 8 ounces of water 2 hours after drug intake as directed by the study doctor. The patients should be instructed to avoid grapefruit juice or Seville orange juice for seven (7) days prior to the first dose of study drug.

Patients should be instructed to take their dose twice a day at approximately the same time each day. Doses should be at least eight (8) hours apart. Patients should fast 2 hours before and for two hours following drug ingestion. During the fasting period, patients can freely drink water. The patient will also be permitted to drink the following clear liquids during the fasting period if necessary: ginger ale, apple juice, cranberry juice. If a planned dose is missed, it can be taken within four hours of the planned time. The patient should resume their normal dosing time the following day. If a dose is not taken within 4 hours of the planned dosing time, the missed dose should not be replaced.

If vomiting occurs, no attempt should be made to replace the vomited dose. If a patient vomits within 4 hours of INC280 dosing, this should be recorded appropriately.

Please see section 14.1.6 for drug accountability and compliance instructions.

3.3 DOSE MODIFICATIONS

All dose modifications should be based on the worst preceding toxicity. Dose modifications will be made only for those AEs thought to be related to INC280.

For each patient, once a dose reduction has occurred, the dose level may not be re-escalated during subsequent treatment cycles with INC280. Dose modifications will follow the scheme outlined in Table 3-3. No more than 2 dose reductions will be allowed per patient.

When study drug is interrupted or permanently discontinued due to an AE or abnormal laboratory value, the patients must be followed at least once a week for 4 weeks, and subsequently in 4-week intervals, until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay of > 14 days from the intended day of the scheduled dose due to adverse events related to INC280, then the patient must be permanently discontinued from study therapy. However, the patient will be followed up for toxicity as previously described. All patients will be followed for adverse events and serious adverse events for 30 days following the last dose of study drug.

Patients who discontinue from the study for a study-related AE or an abnormal laboratory value must be followed as described in Table 3-4.

The investigator must notify the Novartis immediately of any unexpected CTCAE grade ≥ 3 adverse events or laboratory abnormalities. The criteria for interruption and re-initiation of INC280 can be found in Table 3-3.

Table 3-2: INC Dose level table

Dose level	**Dose**
1	400 mg twice per day
-1	300 mg twice per day
-2	200 mg twice per day

Table 3-3: Criteria for interruption and re-initiation of INC280 treatment

Recommended dose modifications for INC280**	
Worst toxicity CTCAE grade* (value)	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing.**
<u>Hematologic</u>	
Neutropenia (ANC)	
Grade 1 (LLN - 1500/mm^3 or LLN – 1.5x10e9/L)	Maintain dose level
Grade 2 (<1500 - 1000/mm^3 or <1.5 - 1.0x10e9/L)	Maintain dose level
Grade 3 (< 1000 - 500/mm^3 or < 1.0 – 0.5x10e9/L)	Discontinue INC280: • If depression lasts for ≤ 7 days (until ANC recovers to ≥1500): Resume treatment at same dose level. • If depression lasts for >7 days (until ANC to recovers to ≥1500): Resume treatment at ↓1 dose level.
Grade 4 (< 500/mm3 or < 0.5x10e9/L)	Discontinue INC280
Thrombocytopenia (PLT)	
Grade 1 or 2 (PLT < LLN - 50,000/mm^3)	Maintain dose level
Grade 3 (<50 – 25x10e9/L)	Discontinue dose until resolved to ≤ Grade 1 or baseline, then: If not associated hemorrhage/bleeding: Resume treatment at same dose level. If associated with hemorrhage/bleeding: Resume treatment at ↓ 1 dose level.
Grade 4 (<25x10e9/L)	Discontinue dose until resolved to ≤ Grade 1 or baseline, then resume treatment at ↓ 1 dose level.

Recommended dose modifications for INC280**	
Worst toxicity CTCAE grade* (value)	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing.**
Febrile Neutropenia	
Febrile neutropenia (ANC < 1.0 x 10^9/L or 1000/mm^3 and a single temperature of >38.3°C (101 °F) or a sustained temperature of >=38 °C (100.4 ° F) for more than one hour.)	Discontinue dose until fever resolved and ANC is at ≤ Grade 1 or baseline, then resume treatment at ↓1 dose level.
Renal	
Serum creatinine	
(< ULN - 2.0 x ULN)	Maintain dose level
(>2.0 -6.0 x ULN)	Discontinue dose until resolved to ≤ 2.0 ULN or baseline, then resume treatment at ↓ 1 dose level. Patients will be instructed to increase their fluid intake until resolution to ≤ 2.0 x ULN or baseline.
Grade 4 (> 6.0 x ULN)	Discontinue INC280

Recommended dose modifications for INC280**	
Worst toxicity CTCAE grade* (value)	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing.**
<u>Hepatic</u>	
Bilirubin	
Grade 1 (> ULN - 1.5 x ULN)	Maintain dose level
Grade 2* (> 1.5 - 3.0 x ULN)	Discontinue dose until resolved to ≤ Grade 1 or baseline, then resume at the same dose level
Grade 3* (> 3.0 - 10.0 x ULN)	Discontinue dose until resolved to ≤ Grade 1 or baseline, then resume at ↓ 1 dose level
Grade 4* (> 10.0 x ULN)	Discontinue INC280
AST or ALT	
Grade 1 or 2 (> ULN - 5.0 x ULN)	Maintain dose level
Grade 3* (> 5.0 – 20.0 x ULN)	Discontinue INC280: • If elevation lasts for ≤ 7 days: Resume treatment same dose level • If elevations lasts for >7 days: Resume treatment at ↓ 1 dose level
Grade 4 * (> 20.0 x ULN)	Discontinue INC280

*** Discontinue INC280 if ≥ Grade 3ALT accompanied by ≥ Grade 2 Bilirubin**

Recommended dose modifications for INC280**	
Worst toxicity CTCAE grade* (value)	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing.**
<u>Pancreas</u>	
Asymptomatic Grade 1 or 2 amylase or lipase (>ULN – 2.0x ULN)	• Maintain dose level
Grade 3 amylase or lipase (> 2.0 - > 5.0 x ULN)	• Continue dosing and monitor laboratory values. If levels do not resolve to grade 2 or less by 14 days after the initial report, discontinue INC280. If levels return to grade 1 or less within 14 days, resume at ↓ 1 dose level
Grade 4 amylase or lipase	• Discontinue INC280
Symptomatic Amylase or lipase elevations of any grade	• Discontinue INC280
<u>Neurologic</u>	
Any Neurological Toxicity Grade 2 or greater	Discontinue INC280. Neurological assessments must be repeated as clinically indicated until resolution to < CTCAE grade 1 or until stabilization. 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.
<u>Cardiac (General)</u>	
Grade 1	Maintain dose level
Grade 2	Discontinue dose until resolved to ≤ Grade 1 or baseline, then resume at ↓1 dose level
Grade 3 or 4	Discontinue INC280

Recommended dose modifications for INC280**	
Worst toxicity CTCAE grade* (value)	**Recommended dose modifications any time during a cycle of therapy, including intended day of dosing.**
<u>Other adverse events+</u>**	
Grade 1 or 2	Maintain dose level
Grade 3	Discontinue dose until resolved to ≤ Grade 1, then ↓1 dose level
Grade 4	Discontinue INC280
All dose modifications should be based on the worst preceding toxicity.	
*Common Toxicity Criteria for Adverse Events (CTCAE Version 4.0).	
** If the investigator deems that a recommended dose reduction or the recommendation to maintain the same dose level is not in the best interest of the patient, this decision may be discussed with Novartis on a case-by-case basis. + Dose modifications for diarrhea, nausea and constipation will only be made for grade 3-4 toxicities that persist despite optimal medical intervention. No dose reductions are necessary for electrolyte abnormalities that can be corrected within 72 hours	

Table 3-4: Follow up evaluations for selected toxicities

Toxicity	***Follow-up evaluation***
Hematology	If febrile neutropenia of any duration occurs, the patient must be followed until resolution. If ≥ CTCAE grade 3 hematologic toxicity occurs, the parameter must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 and then at least weekly until either initiation of retreatment or until stabilization.
Renal	If serum creatinine ≥ CTCAE grade 3 has been demonstrated, this parameter must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 or baseline, and then at least weekly until either initiation of re-treatment or until stabilization. Patients will be instructed to increase hydration until resolution to ≤ CTCAE grade 1 or baseline.
Hepatic	If total bilirubin ≥ 3 x ULN or ≥ CTCAE grade 3 AST or ALT has been demonstrated, these parameters must be repeated at least twice a week until resolution to baseline, and then at least weekly until either initiation of re-treatment or until stabilization. Patients with total bilirubin > 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.

Toxicity	***Follow-up evaluation***
Pancreatic	If serum amylase or serum lipase ≥ CTCAE grade 3, follow until resolution to grade 2 or less
Neurologic	If any neurological abnormality or toxicity ≥ Grade 2 has been demonstrated, neurological assessments must be repeated as clinically indicated until resolution to ≤ CTCAE grade 1 or stabilization. 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 also be performed to monitor for physiological changes in brain activity.
Ocular	If patient reports dark adaptation changes, ocular monitoring will be as follows: • Dilated Eye Examination • Electroretinogram and Dark Adaptation Testing • Humphrey Visual Field 30-2 Sita Fast • Optos color and fundus autofluorescence photos if clinically indicated
Cardiac	Monitor toxicity until resolution to grade 1 or baseline. If applicable, monitor ECGs twice weekly until normalization or stabilization.
Non-laboratory	Patients who experience non-laboratory DLTs must be evaluated at least once a week following demonstration of the toxicity until resolution of the toxicity to allow for re-treatment, until stabilization of the toxicity, or until study completion.

3.4 STUDY CALENDAR

1 cycle = 28 days

Evaluations below may be performed within ± 5days of indicated time in order to accommodate patient schedules, holidays and weather emergencies. Imaging studies and optional tumor biopsies may be performed within ± 5days of indicated time.

While on study therapy, beginning of the cycle assessments (those occurring at week 1) will be performed at the NIH Clinical Center. Mid cycle assessments (occurring during week 3) may be performed at any CLIA certified laboratory (or CLIA equivalent if other than USA) if this is the patient's preference.

Procedure	***Screening/ Baseline***	***Cycle 1***				***Subsequent Cycles***				**Restage**	***Post Therapy Follow-up[5]***
		Wk 1	***Wk 2***	***Wk 3***	***Wk 4***	***Wk 1***	***Wk 2***	***Wk 3***	***Wk 4***		
Informed consent	X										
History and PE	X					X					X
Vital signs	X			X		X					
Performance status	X										**X**
CBC with differential	X	X[2]		X		X		X			
PT/ PTT	X										
Serum β hCG[1]	X	X[2]				X					
Total and direct bilirubin, AST/SGOT, ALT/SGPT, acute care panel, phosphorus	X	X[2]		X		X[2]		X			X

Procedure	***Screening/ Baseline***	***Cycle 1***				***Subsequent Cycles***				**Restage**	***Post Therapy Follow-up[5]***
		Wk 1	***Wk 2***	***Wk 3***	***Wk 4***	***Wk 1***	***Wk 2***	***Wk 3***	***Wk 4***		
albumin, calcium, magnesium, LDH, amylase, lipase, creatine kinase, uric acid, total protein	X	X[2]		X		X[2]		X			
Lipid Panel	X	X				X					
TSH, T3, Free T4	X									X	
Urinalysis/ Urine Creatinine	X									X	
Ocular Monitoring											
Dilated Eye Examination	X[7]										X
Electroretinogram and Dark Adaptation Testing	X[7]										X
Optical Coherence Tomography	X[7]										X
Humphrey Visual Field 30-2 Sita Fast	X[7]										X
Optos color and fundus autofluorescence photos	X[7]										X

Procedure	***Screening/ Baseline***	***Cycle 1***				***Subsequent Cycles***					***Post Therapy Follow-up[5]***
		Wk 1	***Wk 2***	***Wk 3***	***Wk 4***	***Wk 1***	***Wk 2***	***Wk 3***	***Wk 4***	**Restage**	
ECG	X	X		X		X					
Archival tissue for diagnostic evaluation	X										
INC280		Continuous dosing									
Fresh tumor biopsy for biomarker assessment	X									X [6]	
Correlative Research Studies/Pharmacodynamics	X									X	
CT abdomen or MRI abdomen; CT chest if indicated; CT or MRI pelvis if indicated ± bone scan	X	Every 8 weeks for first 32 weeks; every 12 weeks thereafter. Restaging bone scans are performed only in patients with evidence of bone metastases at baseline.									
Brain CT or brain MRI	X	If negative at baseline, will not repeat unless patient becomes symptomatic. If positive then patients will be assessed as above, every 8 weeks for the first 32 weeks; every 12 weeks thereafter.									

Procedure	***Screening/ Baseline***	***Cycle 1***				***Subsequent Cycles***					***Post Therapy Follow-up[5]***
		Wk 1	***Wk 2***	***Wk 3***	***Wk 4***	***Wk 1***	***Wk 2***	***Wk 3***	***Wk 4***	**Restage**	
PET	X	May be performed at restaging to clarify if residual disease or equivocal new foci on conventional imaging represent tumor									
Adverse Events		Continuous (up to 30 days post therapy discontinuation)									
Concomitant Medications		Continuous									

1 In women of childbearing potential only

2Performed prior to dosing

3 In cycle 3 only

4 Odd numbered cycles only. See section 5.1 for collection of blood and urine specimens.

5 See section 3.5 for details

6 First restage only

7As needed

3.5 FOLLOW UP EVALUATIONS

After subjects have stopped taking the study medication for any of the reasons listed in section 3.6.1, they will be seen at NIH, if feasible, for a safety visit within 4-5 weeks of drug discontinuation. The safety assessments may be performed by a local physician and laboratory if patients unable to return to the NIH Clinical Center at this time. If patients are unable to comply with the follow-up visit, this will be documented in the patient chart.

The following assessments will be performed at follow up.

- History and Physical Examination
- CBC with differential, acute care panel, phosphorus, AST, ALT, Total and Direct Bilirubin
- Ocular Monitoring:
    - Dilated Eye Examination
    - Electroretinogram and Dark Adaptation Testing
    - Optical Coherence Tomography
    - Humphrey Visual Field 30-2 Sita Fast
    - Optos color and fundus autofluorescence photos

After the safety visit, if there are no unresolved grade 3 or higher AEs, we may, when feasible contact the patient annually by telephone to find out how they are doing and to determine survival status. If there are unresolved, unexpected grade 3 – 4 AEs, patients will be followed either at the NIH clinical center or by their local physician. In the latter case, we will obtain the physician's record of AEs.

Any scans performed outside of the NIH will also be obtained when possible.

3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

3.6.1 Criteria for removal from protocol therapy

- Completion of protocol therapy
- Progressive disease
- Participant requests to be withdrawn from active therapy
- Unacceptable Toxicity as defined in section 3.3
- Investigator discretion
- Positive pregnancy test

3.6.2 Off-Study Criteria

- Completed study follow-up period
- Patient lost to follow-up
- Investigator discretion
- Participant requests to be withdrawn from study
- Death

Every attempt will be made to complete the follow up evaluation prior to study removal.

3.6.3 Off Protocol Therapy and Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 PERMITTED CONCOMITANT THERAPY

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 (other than study drug) and significant non-drug therapies (including blood transfusions) administered during the study should be recorded.

4.2 PERMITTED CONCOMITANT THERAPY REQUIRING CAUTION AND/OR ACTION

Medications that are weak inducers or inhibitors of CYP3A4 are not prohibited but should be administered with caution.

Short acting gastric acid modulators containing aluminum hydroxide and magnesium hydroxide, (e.g., Maalox®) or calcium carbonate (e.g., TUMS®) can be taken. However, it is recommended to take these drugs at least 4 hours before or 4 hours after administration of INC280. H2 receptor antagonists should be avoided when possible. If patients are using H2 receptor antagonists during the course of this study, patients should take INC280 at least 2 hours before H2 antagonists. Next scheduled dose of INC280 should be taken at least 8 hours after the previous H2 antagonist administration.

Guidance on concomitant medications with CYP3A4/5 interactions and gastric acid pH modulators interactions:

In general, the use of any concomitant medication / therapies deemed necessary for the care of the patient is permitted. However, caution is advised on the use of concomitant medications that are metabolized by CYP3A4/5. Prior to starting study treatment, investigators should carefully review the study subject's current medications for drugs metabolized by these isoenzymes.

Drugs known to interact with CYP3A4 should be used with caution because of the inherent risk of either reduced activity or enhanced toxicity of the respective concomitant medication and/or INC280. Based on in vitro metabolism studies, INC280 is predominantly metabolized by CYP3A4 and to a less extent by aldehyde oxidase. Therefore, strong CYP3A4 inhibitors or inducers or sensitive CYP3A4 substrates with narrow therapeutic index should be prohibited during the course of this study. A list of those medications can be found in Table 4-1. Sensitive CYP3A4/5 substrates can be cautiously used and are listed in Table 4-2. Further, INC280 is a moderate inhibitor of CYP2C8, weak inhibitor of CYP1A2, CYP2C9 and CYP2C19 and a time dependent inhibitor of CYP1A2. The concomitant use of sensitive CYP1A2, CYP2C9, CYP2C9 and CYP2C19 substrates with a narrow therapeutic index is prohibited in this study and listed in Table 4-1. These lists are not exhaustive and additional drug interaction information can be found at the University of Washington Drug Metabolism and Transport Drug Interaction Database at http://druginteractioninfo.org/.

In vitro solubility data indicated that INC280 may have decreased solubility and oral absorption at pH >4. Long-acting proton pump inhibitors are prohibited. Examples of this class of drugs can be found in Table 4-3.

INC280 also shows inhibition to P-gp transporter in vitro. Moderate P-gP inhibitors (which result in substrate AUC≥ 2-fold increase and < 5-fold increase) and P-gP substrates are detailed in Table 4-4. All patients must be carefully monitored for potential toxicity due to an individual concomitant medication. During the study, sensitive P-gp substrates with narrow therapeutic index are prohibited. These are listed in Table 4-1.

Table 4-1: Prohibited medications that are strong CYP3A4/5 inhibitors or inducers or sensitive substrates of CYP3A4, 2C8, 2C9, 2C19 and P-gp transporter with narrow therapeutic index

Strong CYP3A4/5 inhibitors	**Strong CYP3A4/5 inducers**	**Sensitive CYP3A4 substrates with narrow TI**	**Sensitive CYP2C9 substrates with narrow TI**
Macrolide antibiotics: clarithromycin and telithromycin	Carbamazepine	Alfentanil	warfarin
Anti-fungal: Itraconazole, ketoconazole, voriconazole, posaconazole	Efavirenz	Cyclosporine	phenytoin
Anti-virals: lopinavir, indinavir, nelfinavir, ritonavir, saquinavir	Modafinil	Diergotamine, ergotamine	
Conivaptan	Nevirapine	Fentanyl	
Mibefradil	Phenobarbital	Pimozide	
Nefazodone	Phenytoin	Quinidine	
Troleandomycin	Rifampin	Sirolimus	
Grapefruit juice	St John's wort	Tacrolimus	
		Note: the following medications are not available in US: Astemizole, Cisapride, Terfenadine	
• **Sensitive CYP2C19 Substrates with narrow TI**	• **Sensitive CYP2C8 substrates with narrow TI**	• **Sensitive CYP1A2 substrates with narrow TI**	• **Sensitive P-gp substrates with narrow TI**
Methytoin	Paclitaxel	Theophylline Tizanidine Methadone	Digoxin

Source:
1. FDA guidance drug interaction studies: study design, data analysis, and implication for dosing and labeling, 2006.
2. Oncology Clinical Pharmacology internal memo: drug-drug Interactions (DDI) database, 2010

Table 4-2: List of co-medications with known CYP3A4/5 interaction

Drug name	Class	Note
Alfentanil	Analgesic	
Alprazolam	Benzodiazepines	
Astemizole	**Antihistamine/allergic rhinitis**	**Increased exposure of this medication may result in QTc prolongation**
Brecanavir		
Budesonide	Anti-inflammatory corticosteroid	
Buspirone	Antibiotics	
Chlorpheniramine	Anti-histamine	
Diazepam	Benzodiazepine	
Ebastine	Anti-histamine	
Eletriptan	5-HT agonist/anti-migraine	
Everolimus	Immune modulators	
Erythromycin	**Antibiotics**	**Increased exposure of this medication may result in QTc prolongation**
Felodipine	Calcium channel blockers	
Imatinib	Anti-leukemia	
Lovastatin	HMG CoA reductase inhibitors	
Midazolam	Benzodiazepine/sedatives	
Nisoldipine	Calcium channel blockers	
Sildenafil	PDE5 agonist/ erectile dysfunction	
Simvastatin	HMG CoA reductase inhibitors	
Triazolam	Benzodiazepine	

Prohibited medications are marked in **Bold**

Source:
1. FDA guidance drug interaction studies: study design, data analysis, and implication for dosing and labeling, 2006.
2. Oncology Clinical Pharmacology internal memo: drug-drug Interactions (DDI) database, 2010

Table 4-3: List of OTC co-medications that are proton pump inhibitors

Proton pump inhibitors (brand name)
Esomeprazole (Nexium)
Lansoprazole (Prevacid)
Omeprazole (Prilosec)
Pantoprazole (Protonix)
Rabeprazole (Aciphex)
Dexlansoprzole (Dexilant)
Source: MicroMedex 2.0

Table 4-4: List of co-medications that are P-gp inhibitors, substrates or inducers

P-gp inhibitors	**P-gp substrates**	**P-gp inducers**
elacridar (GF120918)	Digoxin	Prednisone
indinavir	Fexofenadine	Corticosteroids
quinidine	Indinavir	Liponavir
valspodar (PSC833)	Vincristine	Tipranavir
	Colchicine	Tenofovir
	Talinolol	Avasimib
	Topotecan	Etravirine
	Paclitaxel	Milk thistle
		Mefloquine
Source: FDA guidance drug interaction studies: http://fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm		

5 BIOSPECIMEN COLLECTION

5.1 CORRELATIVE STUDIES FOR RESEARCH AND PHARMACODYNAMIC ASSESSMENTS

In light of the central role of oncogenic HGF/Met signaling in HPRC and evidence of pathway involvement in sporadic type I papillary RCC as described in section 1.2.1, a multilevel pharmacodynamic interrogation of the HGF/Met signaling pathway is proposed for this clinical trial. The following measurements are proposed at baseline and at later times coinciding with scheduled clinical evaluation: [1] tumor Met protein; [2] tumor phospho-Met; [3] plasma HGF; [4] plasma soluble Met ectodomain (sMet); [5] urinary sMet. The rationale and general protocol for each of these measurements is as follows.

5.1.1 Evaluation of HGF/MET pathway modulation in tumor tissue (optional)

Tumor Met: The abundance of Met protein has been linked to malignancy in several prevalent human cancers; increased MET gene expression is a direct consequence of pathway activation[16,33]. In recent clinical trials of rilotumumab for advanced gastroesophageal cancer and onartuzumab for advanced non-small cell lung cancer, both agents showed superior efficacy in patients with higher tumor Met protein content[34,35]. Met protein abundance as measured in a semi-quantitative manner by immunohistochemistry (IHC) staining has become accepted as a proxy of HGF/Met pathway activation, primarily because of the functional link described above, the correlative link established from prior studies, and the availability of suitable antibodies and fixed tumor tissue used for initial pathological diagnosis. However, this method does not provide precise or absolute values, only those relative to neighboring tissue processed at the same time. We plan to measure tumor Met content using a highly quantitative two-site immunoassay with external reference standards that allows direct comparisons of tumor Met level across individuals or groups as well as historically; tissue for these measurements must be flash-frozen and stored in an ultra-low temperature freezer prior to analysis. Because the tissue sample is mechanically disrupted and extracted with detergent for analysis, the method does not provide histological information.

Tumor phospho-Met: The abundance of phospho-Met, (more precisely, phosphotyrosyl 1235-Met) is directly related to the level of Met kinase activity and downstream signaling[36]. Although this is considered the gold standard marker of Met signaling, the limited availability of monoclonal antibodies with high affinity and target selectivity and lability of Met tyrosyl phosphorylation placed this measurement out of reach of most clinical laboratories. Recently we have overcome this limitation through the use of newly generated monoclonal antibodies, the development of tissue procurement procedures that minimize loss of the labile phosphate group, and analysis using the same two-site immunoassay platform as used to measure Met protein content. Phospho-Met measurement can be corrected for total Met content to provide the stoichiometry of Met phosphorylation; external reference standards are available.

5.1.1.1 Collection of specimen(s)

Tumor biopsies (renal primary or metastases) may be obtained from patients who have easily accessible lesions. Core or excisional biopsy of an easily accessible sentinel lesion (such as cutaneous/subcutaneous lesions, percutaneously accessible hepatic or renal lesions, lymph nodes etc.) may be performed at study entry and again at approximately at 8 weeks following initiation of therapy. It is preferred that at least four (if feasible) core biopsies of 16 - 18 gauge diameter and at least 1cm in length are obtained. Some biopsies may be performed with CT- or Ultrasound

guidance. Biopsies that are to be used solely for research purposes will be obtained only if they can be performed with minimal risk of complications from the procedure and only after the procedure has been explained to the patient and informed consent obtained. The biopsies will be performed by members of the interventional radiology, dermatology or surgical staff.

5.1.1.2 Handling of Specimen(s)

A portion of the biopsies will be frozen in liquid nitrogen immediately and transferred to the UOB laboratory (Contact for receiving and processing specimen: Cathy Vocke, Ph.D. - Tel: 301-496-6353). Prior to freezing and depending on tissue availability, a small portion of the biopsy specimen may be transferred under sterile conditions to the UOB laboratory to be used to establish a tumor cell line.

In addition, attempts will be made to obtain any available archived tumor tissue on all patients to help evaluate MET mutation status (by direct targeted sequencing of MET), evidence of MET/HGF amplification (using comparative genomic hybridization or quantitative PCR).

5.1.1.3 Sites Performing the Study

UOB Laboratory, Center for Cancer Research, NCI and the Molecular Genetics Section, Center for Cancer Research, NCI

5.1.2 Evaluation of plasma HGF and sMET modulation

Plasma HGF: Plasma levels of HGF have been shown to have diagnostic and prognostic value for a variety of human cancers[37], providing a strong rationale to measure baseline plasma HGF and to correlate this with tumor burden (sum of the longest diameters) upon entering the trial. High plasma HGF levels may result from production by the tumor and/or the tumor microenvironment through local feedback mechanisms, suggesting that decreases in plasma HGF while on drug may indicate target inhibition and potentially reduction in tumor burden. Periodic measurement of plasma HGF over the course of the study will be correlated with tumor burden as measured by RECIST criteria. Plasma HGF measurement is performed using the same electrochemiluminescent two-site immunoassay platform as Met and phospho-Met content. The measurement is high quantitative and the use of external reference standards allow lateral and longitudinal comparisons among individuals or groups.

Plasma sMet: Prior studies using human tumor-derived cell lines and human xenograft tumor models suggested that sMet values in plasma and urine correlated with level of malignancy and with overall tumor burden[38]. Subsequent studies using plasma and urine samples obtained from patients seen in the UOB and through several collaborations confirmed these findings[39]. Accumulating indirect evidence links malignancy, increased proteolytic activity, and proteolytic activation of HGF at the target cell surface with increased sMet production. There is also evidence that the Met TK domain is activated as a consequence of ectodomain cleavage, and the degradation of this active TK fragment that rapidly ensues in normal cells may be disrupted in certain cancers, contributing to oncogenesis (manuscript in preparation). In a phase II study of the Met/VEGFR inhibitor foretinib, median plasma sMet increased from baseline and correlated with drug plasma PK and median tumor burden[40]. Further studies are needed to determine whether changes in plasma sMet over the course of treatment can indicate changes in tumor burden in individual patients. Plasma sMet measurement is performed using the same electrochemiluminescent two-site immunoassay platform as Met and phospho-Met content. The measurement is high

quantitative and the use of external reference standards allow lateral and longitudinal comparisons among individuals or groups.

5.1.2.1 Collection of Specimen(s)

Approximately 10mL of plasma will be collected in the presence citrate or EDTA as anticoagulant at baseline and every restaging.

5.1.2.2 Handling of Specimen(s)

Plasma samples will be transferred to the UOB laboratory (Contact for receiving and processing specimen: Cathy Vocke, Ph.D. - Tel: 301-496-6353; Donald P Bottaro, Ph.D.- Tel: 301-496-6353). Samples will be frozen in aliquots and stored in the UOB laboratory until required for study.

5.1.2.3 Site Performing the Study

UOB Laboratory, Center for Cancer Research, NCI

5.1.3 Evaluation of Urinary sMET modulation

Preclinical studies revealed the presence of sMet in urine samples from healthy volunteers and showed that urinary sMet correlated directly with tumor burden in mouse xenografts[38]. We hypothesized that GU malignancies where the HGF/Met signaling pathway contribute to disease progression, and with exposure to the urinary tract, would show increased urinary sMet levels. Indeed, we found significant differences in median urinary sMet between the normal men and men with metastic prostate cancer[41]. In a more recent analysis of 180 individuals with urothelial carcinoma of the bladder (BCa), we found that urinary sMet levels accurately differentiated patients with BCa from those without, patients with muscle-invasive BCa from those with non-muscle-invasive BCa, and that median urinary sMet increased significantly with BCa grade (manuscript in preparation). We hypothesize that patients with papillary RCC will show elevated urinary sMet levels and that changes in this level may indicate changes in tumor burden, and propose the analysis of baseline urinary sMet and periodic measurements that coincide with scheduled clinical evaluations. Urinary sMet is measured using the electrochemiluminescent two-site immunoassay platform using external reference standards and requires normalization to urinary creatinine measured in the same sample.

5.1.3.1 Collection of Specimen(s)

Approximately 10-20 cc of urine will be collected at baseline and every restaging.

5.1.3.2 Handling of Specimen(s)

Urine samples will be transferred to the UOB laboratory (Contact for receiving and processing specimen: Cathy Vocke, Ph.D. - Tel: 301-496-6353; Donald P Bottaro, Ph.D.- Tel: 301-496-6353). Samples will be frozen in aliquots and stored in the UOB laboratory until required for study.

5.1.3.3 Site Performing the Study

UOB Laboratory, Center for Cancer Research, NCI

5.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Research samples will be collected with a view to performing the studies listed above. Samples will be ordered and tracked through a Clinical Trial Data Management System. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. Samples will not be sent outside NIH without appropriate approvals and/or agreements.

Each patient research sample will be assigned a unique patient identifier and relevant sample characteristics (such as timing of sample collection, treatment cycle and day identifiers) will be recorded. The location of all samples will be carefully tracked in the secure UOB database. All stored samples will be coded and no identifying patient information will be on placed on sample containers. Stored samples will be kept in freezers / refrigerators or secure containers located in the Urologic Oncology Branch research laboratories or in the laboratories of collaborators.

Samples will be stored until requested by an authorized researcher(s). All researchers are required to use the samples for research purposes associated with this trial (as per the IRB approved protocol). Subjects will be given the option of consenting to future use of their research samples per the informed consent process with their option declared in the consent document. Samples from those patients who consent to this will be stored permanently. However, these samples will be used only for research studies on active IRB approved protocols covered by a valid informed consent document. Samples will be destroyed at the completion of the study from those subjects who decline future use of their samples. Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples provided they have an IRB approved protocol and patient consent. Any unused samples must be returned to the UOB laboratories as appropriate. If a patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved. The PI will record any loss or unanticipated destruction of samples as a deviation. Reporting will be per the requirements of section **7.2**.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into a 21 CFR Part 11-compliant data capture system provided by the NCI CCR and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

Quality assurance complete records must be maintained on each patient treated on the protocol. These records should include primary documentation (e.g.: laboratory report slips, scan reports, pathology reports, physician notes, etc.) which confirm that:

- The patient met all eligibility criteria
- Signed informed consent was obtained prior to treatment
- Treatment was given according to protocol (dated notes about doses given, complications, and clinical outcomes)
- Toxicity was assessed according to protocol (laboratory report slips, etc.)

- Response was assessed according to protocol (CT and/or MRI scan, lab reports, date noted on clinical assessment, as appropriate)

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. Study drug (or therapy) includes the drug (or therapy) under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy and are recorded.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for 30 days after removal from study treatment or until off-study, whichever comes first.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **7.2.1**.

6.2 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 8 weeks for the first 32 weeks and approximately every 12 weeks thereafter while on study. Response evaluation will consist of CT CAP or MRI scan and a bone scan if bone disease is suspected or present. In addition to a baseline scan, confirmatory scans should also be obtained (≥4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[42] and Prostate Cancer Clinical Trials Working Group criteria (PCWG2)[43]. 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.

6.2.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with INC280.

Evaluable for objective response: Only those patients 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 response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response: Patients 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.

6.2.2 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, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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, and abdominal masses (not followed by CT or MRI), are considered as 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 patient, 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.

6.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. 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 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 slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (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.

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.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from 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 at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, 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 patient 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[43-45]. 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[46].

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.

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.

6.2.4 Response Criteria

6.2.4.1 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.

6.2.4.2 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).

6.2.4.3 Metastatic bone lesions

Disease progression is considered if a minimum of two new lesions is observed on bone scan. New lesions seen by the end of cycle 2 or before cycle 3 (after the first staging bone scan) may represent disease that was not detected on the pre-study scan, and a confirmatory scan will be required in next scheduled staging bone scan unless clinically not indicated. If confirmed, progression should be dated by the initial time when the lesions are first detected. If new lesions are seen after cycle 2, but no additional lesions are seen on confirmatory scans, the scans from after cycle 2 would serve as the baseline scan to evaluate for disease progression). 42Furthermore, new bony lesions on bone scan or CT/MRI will not be considered an indication of disease progression if these lesions were present on the baseline FDG-PET scan.

6.2.4.4 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 Patients 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: Patients 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 Patients 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		

6.2.5 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).

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.

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.

6.2.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

6.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. 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#ctc_40).

7 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING/ IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found **here**. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found **here**.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing

condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.

- A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient convenience) is not considered a serious adverse event.
- Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not

related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor.

8.3 Reporting of Serious Adverse Events

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 Safety Reporting Criteria to the Pharmaceutical Collaborators

Reporting will be per the collaborative agreement.

8.5 Reporting Pregnancy

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.5.1 Maternal exposure

If a participant becomes pregnant during the course of the study, the study treatment should be discontinued immediately, and the pregnancy reported to the Sponsor no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy becomes known.

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (section **8.1.2**) should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.5.2 Paternal exposure

Male participants should refrain from fathering a child or donating sperm during the study and for 28 days after the last dose of Pomalidomide.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 28 days after the last dose should, if possible, be followed up and documented.

8.6 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

8.7 SPONSOR PROTOCOL NON-ADHERENCE REPORTING

Protocol non-adherence is defined as any noncompliance with the clinical trial protocol, GCP, or protocol-specific procedural requirements on the part of the participant, the Investigator, or the study site staff inclusive of site personnel performing procedures or providing services in support of the clinical trial.

It is the responsibility of the study Staff to document any protocol non-adherence identified by the Staff or the site Monitor on the OSRO Site Protocol Non-Adherence Log. The protocol-specific, cumulative non-adherence log should be maintained in the site essential documents file and submitted to OSRO via OSROMonitoring@mail.NIH.gov on the **first business day of each month over the duration of the study**. In addition, any non-adherence to the protocol should be documented in the participant's source records and reported to the local IRB per their guidelines. OSRO required protocol non-adherence reporting is consistent with E6(R2) GCP: Integrated Addendum to ICH E6(R1): 4.5 Compliance with Protocol; 5.18.3 (a), and 5.20 Noncompliance; and ICH E3 16.2.2 Protocol deviations.

9 CLINICAL MONITORING

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary and secondary study endpoints; adherence to the protocol, regulations, ICH E6, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

10 STATISTICAL CONSIDERATIONS

10.1 EVALUATION OF ENDPOINTS

The primary endpoint will be efficacy (RECIST response rate). The study will use a Simon two-stage minimax design. Thirteen patients will be accrued in the first stage. If there are no responses (either CR or PR) in 13 evaluable patients, accrual to the trial will be terminated, and the treatment will be considered ineffective. If at least one patient responds among the 13 patients then 7 additional evaluable patients will be accrued. If 3 or more patients of 20 respond then the treatment will be considered worthy of future investigation. If fewer than 3 patients respond, the treatment will not be considered worthy of additional investigation.

The two-stage minimax design is based on assuming an ineffective response rate of 5% and a targeted effective response rate of 25%. We also assume that the probability of accepting an ineffective treatment and the probability of rejecting an effective treatment are each 10%. With this design, we have a 51% chance of stopping accrual at the end of the first stage if the response rate is 5%.

10.2 EVALUATION OF SECONDARY ENDPOINTS

Secondary objectives are listed in Section 1.1.2. The follow-up times for biomarker endpoints are given in Section 3.4. Analyses will focus on comparing changes in these biomarkers on treatment from the pre-study measurement. Longitudinal changes in continuous biomarkers (eg. plasma HGF) or imaging outcomes will be analyzed using Wilcoxon signed-rank tests (which compares measurements at a single post-treatment time point with measurements at the pre-treatment time point) as well as with linear mixed models (which incorporates all follow-up times when evaluating change). Evaluation of time to progression and progression free survival will be based on restaging studies performed as outlined and along with overall survival will be summarized using Kaplan-Meier curves. Disease control rate will be presented as the proportion of patients with stable disease $\geq$ 6 months, partial response or complete response.

10.3 SAMPLE SIZE CALCULATION

The accrual ceiling of this study will be set at 22 to allow for the replacement of patients that are inevaluable. At an accrual rate of 1-2 patients per month, it expected that the trial will complete accrual within 12-24 months.

11 COLLABORATIVE AGREEMENTS

11.1 AGREEMENT TYPE

This investigational agent for this study, INC280 is being provided to the NIH under a Collaborative Agreement Clinical Materials-Cooperative Research and Development Agreement (CRADA) with Novartis; #02869.

12 HUMAN SUBJECTS PROTECTIONS

12.1 RATIONALE FOR SUBJECT SELECTION

Patients of all races, genders and ethnic origins will be eligible. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

12.2 PARTICIPATION OF CHILDREN

This protocol will exclude children below 18 years of age since there are no safety data available in this group of patients.

12.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section 12.5), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

12.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

12.4.1 Benefits

The potential benefit to a patient who enters study is a reduction in the bulk of his/her tumor, which may or may not have a favorable impact on symptoms and/or outcome.

12.4.2 Risks

12.4.2.1 Study Agent

The primary risks of participation in this study include the possible occurrence of any of a range of side effects from the study agent INC280 which are listed in the section 14.1.3, the investigator brochure and in the consent document. Frequent monitoring for adverse effects and exclusion of subjects at risk for these adverse effects will help to minimize the risks associated with administration.

12.4.2.2 Optional biopsies

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NCI's Clinical Center in Bethesda, Maryland.

Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

Some biopsies may be performed with CT guidance. If that is the case, then this research study involves exposure to radiation from up to 2 CT scans with combined effective dose of 1.60 rem. This is below the guideline of 5.0 rem per year allowed for research subjects by the NIH Radiation Safety Committee.

12.5 RISKS/BENEFITS ANALYSIS

There are currently no standard therapeutic options for patients with metastatic renal cell carcinoma associated with HPRC or for patients with advanced sporadic papillary RCC, who have a poor prognosis with most dying from metastatic disease and its sequelae. Patients participating in this trial (including patients unable to give consent) may derive a benefit from the treatment administered. Although the possible toxicities from the proposed therapy may be potentially serious, given the nature of the underlying disease, they are acceptable. Additionally, we do not anticipate toxicities significantly more severe than those observed with other, approved agents. For these reasons, the risk/benefit ratio of this protocol is favorable; therefore, this protocol involves greater than minimal risk to patients, but presents the potential for direct benefit to individual subjects.

12.6 CONSENT PROCESS AND DOCUMENTATION

The investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol and must be submitted by the investigator with it for IRB approval.

Fertile men and women of child-bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

If there is an optional biopsy for research in the protocol, then the patient will consent at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

12.6.1 Telephone Consent Procedure

Consent on this study may be obtained via telephone according to the following procedure: The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone. A fully executed copy will be returned via mail for the subject's records. The informed consent process will be documented in the medical records.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s). This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NCI CCR.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research

objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 INC280 (IND # 119133)

(For complete information, please see the Investigator Brochure for INC280)

14.1.1 Source, packaging and labeling

INC280 tablets will be supplied by Novartis as film-coated tablet for oral use, packaged in either bottles or blisters, and will be administered on a flat scale and not individually adjusted by weight or body surface area.

Medication will be labeled for Clinical Trial use and will include storage conditions for the drug and the medication number but no information about the patient.

Table 14-1: Packaging and labeling

Study drugs	**Packaging**	**Labeling (and dosing frequency)**
INC280	Tablets in bottles or blisters (100 mg and 200 mg)	Labeled as "INC280"

14.1.2 Supply, receipt and storage

Study drug must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated assistants have access. Refer to the clinical label for storage condition requirements. Upon receipt, INC280 should be stored according to the instructions specified on the drug labels. Study medication will be dispensed by an authorized person at the investigator's site.

Patients will be provided with adequate supply of INC280 for self-administration at home until at least their next scheduled study visit.

14.1.3 Toxicity:

14.1.3.1 Animal Studies

Kidney toxicity was observed in the 28-day monkey study where mild-to-moderate deposits of amphophilic, crystalline-like material surrounded by multinucleated giant cells within the renal interstitium and/or tubular lumen were present in the 75 and 150 mg/kg/day, but not in the 30 mg/kg/day groups.

The findings in pancreas were observed in rats and monkeys in the 28-day studies, including pancreatic acinar cell vacuolation and/or apoptosis without inflammation. In monkeys, a dose of 30 mg/kg/day was identified as a NOAEL because of the low grade and reversible pancreatic findings present at that dose. In rats, the mid-dose groups (60 mg/kg/day in males and 30 mg/kg/day in females) also showed reversible low-grade pancreatic changes. Reversibility has been clearly demonstrated in both species.

Clinical signs indicative of CNS toxicity (seizures, tremors, lethargy, staggered gait, imbalance, splayed limbs), and histopathological findings of white matter vacuolation in thalamus were

observed only in rats of high-dose groups (60 mg/kg/day for females, and 120 mg/kg/day for males) in 28-day toxicity study. No signs of CNS toxicity were observed in Cynomolgus monkeys studies. Additionally, results from the 13-week rat toxicity study reproduced the CNS effects and histopathological findings in the brain and also demonstrated that the CNS effects and brain lesions were reversible.

Changes in serum chemistry liver enzymes (ALT, AST, and/or SDH) were observed in several different studies in rats and monkeys. These changes were restricted to highly variable, minimal-to-mild elevations lacking a clear dose response. The significance of elevations of liver enzymes remains undetermined because of the high degree of individual variability, and the absence of any histological correlate within the liver.

14.1.3.2 Human Studies

In a study of 45 patients in a first in human study of INC280, one DLT, CTCAE Grade 3 AST and alkaline phosphatase increase was reported for a patient at the dose level of 50mg.

Forty-four (97.8%) out of 45 patients experienced adverse events (AEs) any grades and regardless of causality. The most common adverse events (≥15%) were peripheral edema (44.4%), nausea (35.6%), fatigue (33.3%), tremor (28.9%), vomiting (24.4%), abdominal pain (22.2%), headache (20.0%), cough (17.8%), abdominal tenderness, constipation, diarrhea, dizziness and musculoskeletal pain (15.6%, respectively).

The most frequent AEs suspected to be related to INC280 any CTCAE grade, were nausea (26.7%), tremor (24.4%), fatigue (20.0%), peripheral edema (15.6%), and headache (15.6%). Two patients (4.4%) experienced CTCAE Grade 3 or Grade 4 AEs suspected to be treatment related, which were AST (50mg QD) and hypophosphataemia (150mg QD).

Expected Adverse Events are listed in the table below.

MedDRA system organ class	**Preferred Term**
Blood and Lymphatic System Disorders	Anemia, Neutropenia
Ear and Labyrinth Disorders	Deafness
Gastrointestinal disorders	Vomiting Nausea Diarrhea Abdominal pain Pancreatitis
General disorders and administration site conditions	Fatigue, Edema peripheral Asthenia Cellulitis Pruritus Urticaria

MedDRA system organ class	Preferred Term
Infections and infestations	Lung infection
Investigations	Alanine aminotransferase increased Aspartate aminotransferase increased Gamma-glutamyltransferase increased Amylase increased Blood bilirubin increased Lipase increased Amalyse increased Creatine Increased
Metabolism and nutrition disorders	Decreased appetite Hyponatremia Dehydration Hypophagia Hypophosphatemia
Nervous system disorders	Dizziness
Respiratory, thoracic and mediastinal disorders	Dyspnea, cough

Eleven serious adverse events (SAEs) have been reported in 9 (20%) out of 45 patients. They were deep venous thrombosis, electrocardiogram QT prolonged, failure to thrive (all at 10 mg QD), clavicle fracture (20mg QD), ascites, humerus fracture (both at 200mg QD), constipation, pneumonia, staphylococcal sepsis, hepatic encephalopathy (all at 400mg QD), diarrhea (50mg BID). All SAEs were reported as not related to INC280.

14.1.4 Administration procedures

See section 3.2

14.1.5 Incompatibilities

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 C23H21Cl2FN6O2 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.

Please see section 4 on concomitant medications for managing drug interactions.

14.1.6 Drug compliance and accountability

Clinical drug supply must be accounted for and patients will be asked to return all unused study drug and packaging on a regular basis, usually at the time of scheduled clinic visits and at the end of the study or at the time of study drug discontinuation.

Drug accountability and subject compliance will be assessed with drug dispensing and return records as described below.

All oral self-administered investigational agents will be properly accounted for, handled, and disposed in accordance with existing federal regulations and principles of Good Clinical Practice. CRR SOPs on self-administered investigational agents may be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Documenting+Drug+Accountability+for+Oral+Investigational+Agents

The investigator will maintain accurate records of receipt of all INC280, including dates of receipt. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded.

At the conclusion of the study, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed drug accountability ledger to Novartis.

14.1.7 Disposal and destruction

The drug supply will be destroyed at a Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only be permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

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16 APPENDICES

16.1 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.

16.2 APPENDIX B: PATIENT'S PILL/ SIDE EFFECTS DIARY

Today's date _____ Cycle_____ Week_____ Dose_____

Patient Name_____ Patient Study ID _____

(*initials acceptable)*

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 1 week period (1 cycle = 4 weeks)
2. You will take your medication in the morning and evening. **You should not eat anything 2 hours prior to or after the medication; drink a full glass of water with the medication and 2 hours after you take the medication. If you miss the intended time to take your INC 280 by 4 hours or more,** do not take that dose.
3. Record the date, the number of pills you took, and when you took them. Also record that you have fasted.
4. If you have any comments or **notice any side effects**, please record them in the Comments column.
3. Please bring your pill bottle and this form to your physician when you go for your next appointment.

Date	Day #	# of pills taken	Time Taken	Fasted Before	Fasted After	SIDE EFFECTS/COMMENTS	Init
	#1						
	#1						
	# 2						
	# 2						
	# 3						
	#3						
	# 4						
	# 4						
	# 5						
	# 5						
	# 6						
	# 6						
	#7						
	# 7						

Patient's Signature: _____ Date: _____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____ Date patient was removed from study _____

2. Patient's planned daily dose_____ Total number of pills taken this week_____

Physician/Nurse/Data Manager's Signature _____

16.3 APPENDIX C: INSTRUCTION SHEET FOR INC 280

You have been prescribed the medication INC 280. INC 280 is believed to work by blocking MET, a protein in your body which if altered can promote tumor formation and spread. You should take the INC 280 the same time twice a day, at least 8 hours apart. You should fast for 2 hours before and 2 hours after taking INC 280. You should take a full glass of water (8 OZ) with INC 280 and another full glass of water 2 hours after taking INC 280. If necessary, you can take ginger ale, apple juice, or cranberry juice in addition to water during the fasting period. Document the time you take the medication on your diary. If you forget to take your medication at the usual time, you can take it within 4 hours, then resume your usual schedule the next day. If you vomit a dose of INC280, do NOT take another. Bring your medication and your diary with you to every doctor's visit. ALWAYS check with your medical team before beginning any new medication.

There are few important points to remember:

- NO grapefruit juice or Seville orange juice while on INC 280. Avoid for 7 days prior to the first dose
- NO herbal supplements or teas while on INC 280 until you speak with your medical team.
- If you are of reproductive age, you MUST use birth control.
- Report any unplanned surgery or wounds IMMEDIATELY to your medical team so your INC 280 can be adjusted accordingly.
- You MUST wear sunscreen (SPF> 45) when outside.
- If you develop a skin rash, notify your medical team immediately so we can begin medication to prevent the rash from worsening.
- You cannot take long acting proton pump inhibitors while on INC 280 because they will affect the absorption of the medication. Examples of these would be Prilosec (omeprasole); Protonix (pantoprazol); Prevacid (lansoprazol).

Medications to Treat Common Side Effects: When you begin INC 280, the medical team will give you medications for nausea, diarrhea, and constipation. Please notify the medical team if any of these are occurring, document in your diary, and begin the appropriate medication listed below. Please be sure to have a working thermometer at home so you can check your temperature when instructed to do so.

For Nausea:

- Prochlorperazine / Ondansetron: Take as directed.

For Diarrhea:

- Loperamide 2mg tablets to be taken for diarrhea, as directed.
- Diet: BRAT diet – bananas, rice, applesauce, toast – can be helpful

For Constipation:

- Docusate 100mg – take 1-2 initially for constipation, then 1 a day as needed

If questions or problems during the week please contact:

Erin Purcell RN research nurse; 240-858-3933 OR erin.purcell@nih.gov.

After 5pm or on weekends call the NIH page operator: 301-496-1211 and ask to speak with Urologic Oncology fellow. In case of an emergency, go to your nearest hospital emergency department.