An Open Label Randomized Phase I/II Trial of TAK-228 Compared to Sorafenib in Patients with Advanced or Metastatic Hepatocellular Carcinoma: Big Ten Cancer Research Consortium BTCRC-GI13-002

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Trial Supported by
Millennium Pharmaceuticals
(IISR-2014-100530)

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Investigational New Drug (IND) Application #
128501

Initial Protocol Version Date: 10NOV2015

Amendment Version Date:
28NOV2016
13NOV2017 (current)

PROTOCOL SIGNATURE PAGE

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VERSION DATE: 13NOV2017

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to BTCRC Administrative Headquarters and keep a record for your files.

_____ _____
Signature of Investigator Date

_____
Investigator Name (printed)

_____
Investigator Title

_____
Name of Facility

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Location of Facility (City and State)

_____ ❑ Not Submitting to IRB
Expected IRB Approval Date

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STUDY SYNOPSIS

TITLE	An Open Label Randomized Phase I/II Trial of TAK-228 Compared to Sorafenib in Patients with Advanced or Metastatic Hepatocellular Carcinoma: Big Ten Cancer Research Consortium BTCRC-GI13-002
PHASE	I/II
TOTAL NUMBER OF SUBJECTS	Phase I: up to 18 subjects Phase II: 100 subjects
OBJECTIVES	**Phase I:** **Primary Objective:** The Primary objective of this prospective, open label, dose escalation study is to determine the maximum tolerated dose (MTD) of TAK-228. **Secondary Objectives:** 1. Characterize adverse effects (AE) 2. Measure overall survival (OS) 3. Evaluate time to progression (TTP) 4. Measure progression-free survival (PFS) 5. Determine objective response rate (ORR) and disease control rate (DCR) at 16 and 24 weeks **Phase II:** **Primary Objective:** The primary objective of this prospective, open label, randomized study is to evaluate time to progression (TTP) associated with TAK-228 in the first line setting of advanced hepatocellular carcinoma (HCC), compared to a control arm treated with sorafenib. **Secondary Objectives:** 1. Measure overall survival (OS) 2. Measure progression-free survival (PFS) 3. Characterize adverse effects (AE) 4. Determine objective response rate (ORR) and disease control rate (DCR) at 16 and 24 weeks **Correlative Objectives:** 1. Assess pharmacokinetics (PK) of TAK-228 2. Evaluate mTOR and PI3K/Akt expression and phosphoproteins via immunohistochemistry (IHC) 3. Characterize oncogene expression affecting mTOR activation via targeted deep sequencing assay **4.** Assess tumor necrosis and modified RECIST (mRECIST) criteria
STUDY DESIGN	This will be an open-label, randomized phase I dose escalation trial followed by a phase II clinical trial. Eligible subjects in the phase I trial will receive TAK-228 in escalating doses.

	Eligible subjects in the phase II trial will be 1:1 randomized to either TAK-228 or sorafenib arm. Block randomization stratified by Child-Pugh (CP) score (5-6 vs. 7) will be adopted with varying block sizes.
KEY ELIGIBILITY CRITERIA	1. Measurable advanced or metastatic HCC. Phase II subjects only: tissue biopsy will be required prior to registration if HCC archived tissue is not available for correlative studies. Advanced HCC is defined as disease not amenable to surgery, ablation, transplant, or embolic therapy. 2. Prior locoregional liver directed therapy is permitted, as long as treatment was ≥ 6 weeks prior to study entry, and demonstration of progression per RECIST v1.1 3. ECOG PS 0-1-2 4. Child-Pugh Score ≤7 5. No systemic therapy allowed for the phase II cohort. No restrictions for prior systemic therapy for the phase I cohort; phase I patients may also be treatment naïve.
OUTCOME MEASURES	**Phase I:** Primary Endpoint: The primary endpoint is determination of the maximum tolerated dose (MTD) for TAK-228. MTD is defined as the dose level at which fewer than 33% of subjects experience a dose limiting toxicity (DLT). Secondary Endpoints: 1. Adverse effects (AE) as defined by CTCAE v4. 2. Overall Survival (OS) as defined by the time from randomization to date of death from any cause. 3. Time to progression is defined as the time from randomization until tumor progression as defined by RECIST v1.1. 4. Progression free survival (PFS) as defined as time from randomization to tumor progression or death from any cause. 5. Objective Response Rate (ORR) defined as complete response (CR)+partial response (PR) and Disease Control Rate (DCR), as a sum of stable disease (SD for 8 weeks or longer), partial response (PR), and complete response (CR), as defined by RECIST v1.1. **Phase II:** Primary Endpoint: The primary endpoint is evaluation of time to progression, which is defined as the time from randomization until tumor progression as defined by RECIST v1.1. Secondary Endpoints: 1. Overall Survival (OS) as defined by the time from randomization to date of death from any cause. 2. Progression free survival (PFS) as defined as time from randomization to tumor progression or death from any cause. 3. Adverse effects (AE) as defined by CTCAE v4. 4. Objective Response Rate (ORR) defined as complete response (CR)+partial response (PR) and Disease Control Rate (DCR), as a sum of stable disease (SD for 8 weeks or longer), partial response (PR), and complete response (CR), as defined by RECIST v1.1.

	Correlative Endpoints: 1. Assess Pharmacokinetics (PK) in first 10 subjects in TAK-228 arm (Arm A). 2. Evaluate mTOR and PI3K/Akt expression and phosphoproteins via immunohistochemistry (IHC) of phosphorylated Akt, 4EBP1, S6 kinase, and ERK1/2. 3. Characterize oncogene expression affecting mTOR activation via targeted deep sequencing assay designed to interrogate genes commonly mutated in human cancers. 4. Assess tumor necrosis and modified RECIST (mRECIST) criteria
STATISTICAL CONSIDERATIONS	Phase I: The primary endpoint for this Phase I study is MTD. We will establish that dose is safe if we observe less than a 33% chance for DLT at a given dose level during the first cycle of therapy. A conventional 3x3 design will be utilized. Phase II: Therapy with sorafenib in subjects with Child-Pugh A (CPA) cirrhosis was associated with a median TTP of 5.5 months. Given inclusion of CP 7 subjects (technically CPB), we would anticipate a median TTP of 12 weeks for sorafenib. In this study, we assume that TAK-228 will increase TTP from 50% to 70% at week 12. A 10% dropout rate is expected for the sorafenib arm and a similar dropout pattern is expected for the TAK-228 arm. Enrollment is expected to be completed in 24 months. Subjects will be followed for a total of 2 years after progression. Two-sided log-rank test will be used to compare TTP at type I error level 0.05. Consequently, N=44 subjects per group are required to obtain a power level of 0.80. We further adjust the sample size to N=50 per group to account for potentially unevaluable subjects. Analyses will include Kaplan-Meier curves and log-rank tests for TTP, OS, and PFS, and exact binomial confidence intervals and chi-square or Fisher Exact tests for ORR, DCR, and adverse events. For OS, Cox regression will be used to evaluate the effects of oncogenic abnormalities on survival times.
ENROLLMENT PERIOD	Enrollment period 24 months
TOTAL STUDY DURATION	Estimated accrual: 5 subjects per month Estimated total duration of study: 42 months

INDEX

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
4E-BP1	eukaryotic initiation factor eIF4E-binding protein 1
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BID	*bis in die*; twice a day
BUN	blood urea nitrogen
CBC	complete blood count
CRP	C-reactive protein
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
DTC	differentiated thyroid carcinoma
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	End of Treatment (visit)
GBM	glioblastoma multiforme
Hb	Hemoglobin
HCC	hepatocellular carcinoma
Hct	Hematocrit
HFSR	hand-foot skin reaction
IB	Investigator's Brochure
ICF	informed consent form
IRB	institutional review board
LDH	lactate dehydrogenase
LFT	liver function test(s)
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
mTORC1	mTOR complex 1
mTORC2	mTOR complex 2

Abbreviation	Term
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OCT	organic cation transporter
OS	overall survival
PDGF	platelet-derived growth factor
PFS	progression free survival
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PTEN	phosphatase and tensin homolog
QD	*quaque die*; every day
QTc	rate-corrected QT interval (milliseconds) of electrocardiogram
RCC	renal cell carcinoma
S6K1	ribosomal protein S6 kinase
SAE	serious adverse event
TSH	thyroid stimulating hormone
VEGF	vascular endothelial growth factor

PHASE I SCHEMA

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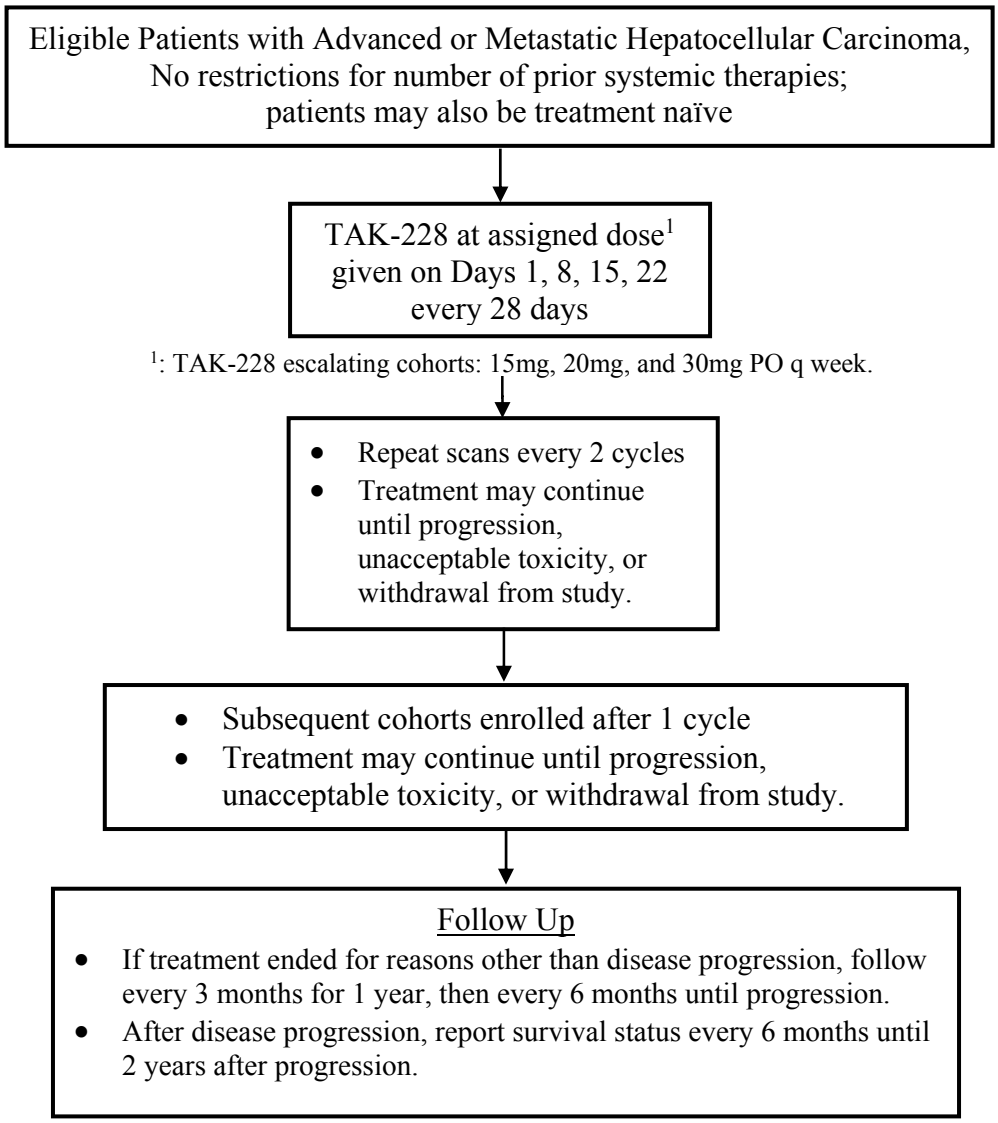
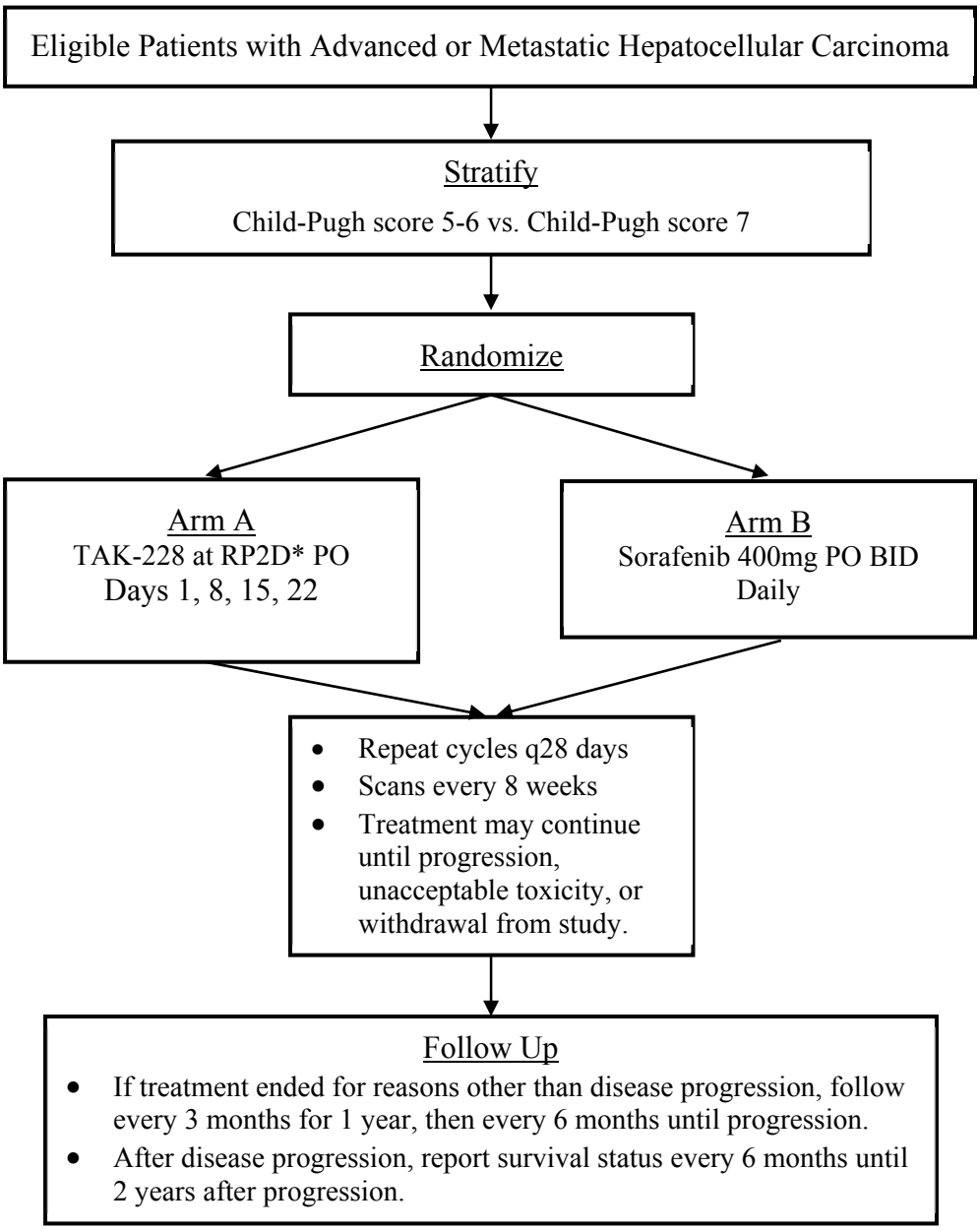


PHASE II SCHEMA

An Open Label Randomized Phase I/II Trial of TAK-228 Compared to Sorafenib in Patients with Advanced or Metastatic Hepatocellular Carcinoma: Big Ten Cancer Research Consortium BTCRC-GI13-002



*RP2D: recommended Phase II dose

1 BACKGROUND & RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

- Pathologically confirmed hepatocellular carcinoma (HCC) not amenable to liver transplantation
  - Locally advanced, unresectable, or metastatic disease
- At least 1 lesion accurately measured in ≥ 1 dimension according to RECIST v1.1 criteria

1.1.2 Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide, and the third most common cause of global cancer related mortality[1,2]. Prognostic and therapeutic options are dependent upon the severity of underlying liver disease, and median overall survival (OS) for metastatic or locally advanced disease is estimated at 5-8 months. HCC is relatively refractory to cytotoxic chemotherapy, likely due to over expression of multidrug resistant genes[3], protein products such as heat shock 70[4] and P-glycoprotein[5], and p53 mutations. Presently, systemic therapeutic options in the locally advanced or metastatic setting are limited to sorafenib, an oral multikinase inhibitor targeting Raf kinase, vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF) receptor tyrosine kinase signaling.

1.1.3. Systemic Therapy for Advanced HCC

Sorafenib was approved on the basis of two randomized, placebo-controlled, phase III studies[6,7] demonstrating significant improvement in overall survival (OS), progression free survival (PFS), and a manageable toxicity profile. In the SHARP trial[7], median survival improved by 2.8 months with sorafenib in comparison to placebo (10.7 months vs. 7.9 months; hazard ratio [HR], 0.69; 95% confidence interval [CI], 0.55–0.87; $p < 0.001$), while in the Asia-Pacific trial[6], median OS improved by 2.3 months with sorafenib in comparison to placebo (6.5 months vs. 4.2 months; HR, 0.68; 95% CI, 0.50–0.93; $p = 0.014$). Despite low response rates in both studies (respectively, 2%; 3%), the median time to progression almost doubled in both studies (SHARP: 2.8 months to 5.5 months ($p < 0.001$); Asia-Pacific: 1.4 months to 2.8 months, $p<0.001$). Since the approval of sorafenib in 2007, no additional agents have been FDA approved for HCC treatment. There is an urgent and unmet need for new therapeutic options for first and second line treatment of advanced HCC.

1.1.4 The mTOR Signaling Pathway and HCC

The mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase belonging to the phosphoinositide 3-kinase (PI3K)-related kinase family, and is implicated in cellular proliferation, angiogenesis, growth, and lipid metabolism[8]. mTOR is present in two multiprotein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2).

Signaling molecules upstream of mTORC1 include phosphatase and tensin homolog (PTEN), tuberous sclerosis complex (TSC proteins), adenosine monophosphate kinase (AMPK), the Rag guanosine triphosphatases (GTPases), and PI3K/Akt. mTORC1 is comprised of mTOR, mammalian LST8 (mLST8), DEPTOR, regulatory-associated protein of mTOR (RAPTOR), and proline-rich Akt substrate 40kDa (PRAS40). mTORC1 is activated by multiple inputs including the Wnt pathway, proinflammatory cytokines, and growth factors; growth factors including insulin

and insulin-like growth factor 1 activate mTORC1 via PIK3-Akt and Ras-Raf-MEK-ERK signaling pathways[9]. mTORC1 activation results in phosphorylation of two downstream mTOR pathway proteins, ribosomal protein S6 kinase (S6K1) and the eukaryotic initiation factor eIF4E-binding protein 1 (4E-BP1), both of which are involved in protein translation resulting in cell growth, angiogenesis, and proliferation[10]. In addition to protein synthesis and lipogenesis, mTORC1 activation also results in autophagy inhibition and lysosome biogenesis[9].

mTORC2 is comprised of mTOR, mLST8, DEPTOR, PROTOR, RICTOR, and mSIN1; mTORC2 phosphorylates Akt at Ser473, and is implicated in actin cytoskeleton organization, cell migration, survival, and proliferation[8].

mTORC1 and mTORC2 pathways are upregulated in 40-50% of HCC[11], and mTOR activation in HCC is associated with deregulation of multiple pathways including EGF, IGF, and PTEN[12], and early recurrence, poor differentiation, and worse prognosis[12,13]. Notably, mTOR pathway activation is largely dependent on ligand dependent receptor activation; recent studies utilizing PCR[12] and next generation sequencing[14-16] report low frequency of alterations of copy number or somatic mutations of PTEN, mTOR, PIK3CA. Evaluation of the mTOR signaling pathway in 351 human HCC samples revealed abnormalities affecting mTOR signaling (as evaluated by p-RPS6 immunohistochemistry) in about half of the patients and was associated with worse outcome[12]. mTOR activation may also be implicated in sorafenib resistance; high expression of ribosomal S6 phosphorylated at serine residue 235/236 was found to be significantly correlated with the resistance of HCC cells to sorafenib[17].

1.1.5 mTOR Inhibitors in HCC

1.1.5.1 First generation mTOR inhibitors

mTORC1 is the target for the macrolide antibiotic rapamycin (sirolimus), and is inhibited by a complex of rapamycin and FKBP12 protein. First generation mTOR inhibitors include rapamycin and rapalog derivatives including everolimus, temsirolimus, deforolimus (or ridaforolimus), and Nab-rapamycin[9].

Several *in vitro* and *in vivo* preclinical studies support rapalog efficacy in inhibiting HCC tumor growth; in human HCC cell lines, sirolimus, everolimus, and temsirolimus demonstrated successful inhibition of cell growth and proliferation[10,12,14,18-20], while in HCC mouse and rat models, sirolimus and everolimus reduced tumor volume and increased survival in comparison to controls[10,12,14,18-21].

Rapalog efficacy is under evaluation in active clinical trials in multiple HCC settings, including adjuvant therapy post liver transplant, adjuvant therapy post transcatheter arterial chemoembolization (TACE), and advanced HCC both first and second line (single agent, and in combination with other biologics)[9]. Rapamycin analogs utilized in the post-transplant immunosuppressive setting have been demonstrated to reduce risk of HCC recurrence[22-28] and improve survival[24] in case reports and retrospective reports. The combination of sirolimus and sorafenib for HCC recurrence post-transplant demonstrated efficacy with improved survival and time to progression in two small retrospective analysis[29,30], while two case studies reported partial or complete response for subjects with HCC recurrence post-transplant[31,32]. However, prospective data are lacking.

Rapalog efficacy in the advanced HCC setting is uncertain; phase II studies of first line sirolimus demonstrated median OS 6.1 months, and a disease control rate of 43%[33]. A phase III study of second line everolimus following sorafenib failure failed to show survival benefit for everolimus in comparison with best supportive care (median OS 7.6 vs. 7.3 mos.; HR 1.05, 95% CI [0.86-1.27]; p=0.675)[34].

1.1.5.2 Second Generation mTOR inhibitors in HCC

Rapalog efficacy may be limited due to three reasons: 1) mTORC1 inhibition results in upregulation/activation of PI3K-Akt with MAPK and RAS signaling, likely potentiating tumorigenesis; 2) mTORC1 blockage results in inhibition of cell growth and not cell death; 3) mTORC2 is not inhibited by rapalogs[9]. Additionally, recent studies showed that rapamycin inhibited only S6K1, but did not impact 4EBP1 phosphorylation and cap-dependent translation.

Second generation mTORC inhibitors are able to block phosphorylation of all targets of mTORC1 and mTORC2 via competitive binding to the adenosine 5' triphosphate (ATP) pocket on mTOR. MLN 0128 is such an inhibitor, which has recently undergone phase I evaluation in subjects with advanced solid and hematologic malignancies. Following establishment of the MTD (reported at ASCO 2012), subjects with select advanced, refractory solid tumors, including NSCLC, HCC, NET, GBM and breast were enrolled in expansion cohorts of up to 20 evaluable subjects. TAK-228 was dosed at 45 mg once daily in 28-day cycles until disease progression. Encouraging signals of biomarker and clinical activity were observed in HCC and NSCLC. Due to the frequency of dose reductions and interruptions, 30 mg once daily is recommended for future studies [35].

1.1.5 TAK-228

Millennium has developed TAK-228, which is a novel, highly selective, orally bioavailable adenosine 5' triphosphate (ATP)-competitive inhibitor of the serine/threonine kinase referred to as the mechanistic target of rapamycin (mTOR). TAK-228 (formerly MLN0128; INK128) targets 2 distinct mTOR complexes, mTORC1 and mTORC2.

TAK-228 selectively and potently inhibits mTOR kinase (IC_{50} = 1.1 nM), inhibits mTORC1/2 signaling, and prevents cellular proliferation. The mTOR is a kinase that regulates cell growth, translational control, angiogenesis, and cell survival by integrating nutrient and hormonal signals. mTOR kinase plays a key role in several pathways that are frequently dysregulated in human cancer.[36] mTORC1 is best known as a key regulator of protein translation through phosphorylation of 4EBP1 (the eukaryotic translation Initiation Factor 4E-binding Protein 1) and ribosomal protein S6 (known as S6) kinase. mTORC2 is best known for its ability to fully activate protein kinase B (Akt) by phosphorylation on the S473 site, which regulates proliferation and survival pathways[37].

The mTORC is an important therapeutic target that is a key intracellular point of convergence for a number of cellular signaling pathways. Inhibiting mTOR may inhibit abnormal cell proliferation,tumor angiogenesis, and abnormal cellular metabolism, thus providing the rationale for mTOR inhibitors as potential agents in the treatment of a number of indications including solid tumor and hematological malignancies, as either monotherapy or in combination with other chemotherapeutic agents. Like rapamycin, several newly approved rapalogs (temsirolimus and everolimus) are specific and allosteric inhibitors of mTORC1, and only partially inhibit mTORC1 signaling pathways. They do not directly inhibit mTORC2, which has shown to be an emerging

target in cancer research. TAK-228 was developed to address the incomplete inhibition of the mTOR pathway by rapalogs by targeting both mTORC1 and mTORC2.

In oncology, TAK-228 is being investigated as a treatment for advanced solid tumors and hematologic malignancies, either as monotherapy or in combination with chemotherapy, other molecularly targeted therapies, or anti-hormonal agents.

1.2 Nonclinical Summary

1.2.1 Pharmacology

TAK-228 selectively and potently inhibits mTOR kinase (the concentration inhibiting 50% of enzyme activity [IC_{50}] is 1.1 nM), inhibits mTORC1/2 signaling, and prevents cellular proliferation.

TAK-228 inhibited phosphorylation of downstream modulators of mTORC1 and mTORC2 in human U87 glioblastoma tumor xenograft models in mice and showed strong tumor growth inhibition (TGI) at tolerable oral (PO) doses in all 8 xenograft models tested (see IB Ed8 for details).

1.2.2 Safety Pharmacology

TAK-228 has a low potential to affect the human ether-à-go-go related gene (hERG) potassium ion channel and did not affect cardiovascular (CV) parameters in vivo in telemeterized monkeys.

1.2.3 Drug Metabolism and Pharmacokinetics

TAK-228 was rapidly absorbed after PO administration to mice, rats, dogs, and monkeys, with high oral bioavailability. [^{14}C]TAK-228 was rapidly and widely distributed throughout the body in Long-Evans rats; radioactivity was eliminated from most tissues at 48 hours post-dose. TAK-228 displayed dose-proportional plasma exposures, a moderate propensity to cross the blood-brain barrier, and was modestly bound (70.5%) to human plasma proteins. TAK-228 distributed mainly to the plasma of human blood. There was no obvious concentration-dependent red blood cell (RBC) distribution of TAK-228 in human blood.

TAK-228 did not inhibit P-glycoprotein, but did inhibit breast cancer-resistance protein (BCRP), organic cation transporter (OCT)1 and OCT2.

Recently completed in vitro metabolism experiments in human hepatocytes using ^{14}C-labeled TAK-228 suggest that TAK-228 is metabolized primarily via CYP1A2 (approximately 31%-40%), with a minor contribution from CYP3A4 (approximately 11%-22%). These data suggest that TAK-228 is also metabolized by direct glucuronidation (approximately 22%) and an unidentified non-uridine diphosphate glucuronosyl transferase pathway (approximately 18%). The new data differ from the previous in vitro CYP phenotyping data obtained using recombinant CYP enzymes, which suggested the involvement of CYP2C9 (approximately 35%), CYP2C19 (approximately 28%), and CYP3A4 (approximately 28%) in TAK-228 metabolism. In addition, physiologically based PK modeling and simulation using the new metabolism data for TAK-228 suggest that the risk for a metabolism-based drug-drug interaction with TAK-228 appears to be low. Therefore, strong CYP1A2 inhibitors and CYP inducers should be administered with caution and at the discretion of the investigator during the study.

1.2.4 Toxicology

The toxicologic profiles obtained in the Good Laboratory Practice (GLP)-compliant and non-GLP-compliant studies in rats and monkeys were generally consistent with pharmacologic inhibition of mTORC1/2 activity. Observed toxicities were mostly consistent between sexes. TAK-228 repeat-dose GLP studies include completed 28-day and preliminary 3-month toxicology studies in rat and monkeys, and embryo-fetal studies in rats and rabbits.

The primary dose-limiting toxicities (DLTs) of TAK-228 in rats and monkeys were secondary to an exaggerated pharmacologic response and consisted of body weight loss and associated clinical observations that included hunched posture, dehydration, gastrointestinal (GI) distress and decreased activity, appetite, and body temperature. In addition to the previously mentioned effects, a single monkey in the 3-month toxicology study demonstrated a DLT of skin toxicity characterized as progressive acanthosis. The highest exposures tolerated in the preliminary 3-month rat and monkey toxicology studies were 1233 and 194 ng·hr/mL, respectively.

Adverse effects in rats included body weight loss, decreased activity, increased glucose and insulin levels, alterations in white blood cells, bone marrow and lymphoid depletion, thymic necrosis, oligospermia, testes degeneration/atrophy, nonglandular stomach epithelial degeneration/ulceration/hyperplasia, pancreatic islet degeneration and fibrosis, lens fiber degeneration with cataract correlate, adrenal cortex hypertrophy, pituitary atrophy secondary to body weight loss, liver hepatocellular vacuolation, retinal dysplasia with or without optic nerve atrophy, and alveolar histiocytosis. The alveolar histiocytosis was only present in the 28-day rat study and was absent in the 3-month rat study. Both retinal dysplasia and alveolar histiocytosis are thought to be potential background findings. The pancreatic islet degeneration and fibrosis, as well as the other findings of lens fiber degeneration, pituitary atrophy, and liver vacuolation, were consistent with the mechanism of action (MOA) and effects observed with other rapalogs. The microscopic findings observed in the testes, epididymides, and eyes in the 28-day and/or 3-month rat studies were not resolved after a 14-day recovery period, while partial to complete resolution was seen in the pancreas, adrenal gland, pituitary, liver, lungs, thymus, nonglandular stomach, and bone marrow.

The adverse effects in monkeys included hunched posture, dehydration, GI distress, and decreased activity, appetite, and body weight; increased glucose and insulin; lymphoid and bone marrow depletion; adrenal hypertrophy/hyperplasia; pancreatic and salivary gland acinar cell secretory depletion; neutrophilic inflammation of GI tract with occasional erosion and ulceration, skin effects including ulceration, epidermal hyperplasia, acanthosis and hyperkeratosis; and adipose tissue depletion. Additionally, there were sporadic inflammatory findings among some animals that were of uncertain association to the test article. The findings in the pancreas, adrenal glands, and salivary glands may have been related to a stress response or reduced food consumption. The findings observed in repeat-dose monkey studies were generally reversible after a 14-day recovery period.

The findings in rat and monkey repeat-dose toxicology studies with TAK-228, including bone marrow and lymphoid depletion; GI, liver, pancreas, and skin effects; and effects on glucose and insulin levels, can be monitored in clinical trials. The toxicities seen in the repeat-dose toxicology studies, such as GI effects and glucose and insulin increases, are consistent with the treatment-

emergent adverse events (TEAEs), including mucositis and hyperglycemia, observed to date in subjects receiving TAK-228.

Rat and rabbit range-finding embryo-fetal studies demonstrated teratogenic, fetotoxic, and abortive effects with TAK-228. Embryo-fetal lethality and/or teratogenic effects have been reported with the mTORC1 inhibitors rapamycin and the rapalogs.

TAK-228 was negative for genotoxicity in an in vitro bacterial mutagenesis (Ames) assay, an in vivo rat micronucleus assay, and an in vivo rat comet assay. An in vitro chromosomal aberration assay with TAK-228 in human peripheral blood lymphocytes (PBLs) was positive for chromosomal aberrations in the presence and absence of metabolic activation. However, the weight of evidence from the combined results of a negative mutagenicity assay and negative genotoxicity assessments in 2 in vivo assays in 3 tissues (bone marrow, liver, and duodenum) demonstrate that TAK-228 does not present a genotoxic risk.

TAK-228 was negative for phototoxicity in the 3T3 fibroblast assay.

1.3 Clinical Experience with TAK-228

TAK-228 is in clinical development as a single agent in 3 phase 1 studies including study INK128-001[38] in subjects with advanced solid malignancies, study INK128-002[39] in subjects with multiple myeloma [MM], non-Hodgkin lymphoma [NHL] and Waldenström macroglobulinemia [WM]) and study C31002 to measure the effect of TAK-228 on QTc interval in subjects with advanced solid malignancies. It is also being investigated in combination with paclitaxel (with or without trastuzumab) in subjects with advanced solid tumors (Ph1 study INK128-003), and in combination with exemestane or fulvestrant in women with ER+/HER2– (estrogen receptor-positive /human epidermal growth factor receptor 2 protein-negative) advanced or metastatic breast cancer (Ph1b/2 study C31001).

TAK-228 dosing regimens tested thus far include QD, QW, QD×3days per week (once daily for 3 consecutive days followed by a 4-day dosing holiday every week), and QD×5days per week (once daily for 5 consecutive days followed by a 2-day dosing holiday every week).

Please note that the data described in this section was obtained with the original unmilled TAK-228 active pharmaceutical ingredient (API); the current manufacturing process produces milled TAK-228 API (see section 1.4).

The table below summarizes TAK-228 doses, schedules, and active pharmaceutical ingredient (API) studied as well as evaluable PK population studies in all these studies. Details on PK and safety information for each study are available in the current IB edition.

Summary of TAK-228 Clinical Studies

Study No.; Phase	Study Design	Dose (Schedule)	Evaluable PK Population
INK128-001 Phase 1	Multiple ascending doses in patients with advanced solid malignancies. (unmilled)	*TAK-228* 2, 4, 5, 6, and 7 mg (QD) 7, 10, 15, 20, 30, and 40 mg (QW) 6, 9, 12, 16, and 20 mg (QD×3d QW) 7, 10, and 13 mg (QD×5d QW)	106
INK128-002; Phase 1	Multiple ascending doses in patients with relapsed or refractory multiple myeloma or WM. (unmilled)	*TAK-228* 2, 4, 6, and 7 mg (QD) 9 and 12 mg (QD×3d QW)	39
INK128-003; Phase 1	Multiple ascending doses +paclitaxel (80 mg/m^2) in patients with advanced solid malignancies (a) (unmilled)	*TAK-228* 6, 7, 8, 9, and 10 mg (QD×3d QW) 7 mg (QD×5d QW) 30, 40 mg (QW)	47
MLN0128-1004; Phase 1	Open-label, ±paclitaxel; food effect on TAK-228 PK (milled vs unmilled); food effect on PK of TAK-228 (milled) ±paclitaxel	*TAK-228 (milled/unmilled)* 4 mg (QD) 20, 30 mg (QW) *TAK-228+paclitaxel*: 6 mg (3 QD×3d)+paclitaxel (80 mg/m^2 on Days 1, 8, and 15)	39
C31001; Phase 1b/2	TAK-228 (milled/unmilled) +exemestane or fulvestrant	*TAK-228+exemestane or fulvestrant (patients continue prestudy regimen)* 5 mg (QD, unmilled) 3 or 4 mg (QD, milled)	18
C31002; Phase 1	TAK-228 effect on QTc interval in patients with advanced solid tumors (unmilled)	*TAK-228* 40 mg	43

Data are preliminary for ongoing studies. Data cutoff date: 09 Dec 2015.

Abbreviations: ECG=electrocardiogram, PK=pharmacokinetic(s), QD=once daily, QD×3d QW=once daily for 3 consecutive days followed by a 4-day dosing holiday every week, QD×5d QW=once daily for 5 consecutive days followed by a 2-day dosing holiday every week, QT=interval on ECG between the start of the Q wave and end of the T wave, QTc=QT interval corrected for heart rate, QW=once weekly, WM=Waldenström macroglobulinemia.

(a)TAK-228 doses were administered in 4-week (28-day) cycles in combination with 80 mg/m^2 paclitaxel (dosed once weekly for 3 weeks [Q3W]).

1.3.1 Pharmacokinetics

Overall, pharmacokinetic (PK) data from Studies INK128-001, INK128-002, and INK128-003 indicate that TAK-228 exhibits fast oral absorption (time to reach C_{max} [t_{max}], generally between 1-4 hours after dosing); has dose-linear PK, with a mean plasma half-life of approximately 8 hours. TAK-228 does not accumulate meaningfully in plasma when dosed as frequently as once daily (QD) under any of 4 tested dosing regimens. The PK of TAK-228 was generally consistent across 3 phase I studies, suggesting no appreciable difference in the PK of TAK-228 among subjects with advanced solid tumors or subjects with MM or WM.

There were no meaningful differences in the PK of TAK-228 when administered 24 hours after a 30-minute IV infusion of 80 mg/m2 paclitaxel (Study INK128-003) compared with single-agent TAK-228 (Studies INK128-001 and INK128-002). The PK of paclitaxel also remained generally unaffected by TAK-228 co-administration, indicating the lack of a PK interaction between TAK-228 and paclitaxel.

There were no readily apparent differences in either the Cmax or AUC of 4 mg TAK-228 unmilled or milled capsules when administered under fasted conditions.

Compared to the fasted state, when 4 mg of milled TAK-228 API was administered following a standard high-fat breakfast, there was an approximately 38% reduction in Cmax and a delay in tmax (median tmax 6 hours [fed] vs. 2 hours [fasted]), but there was no meaningful change in AUC. The differences observed when TAK-228 was dosed under fed versus fasted conditions may help explain the different MTDs determined for TAK-228 QD dosing in Study INK128-001 compared with study MLN0128-1004.

There were no readily apparent differences in the PK of TAK-228 when administered in conjunction with either 25 mg exemestane or with 500 mg fulvestrant.

1.3.2 Safety

As of the clinical data cutoff (09 December 2015), a total of 438 subjects had received ≥ 1 dose of study drug across studies. A total of 20 deaths occurred within 30 days of the last study drug dose. Of these fatal events, 1 death (ventricular fibrillation and cardiac arrest; Study INK128-001) was considered related to TAK-228.

Across the studies and regardless of causality or dosing regimen, the most common TEAEs included nausea, fatigue, hyperglycemia, vomiting, diarrhea, stomatitis, and decreased appetite.

1.4 Updated Manufacturing Process

A new TAK-228 capsule containing milled active pharmaceutical ingredient (API) is available for new clinical studies in 1 mg, 3 mg and 5 mg strengths.

The milled API, may result in faster absorption profile with possibly higher maximum concentration (Cmax), which could result in a different safety profile compared to the previous unmilled API capsules. Therefore, ongoing studies (C31001, C31002 and MLN0128-1004 [A Phase I, open label study to evaluate the safety, tolerability, and pharmacokinetics of TAK-228 as a single agent and in combination with paclitaxel in adult subjects with advanced non-hematological malignancies]), with the new milled API will determine the recommended phase 2 dose (RP2D) for single agent TAK-228 (QD and QW) and QD×3days per week in combination with paclitaxel, as well as the effect of high-fat meal on the PK of milled API.

1.5 Clinical Summary of Safety

1.5.1 Special Warnings and Precautions for Use

Insulin and Glucose Levels

Hyperglycemia and hyperinsulinemia are known toxicities associated with inhibition of mTOR and related pathways based on nonclinical studies.

A rise in fasting plasma glucose has been observed as early as 1 to 2 days following oral administration of TAK-228. Daily in-home glucose monitoring and early initiation of treatment of the hyperglycemia are essential. For subject self-monitoring of blood glucose, a finding of fasting

blood glucose ≥ 150 mg/dL measured by glucometer would initiate closer monitoring of serum glucose and possible intervention. Subjects with Grade 1 hyperglycemia (fasting serum glucose [FSG] > the upper limit of the normal range ≤ 160 mg/dL) are treated with oral hypoglycemic agents (eg, metformin), and subjects with ≥ Grade 2 hyperglycemia (FSG > 160 mg/dL) are treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated. Daily home monitoring and early treatment have resulted in good control of glucose levels for the majority of TAK-228-treated subjects who developed hyperglycemia.

Cardiac Effects

Cardiac events (including QT interval corrected for heart rate prolongation and arrhythmias) have been infrequently observed in clinical studies of TAK-228. As of 9 December 2015, there has been 1 report of ventricular fibrillation and cardiac arrest post dose that had a fatal outcome and was assessed as related to TAK-228. Routine cardiac monitoring with baseline and on-study electrocardiograms (ECGs) and physical examination constitute the core cardiac safety monitoring in all TAK-228 studies.

Preliminary results from a dedicated study of the effects of TAK-228 on the QTc interval (study C31002) show lack of clinically relevant effects on QTc interval, PR and QRS intervals, minimal effects on heart rate, and absence of treatment-emergent ECG morphology findings and therefore the treatment with TAK-228 is not associated with clinically meaningful effects on the overall electrocardiographic safety profile (further details available in the current IB version).

For subjects showing any signs of cardiac instability after TAK-228 dosing, additional monitoring onsite before clinic discharge should be considered.

Renal Function

Elevations in creatinine (regardless of causality) have been observed in subjects receiving TAK-228, all of which have been reversible with drug interruption and/or supportive care with IV hydration. Further evaluation of the renal insufficiency with urine electrolytes suggested a pre-renal etiology with a low fractional excretion of sodium < 1%. However, the adverse event cases were confounded by multiple factors such as nausea, vomiting, hyperglycemia, concomitant medications with GI side effects such as metformin, and hydronephrosis, any of which may have also contributed to dehydration and elevated creatinine. Subjects should be encouraged to drink at least 20 ounces of fluids a day, especially on days requiring fasting (per protocol), with administration of IV fluids in the clinic as indicated to avoid dehydration. Each dose of TAK-228 should be taken orally with 8 ounces (240 mL) of water.

Baseline macroscopic urinalysis and routine serum chemistries along with other safety laboratory assessments are performed in all TAK-228 studies. Additionally, microscopic urinalysis, a 12-hour urine collection, spot urine electrolytes, protein and creatinine, and serum chemistry should be collected at any time when the serum creatinine is ≥ Grade 1, according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4, to further evaluate possible etiologies for the renal dysfunction.

Rash

Rash observed in clinical studies of TAK-228 tends to be maculopapular and pruritic and has ranged from Grade 1 to 3. For the most part, rash and pruritus improve with antihistamines, topical

steroid creams, and/or dose interruption. Some subjects have required pulse systemic steroids, dose reduction, and/or study treatment discontinuation.

Pneumonitis
Pneumonitis is a known potential risk of mTOR inhibitors. Early recognition, prompt intervention, and a conservative risk management approach are recommended due to pneumonitis that has been observed with rapalog therapy and with TAK-228 administration. Symptoms of pneumonitis will be closely monitored in all TAK-228 study subjects.

1.5.2 Interactions With Other Medicaments and Other Forms of Interaction

Clinical drug-drug interaction studies have not been conducted with TAK-228. At this time, there are no known drug interactions. In vitro data, including cytochrome P450 induction/inhibition and transporter inhibition studies conducted for TAK-228, suggest a low risk for TAK-228 to precipitate a drug-drug interaction. Although potential drug-drug interactions with TAK-228 cannot be ruled out based on the known metabolism characteristics of TAK-228, the potential risk is considered low.

See also Section 10.1.8, Special Warnings and Special Precautions for Use.

1.6 Study Rationale

The mTOR pathway is an important target implicated in HCC pathogenesis. Although mTORC1 inhibitors have not demonstrated efficacy in the second line post sorafenib failure, two important confounders include the requirement for prior sorafenib exposure with resultant poor prognosis study group, and the upregulation/activation of the Akt pathway resulting from everolimus mTORC1 inhibition. TAK-228 is a novel dual mTORC1 and mTORC2 inhibitor with encouraging signals of clinical activity in phase I HCC trials.

Accordingly, we propose an open label, randomized phase I/II study of TAK-228 versus sorafenib, the current standard of care.

The primary endpoint of the phase I study will be to determine the maximum tolerated dose (MTD) of the milled API capsules of TAK-228. Three dose levels will be evaluated.

The primary endpoint of the phase II study will be time to progression rather than progression-free survival, as in the HCC population death due to non-cancer related underlying liver disease (e.g. cirrhosis) is not uncommon.

Although the primary goal of the phase II clinical trial is to evaluate time to progression, this study is important because other correlatives will provide critical information. In addition to characterizing pharmacokinetics, we plan to assess diagnostic tissue for evaluation of phosphorylated Akt, mTOR, 4EBP1, and S6 kinase[40], and correlate this with subject outcomes. Additionally, we plan to characterize oncogene expression affecting mTOR activation via targeted deep sequencing assay designed to interrogate the coding exons of approximately 200 genes commonly mutated in human cancers[41].

2 OBJECTIVES AND ENDPOINTS

2.1 Phase I Objectives

2.1.1 Primary Objective

The primary objective of this prospective, open label dose escalation study is to establish the maximum tolerated dose of TAK-228 in the first line setting of advanced hepatocellular carcinoma (HCC).

2.1.2 Secondary Objectives

- Characterize adverse effects (AE)
- Measure overall survival (OS)
- Evaluate time to progression (TTP)
- Measure progression-free survival (PFS)
- Determine objective response rate (ORR) and disease control rate (DCR) at 16 and 24 weeks

2.2 Phase II Study Objectives

2.2.1 Primary Objective

The primary objective of this prospective, open label, randomized study is to evaluate time to progression (TTP) associated with TAK-228 in the first line setting of advanced hepatocellular carcinoma (HCC), compared to a control arm treated with sorafenib.

2.2.2 Secondary Objectives

- Measure overall survival (OS)
- Measure progression free survival (PFS)
- Characterize adverse effects (AE)
- Determine radiographic response via objective response rate (ORR) and disease control rate (DCR) at 16 and 24 weeks

2.2.3 Correlative Objectives

- Assess pharmacokinetics (PK) of TAK-228
- Evaluate mTOR and PI3K/Akt expression and phosphoproteins via immunohistochemistry (IHC)
- Characterize oncogene expression affecting mTOR activation via targeted deep sequencing assay
- Assess tumor necrosis and modified RECIST (mRECIST) criteria

2.3 Phase I Study Endpoints

2.3.1 Primary Endpoint

The primary endpoint is determination of the maximum tolerated dose of TAK-228. MTD is defined as the dose level at which fewer than 33% of subjects experience a dose limiting toxicity (DLT).

2.3.2 Secondary Endpoints

- Adverse effects (AE) as defined by CTCAE v4
- Overall survival (OS) as defined by the time from randomization to date of death from any cause.
- Time to progression (TTP) as defined as the time from randomization until tumor progression as defined by RECIST v1.1.
- Progression free survival (PFS) as defined by time from randomization to tumor progression or death from any cause.
- Objective response rate (ORR) as defined as complete response (CR) + partial response (PR), and disease control rate (DCR) as defined by RECIST v1.1, as a sum of stable disease (SD for 8 weeks), partial response (PR), and complete response (CR)

2.4 Phase II Study Endpoints

2.4.1 Primary Endpoint

The primary endpoint is determination of the time to progression (TTP), which is defined as the time from randomization until tumor progression as defined by RECIST v1.1.

2.4.2 Secondary Endpoints

- Overall survival (OS) as defined by the time from randomization to date of death from any cause.
- Progression free survival (PFS) as defined by time from randomization to tumor progression or death from any cause
- Adverse effects (AE) as defined by CTCAE v4
- Objective response rate (ORR) as defined as complete response (CR) + partial response (PR), and disease control rate (DCR) as defined by RECIST v1.1, as a sum of stable disease (SD for 8 weeks), partial response (PR), and complete response (CR)

2.4.3 Correlative Endpoints

- Assess Pharmacokinetics (PK) in first 10 subjects in TAK-228 arm
- Evaluate mTOR and PI3K/Akt expression and phosphoproteins via immunohistochemistry (IHC) of phosphorylated Akt, 4EBP1, S6 kinase, and ERK1/2
- Characterize oncogene expression affecting mTOR activation via targeted deep sequencing assay designed to interrogate genes commonly mutated in human cancers.
- Assess tumor necrosis and modified RECIST (mRECIST) criteria.

3 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Each subject must meet all of the following inclusion criteria to be enrolled in the study:

3.1.1 Male or female subjects 18 years or older at the time of informed consent.

3.1.2 Voluntary written consent must be signed before performance of any study related procedure not part of standard medical care, with the understanding that the subject may withdraw consent at any time without prejudice to future medical care.

3.1.3 Females of childbearing potential must agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug, or agree to completely abstain from heterosexual intercourse.

3.1.4 Females of childbearing potential must have a negative serum pregnancy test within 7 days prior to prior to registration for protocol therapy.
NOTE: Female subjects are considered of childbearing potential unless they are surgically sterile (they have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months.

3.1.5 Male subjects, even if surgically sterilized (i.e., status post-vasectomy), must agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, or agree to completely abstain from heterosexual intercourse.

3.1.6 Subjects must have a diagnosis of measurable advanced or metastatic hepatocellular carcinoma. Advanced HCC is defined as disease not amenable to surgery, ablation, transplant, or embolic therapy.

3.1.7 Phase II subjects must be willing to provide a tissue biopsy prior to registration if archived HCC tumor tissue is not available for correlative studies.

3.1.8 For the phase I cohort, subjects will have no restrictions on the number of prior systemic therapies; phase I patients may also be treatment naïve.

3.1.9 Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.

3.1.10 Adequate organ function, as specified below, within 28 days before study registration:

3.1.10.1 Bone marrow reserve consistent with: absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L; platelet count $\geq$ 50 x 10^9/L; hemoglobin $\geq$ 9 g/dL;

3.1.10.2 Hepatic: total bilirubin $\leq$ 2 x upper limit of normal (ULN), transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase-AST/SGOT and alanine aminotransferase/serum glutamic pyruvic transaminase-ALT/SGPT) $\leq$ 5 x ULN

3.1.10.3 Renal: creatinine clearance $\geq$50 mL/min based either on Cockcroft-Gault estimate or based on urine collection (12 or 24 hour);

3.1.10.4 Metabolic: Glycosylated hemoglobin (HbA1c) $\leq$7.0%, fasting serum glucose ($\leq$ 130 mg/dL) and fasting triglycerides $\leq$ 300 mg/dL.

NOTE: Subjects with a history of transient glucose intolerance due to corticosteroid administration are allowed in this study if all other inclusion/exclusion criteria are met.

3.1.11 Ability to swallow oral medications.

3.1.12 Measurable disease according to RECIST v1.1 and obtained by imaging within 28 days prior to registration for protocol therapy.
NOTE: A subject with prior brain metastasis may be considered if they comply with inclusion criteria 3.1.13 below.

3.1.13 Subjects who have a history of brain metastasis are eligible for the study provided all the following criteria are met:

3.1.13.1 Must have completed their treatment for brain metastasis
3.1.13.2 Must be asymptomatic
3.1.13.3 Must not have evidence of disease progression for ≥3 months or hemorrhage after treatment;
3.1.13.4 Must be off-treatment from dexamethasone for 4 weeks prior to study registration and
3.1.13.5 Must not have an ongoing requirement for dexamethasone or anti-epileptic drugs.

3.1.14 Prior locoregional liver directed therapy is allowed as long as treatment was at least 6 weeks prior to study registration, and clear progression is demonstrated by RECIST v1.1 criteria. Subject must have recovered from the acute toxic effects (≤ grade 1 CTCAE v4) of previous anti-cancer treatment prior to study enrollment; the only exception is that grade 2 neuropathy is permitted.

3.1.15 Prior radiation therapy is allowed to < 25% of the bone marrow, but is not permitted within 28 days prior to study registration.

3.1.16 Estimated life expectancy ≥ 3 months as determined by the treating physician.

3.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not to be enrolled in the study:

3.2.1 Female subjects who are both lactating and breastfeeding

3.2.2 Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

3.2.3 Treatment with any investigational products within 28 days prior to study registration.

3.2.4 No prior systemic treatment is allowed for subjects in the phase II cohort.

3.2.5 Failed to recover from the reversible effects of prior anticancer therapies with the exception of alopecia and grade 2 neuropathy.

3.2.6 Have initiated treatment with bisphosphonates less than 30 days prior to study registration. Concurrent bisphosphonate use is only allowed if the bisphosphonate was initiated at least 30 days prior to study registration.

3.2.7 Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of TAK-228.

3.2.8 No condition that could affect the absorption of study drug, including any of the following:
- Malabsorption syndrome
- Disease significantly affecting gastrointestinal function
- Bowel obstruction or sub-obstruction

3.2.9 History of any of the following within the last 6 months prior to study registration:
- 3.2.9.1 Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures
- 3.2.9.2 Ischemic cerebrovascular event, including TIA and artery revascularization procedures
- 3.2.9.3 Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation or ventricular tachycardia)
- 3.2.9.4 Placement of a pacemaker for control of rhythm
- 3.2.9.5 New York Heart Association (NYHA) Class III or IV heart failure (See Study Procedures Manual)
- 3.2.9.6 Pulmonary embolism

3.2.10 Significant active cardiovascular or pulmonary disease at the time of study registration, including:
- 3.2.10.1 Uncontrolled high blood pressure (i.e., systolic blood pressure >160 mm Hg, diastolic blood pressure > 95 mm Hg)
- 3.2.10.2 Pulmonary hypertension
- 3.2.10.3 Uncontrolled asthma or O_2 saturation < 90% by ABG (Arterial Blood Gas) analysis or pulse oximetry on room air
- 3.2.10.4 Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention, or history of valve replacement
- 3.2.10.5 Medically significant (symptomatic) bradycardia
- 3.2.10.6 History of arrhythmia requiring an implantable cardiac defibrillator
- 3.2.10.7 Baseline prolongation of the rate-corrected QT interval (QTc) (e.g., repeated demonstration of QTc interval > 480 milliseconds, or history of congenital long QT syndrome, or torsades de pointes)

3.2.11 Initiation of treatment with hematopoietic growth factors, transfusions of blood and blood products, or systemic corticosteroids (either IV or oral steroids, excluding inhalers) within 1 week prior to study registration (subjects already receiving erythropoietin on a chronic basis for ≥ 28 days are eligible).

3.2.12 Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active infection, or any other condition that could compromise participation of the subject in the study.

3.2.13 Cirrhosis with Child-Pugh score > 7 (see Study Procedures Manual)

3.2.14 Variceal bleeding within 1 month prior to study registration.

3.2.15 Refractory encephalopathy or ascites

3.2.16 Known HIV positivity

3.2.17 Hepatitis B surface antigen (HBsAg) positivity without active treatment. A subject found to be HBsAg positive should be on antiviral therapy for at least two weeks prior to study registration.

3.2.18 Subjects who are taking proton pump inhibitors (PPIs) within 7 days of study registration or who require treatment with PPIs throughout the trial or those who are taking H2 receptor antagonists within 24 hours of study registration.

4 SUBJECT REGISTRATION

All subjects must be registered and randomized through BTCRC Administrative Headquarters' electronic data capture (EDC) system.

Subjects must be registered and randomized prior to starting protocol therapy. Subjects must be randomized within 1 business day of registration and should begin therapy within 5-10 business days of randomization. Beginning therapy outside that timeframe will not be considered a deviation.

Detailed guidelines for subject registration and randomization can be found in the electronic case report form (eCRF) guidelines associated with this protocol.

Blinding
The study treatment is not blinded to the subject or the investigator.

5 STUDY DESIGN AND TREATMENT PLAN

5.1 Overview of Study Design

This is an open label, multi-center, randomized phase I/II study of TAK-228 versus standard sorafenib.

5.2 Number of Subjects

Phase I: Up to 18 subjects will be registered.

Phase II: The total number of subjects to be registered and randomized is 100.

5.3 Duration of Study

Study duration will be from time of registration until treatment cessation, due to progression, death, or withdrawal for any reason.

Study cycles are defined as a period of 28 days.

5.4 Phase I Dose Escalation Study

5.4.1 Phase I Treatment Plan

All Phase I subjects will receive TAK-228. TAK-228 will be administered orally on days 1, 8, 15 and 22 in successive cohorts. The escalation phase will follow a standard "3+3" design. Subjects will be accrued to each dose level in cohorts of up to 3-6 evaluable subjects. Escalation will continue until 2 DLT are observed in a cohort, or until the highest planned dose level is reached.

After informed consent and study registration, subjects will receive protocol therapy according to the table below.

Dose Cohort	# of Subjects	TAK-228	TAK-228 capsules: Number and Strength
1 (start)	3-6	15mg QW	Three 5-mg capsules
2	3-6	20mg QW	Four 5-mg capsules
3	3-6	30mg QW	Six 5-mg capsules

5.4.2 Phase I Maximum Tolerated Dose (MTD) and Dose Escalation Rules:

To define the Maximum Tolerated Dose (MTD), subjects will be evaluated for DLT in the first 28 days of treatment (1 cycle).

Note: A withdrawal or death within the first 4 weeks not related to treatment will not be considered a DLT.

The MTD is defined as the dose level at which fewer than 33% of subjects experience a dose limiting toxicity (DLT), and specifically is the dose level at which less than 2 out of 6 subjects experience DLT. The MTD will be the recommended dose for the Phase II component of the study.

Subjects will initially be enrolled onto dose level 1. Three to six evaluable subjects will be enrolled at each dose level. All subjects assigned to a dose level must be followed for at least 4 weeks before dose escalation to the next cohort level can begin.

Note: Subjects not evaluable for DLT assessment (i.e. do not complete at least 1 cycle of therapy due to reasons other than toxicity) on the Phase I portion of the protocol will be replaced for determination of dose escalation.

The following rules will be followed:

- An initial three subjects will be enrolled at dose level +1. If all 3 subjects in dose level +1 complete 4 weeks of therapy without dose limiting toxicity (DLT), the study will proceed to enroll 3 subjects at dose level +2. If all 3 subjects in dose level +2 complete 4 weeks of therapy without DLT, the study will proceed to enroll 3 subjects at dose level +3. If all 3 subjects in dose level +3 complete 4 weeks of therapy without DLT, 3 more subjects will be enrolled to ensure that only 0-1 of 6 subjects have a DLT and then proceed to the Phase II

cohort. As dose level +3 represents the full dose of TAK-228, there will be no further dose escalation beyond dose level +3.

- Alternatively, if 1 of the first 3 subjects in any given dose cohort experiences DLT, an additional 3 subjects will be enrolled at that dose level. If only 1 of the total 6 subjects in a dose level experience DLT, the study will proceed to the next dose level as planned. If 2 of the total 6 subjects in any given dose cohort experience DLT, the next lower dose level will be explored and considered the maximum tolerated dose (MTD) if no more than 1 of 6 subjects experience a DLT. That dose will be recommended for the Phase II study.

- If 2 or more DLTs are reached in dose level +1, the study will be put on hold and a protocol amendment will be considered.

Dose Escalation Rules

Number of subjects with DLT at given dose level	**Escalation decision**
0 out of 3	Enter 3 subjects at the next dose level.
≥2 out of 3	Dose escalation will be stopped. This dose level will be declared the **maximum administered dose**. Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that next lowest dose level.
1 out of 3	Enter at least 3 more subjects at this dose level: • If 0 of these additional 3 subjects experience DLT, proceed to the next dose level. • If 1 or more of these additional 3 subjects experience DLT, then dose escalation is stopped and this dose is declared the maximum administered dose. Three (3) additional subjects will be entered at the next lowest dose level if only 3 subjects were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximum administered dose	This will be defined as the MTD. This dose level will be the recommended Phase II dose.

5.4.3 Phase I Dose-Limiting Toxicities (DLTs):

The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4 (http://ctep.cancer.gov) will be used to characterize toxicities.

DLT is defined as an adverse event related (possible, probable or definite) to study treatment occurring during the first cycle of therapy and fulfilling one of the following criteria:

- ≥ grade 4 hematologic toxicity or ≥ grade 3 non hematologic toxicity (excluding transaminitis < 10x ULN lasting less than one week, nausea or emesis or diarrhea of no longer than 48 hours duration without medical intervention). Grade 4 vomiting or diarrhea is considered DLT.
- Delay of Cycle 2 for greater than 2 weeks due to drug-related toxicities
- Grade 3 or 4 febrile neutropenia regardless of duration
- Grade 3 thrombocytopenia with clinically significant bleeding (assessed with standard of care labs)
- Grade 4 thrombocytopenia regardless of duration.

DLTs will be counted based on the number of subjects with DLT at a given dose level, not the absolute number of DLTs. No single subject can trigger more than one DLT event.

Additional subject cohorts will not be enrolled at the next dosing level until all subjects at the current dosing level complete all planned treatment for cycle 1 (defined as 4 doses of TAK-228) and are able to start cycle 2 with no more than a 2-week delay.

Intra-subject dose escalation is not permitted.

Once the maximum tolerated dose of TAK-228 is determined, enrollment will continue until at least 6 subjects total are accrued at the maximum tolerated dose.

5.5 Phase II Study

5.5.1 Phase II Stratification Factors and Randomization Process Prior to Initiating Study Treatment

Randomization will take place following completion of the screening evaluations and eligibility assessments. Stratification factors will be employed during randomization to minimize between-arm assignment imbalance.

1 Child-Pugh score 5-6
2 Child-Pugh score 7

Within the strata, subjects will be randomly assigned with equal probability to either the investigational arm (Arm A: TAK-228) or the control arm (Arm B: sorafenib).

5.5.2 Phase II Treatment Plan

Subjects will be randomized to receive either TAK-228 or sorafenib.

5.5.1 Arm A: MLN 0128 will be administered orally at the recommended phase II dose (RP2D) once weekly. Dose modification will be allowed for grade 3 or higher toxicities, or intolerable grade 2 toxicities.

5.5.2 Arm B: Sorafenib will be administered at 400mg PO BID daily, with dose adjustment per standard of care.

5.5.3 Study evaluations will include medical histories that will capture information about drug toxicity and performance status. Subjects will undergo routine physical examinations, including vital signs; height, weight, and measurement for body surface area. Laboratory measurements will be obtained throughout the study as needed. Tissue samples will be evaluated for mTOR and PI3K/Akt pathway proteins and phosphoproteins by IHC expression. A schedule of activities is presented in the study calendar. To complete this trial in a timely manner, the primary end point is time to progression.

	Drug	**Dose**	**Route of administration**	**Length of cycle**
Arm A	TAK-228	RP2D once weekly	oral	28 days
Arm B	Sorafenib	400mg BID daily	oral	

5.6 Criteria for administration of subsequent treatment cycles

A new treatment cycle will only be initiated when all of the following conditions are met:

- ANC $\geq 1.5 \times 10^9$/L
- Platelets $\geq 50 \times 10^9$/L
- Non-hematologic treatment related toxicities have improved to grade 1 or resolved (CTCAE v. 4)

Institution standards should be followed for hydration and symptom management.

5.7 Pre-medication

None is required, but can be utilized per clinician discretion.

5.8 Drug Administration

5.8.1 TAK-228 Administration

TAK-228 will be administered once weekly at approximately the same time each day. It is recommended that each dose of TAK-228 be given orally with 8 ounces (240 mL) of water. TAK-228 should be administered on an empty stomach. Subjects should be instructed to refrain from eating and drinking (except for water and prescribed medications) for 2 hours before and 1 hour after each dose.

Subjects should be instructed to take their study medication at approximately the same time on each scheduled dosing day and not to take more than the prescribed dose at any time. Subjects should swallow the study medication whole and not chew it, open it, or manipulate it in any way

before swallowing. If a subjects does not take their TAK-228 dose within ±24 hours of the QW scheduled dosing time, the dose should be skipped and considered a missed dose. Subjects should record any missed doses in their diary and resume drug administration at the next scheduled time with the prescribed dosage. Under no circumstance should a subjects repeat a dose or double-up doses.

TAK-228 will be administered only to eligible subjects under the supervision of the investigator or identified sub-investigator(s) during Cycle 1 for all TAK-228 subjects and during Cycle 2 Day 1 for the first 10 subjects randomized to Phase II arm A; subsequent doses may be taken at home.

Cycles are repeated every 28 days.

5.8.2 TAK-228 Missed doses:
If severe emesis or mucositis prevents the subject from taking an TAK-228 dose, that dose will be skipped. If emesis occurs after study medication ingestion and whole capsule(s) are visible in the vomitus, replacement capsule(s) should be taken; otherwise, the dose will not be re-administered, and subjects should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Subjects should record the time of the emesis in their dosing diary (see the Study Procedures Manual). Under no circumstance should a subject repeat a dose or double-up doses.

5.8.3 Sorafenib Administration:
Sorafenib should be administered on an empty stomach, 1 hour before or 2 hours after eating. It is recommended that each dose of sorafenib be given orally with 8 ounces (240 mL) of water. Sorafenib may be taken at home from the start.

Cycles are repeated every 28 days.

5.8.4 Sorafenib Missed Doses:
Missed doses can be taken up to 4 hours of the time that the dose was scheduled. If the timing is beyond 4 hours, the subject will skip the dose and take the next dose as scheduled. Under no circumstances should a subject double-up doses.

5.9 Supportive Care

TAK-228 and sorafenib are associated with adverse effects. The following medications may be given to subjects depending on the side effects they report: acetaminophen for fevers, meperidine for chills, anti-emetics for nausea and vomiting.

There is no restriction on use of topical medications/lotions for prevention of hand-foot syndrome caused by sorafenib.

5.10 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Other investigational agents including mTOR, PI3Kinase and AKT inhibitors
- Other anticancer therapies including chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation or surgery (subjects can have palliative radiation or surgery in the

study for pre-existing lesions)
- Systemic corticosteroids (either IV or oral steroids, excluding inhalers), unless necessary for treatment of TAK-228 related AE, ie, rash (pre-medication for paclitaxel combo)
- Anti-epileptic drugs for subjects with treated brain metastasis
- Concomitant administration of any proton pump inhibitor (PPI) is not permitted during the study. Subjects receiving PPI therapy before enrollment must stop using the PPI for 7 days before their first dose of study drugs. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.

5.11 Permitted Concomitant Medications and Procedures

Prophylactic use of anti-emetic, anti-nausea, and antidiarrheal medications is encouraged and may be used prior to first dose of TAK-228 or sorafenib and as needed throughout the study prior to each dosing and as clinically indicated per standard practice. When selecting an anti-emetic agent, drugs that do not have an effect on the QT interval, such as palonosetron, are preferred.

Histamine H2 receptor antagonists may be allowed, if needed provided that the histamine H2 receptor antagonist is not taken within 12 hours before and within 6 hours after study drug administration. Subjects receiving histamine H2 receptor antagonists before enrollment must stop using these medications for at least 24 hours before their first dose of study drug. Examples of histamine H2 receptor antagonists include ranitidine, famotidine and nizatidine. Cimetidine, a moderate cytochrome P450 (CYP)1A2 inhibitor, is not recommended as a first choice H2 receptor antagonist.

Neutralizing antacid preparations (acid neutralizers) and calcium supplements are not permitted during Cycle 1 on study drug administration days in the phase 1/1b portion of the study, but may be taken as needed on non-TAK-228 administration days. However, for all other cycles in the phase 1b portion of the study and throughout the phase 2 portion of the study, administration of neutralizing antacids and calcium preparations is permitted except from 2 hours before until 2 hours after TAK-228 administration. Some anti-gas preparations may also have antacid properties, and should also not be permitted from 2 hours before until 2 hours after study drug administration.

Strong CYP1A2 and CYP inducers should be administered with caution, at the discretion of the investigator (see SPM). Alternative treatments, if available, should be considered.
- Moderate CYP1A2 inhibitors: cimetidine, methoxsalen
- Strong CYP1A2 inhibitors: fluvoxamine, ciprofloxacin
- Clinically significant enzyme inducers: rifampin, rifapentine, rifabutin, phenytoin, carbamazepine, phenobarbital, St. John’s Wort.

Other medications considered necessary for the safety and wellbeing of the subjects may be administered at the discretion of the investigator.

5.12 Precautions and Restrictions

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with study drug. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, Bacille Calmette-Guerin, yellow fever, varicella, and TY21a typhoid vaccines.

No dietary restrictions will be imposed on study subjects other than daily fasting for glucose monitoring.

Subjects who show evidence of hyperglycemia during the study should be encouraged to follow a low carbohydrate diet.

Pregnancy
It is not known what effects TAK-228 has on human pregnancy or development of the embryo or fetus. Therefore, female subjects participating in this study should avoid becoming pregnant, and male subjects should avoid impregnating a female partner. Non-sterilized female subjects of reproductive age group and male subjects should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female subjects must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the informed consent form through 90 days (3 months) after the last dose of study drug, or agree to completely abstain from heterosexual intercourse.

Male subjects, even if surgically sterilized (i.e., status post-vasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 120 days (4 months) after the last dose of study drug, or completely abstain from heterosexual intercourse.

6 DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Section 7.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring protocol therapy interruption or discontinuation at each study visit for the duration of their participation in the study.

Subjects discontinued from the treatment phase of the study for any reason will be evaluated at least 30 days (± 7) after the last dose of protocol therapy.

Phase I component:
Dose modifications of TAK-228 during Cycle 1 of treatment in the Phase I component of the study will follow criteria specified (Section 5.4.3) and will be considered DLT (inability to deliver TAK-228 at the intended dose level).

In second and subsequent cycles, the guidelines outlined for dose adjustments for the Phase II component of the protocol should be followed.

Phase II component:
Subjects will be monitored for toxicity. Appropriate adjustment of dose, delay or discontinuation of drugs will be made as outlined below for each drug.

6.1 Treatment-Limiting Adverse Events

A **treatment-limiting adverse event** is any adverse event related to protocol therapy experienced during the study resulting in treatment termination.

6.2 TAK-228 Dose Modifications

TAK-228 dosing should be withheld for ≥ Grade 2 renal insufficiency or ≥ Grade 3 TAK-228-related toxicities. If the event resolves to Grade ≤ 1 or baseline values within 28 days of interrupting therapy, the subject may resume study treatment at a dose reduction.
See table of dose adjustments below according to the schedule applied in this protocol.

If TAK-228 dosing is delayed for > 28 consecutive days for TAK-228-related toxicity despite supportive treatment per standard clinical practice or more than 2 dose reductions of TAK-228 is required in a subject, stop TAK-228 therapy, discontinue the subject from the study drug administration, and complete the follow-up visit within 30 days of the last administration of TAK-228.

See Section 6.4 for management of TAK-228 dosing for specific clinical events.

Table of Dose Adjustments for TAK-228 dosing on a weekly (QW) schedule

Dose Level*	Dose	TAK-228 capsules: Number and Strength
1	30 mg	Six 5-mg capsules
-1	20 mg	Four 5-mg capsules
-2	15 mg	Three 5-mg capsules
-3	10 mg	Two 5-mg capsules
-4	Discontinue	

*Level 1 represents the RP2D dose. If the RP2D is found to be 20mg, level -1 will be 15mg and level -2 will be 10mg. Likewise, if the RP2D is found to be 15mg, level -1 dose will be 10mg and level -2 will be to discontinue and protocol amendment will be submitted.

6.3 Management of TAK-228 Clinical Events

6.3.1 Management of Hyperglycemia

In addition to obtaining fasting serum glucose (FSG) levels at clinic visits, all subjects receiving TAK-228 will be given a glucometer to monitor their daily fasting blood glucose (FBG) levels at home. The level should be collected daily, pre-dose on dosing days, and at approximately the same time each day.

All subjects receiving TAK-228 will be provided an in-home glucometer. Subjects will be trained on proper use of the glucometer and instructed to collect a daily FBG level every morning (predose on dosing days). Subjects will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. Site investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia.

Subjects will be instructed to notify the site staff immediately with any abnormal readings (ie, ≥ 150 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic. If no irregularities in the fasting blood glucose level are observed during a minimum of 2 consecutive months, the frequency of in-home fasting blood glucose testing may be reduced to a minimum frequency of once weekly if the investigator approves. Subjects will continue to notify the investigator of fasting blood glucose levels that exceed 150 mg/dL and, if blood glucose levels are not well-controlled, or if the subject requires either oral hypoglycemic agents or insulin to control blood glucose levels, the frequency of in-home testing of fasting blood glucose levels will be reinstated to daily.

In the event that any FSG reading performed at the site indicates hyperglycemia (> upper limit of normal [ULN] or ≥ 110 mg/dL), the study staff should first ascertain that the subject was fasting at the time of the blood draw (ie, nothing by mouth for at least 8 hours prior to blood being obtained), had continued to take their concomitant antiglycemic medications should the subject have underlying diabetes mellitus, and repeat the FSG as needed. If the repeat FSG continues to demonstrate hyperglycemia, investigators should initiate steps to aggressively manage the hyperglycemia per standard clinical practice. The following guidelines are provided to aid the investigator in initiating antiglycemic therapies.

Based on the clinical experience from TAK-228 trials, most episodes of hyperglycemia observed occurred within the first 60 days after initiation of treatment with TAK-228 and have been either Grade 1 or 2 that have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since instituting a standard regimen for early treatment of hyperglycemia.

All subjects developing hyperglycemia on the study should have their glucose closely monitored by study staff. The investigator may choose either to continue close monitoring of subjects who develop Grade 1 hyperglycemia (FSG > ULN ≤ 160 mg/dL) or, alternatively, consider initiating treatment with an oral hypoglycemic agent, such as

metformin. All subjects with Grade ≥ 2 hyperglycemia (FSG > 160 mg/dL) must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated. The investigator should consult an endocrinologist if needed to aid in optimizing the subject's hyperglycemia treatment plan.

It is recommended that subjects be treated initially with a fast acting insulin sensitizer such as metformin at 500 mg PO QD, and titrate up to a maximum of 1000 mg PO BID as needed. Concurrent addition to metformin of DPP-4 inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution due to the higher risk of inducing hypoglycemia in subjects. The dose of oral hypoglycemic agents should be adjusted in subjects with renal insufficiency. In addition, subjects should also be encouraged to follow a low carbohydrate diet once hyperglycemia is first observed.

Guidance for TAK-228 dose management in the event of hyperglycemia is provided in the table below.

Management of Hyperglycemia

Grade	Description	Treatment	TAK-228 Dose Modification
1	Fasting blood sugar > ULN–160 mg/dL	Continue close monitoring of blood sugars. Initiate oral hypoglycemic agent.	None.
2	Fasting blood sugar > 160–250 mg/dL	Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None.
≥3	Fasting blood sugar > 250 mg/dL	Initiate oral hypoglycemic agent and/or insulin.	Hold drug until ≤ Grade 2. Resume TAK-228 based on timing of recovery: ≤ 1 week: resume at same dose and schedule; >1 but ≤ 3 weeks: reduce dose > 3 weeks: stop TAK-228 and discontinue subject from the study.

Prevention/Prophylaxis

- Follow fasting serum glucose levels during clinic visits.
- Monitor home glucometer test results.
- Check HbA1c levels every 3 months during therapy.
- Life-style modifications, as appropriate (balanced diet, limit alcohol consumption, increase physical activity).
- Most episodes of Grade 1 and 2 hyperglycemia respond quickly to oral metformin.
- Early initiation of therapy is recommended to prevent higher-grade hyperglycemia.
- Fasting blood glucose levels ≥ 150 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.

Abbreviations: dL = deciliters; mg = milligrams; ULN = upper limit of normal.

6.3.2 Management of Noninfectious Pneumonitis

Guidance for TAK-228 dose management in the event of noninfectious pneumonitis is shown in the table below.

Management of Non-infectious Pneumonitis

Grade	Description	Treatment	TAK-228 Dose Modification
1	Asymptomatic: Radiographic findings only	Rule out infection and closely monitor.	None.
2	Symptomatic: Not interfering with ADLs	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ Grade 1.	Interrupt TAK-228 treatment: When symptoms ≤Grade 1, reinitiate TAK-228 at a dose reduced by 1 level. If no recovery within 4 weeks, then discontinue TAK-228.
3	Symptomatic: Interfering with ADLs; Requires administration of O_2	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ Grade 1.	Interrupt TAK-228 until symptoms resolve to ≤Grade 1. Consider reinitiating TAK-228 at a dose reduced by 1 level. If toxicity recurs at Grade 3, discontinue TAK-228.
4	Life-threatening: Ventilatory support indicated	Rule out infection and consider treatment with corticosteroids.	Discontinue TAK-228 treatment.

Abbreviations: ADL = activities of daily living; O_2 = oxygen gas.

6.3.3 Management of Hyperlipidemia

Guidance for TAK-228 dose management in the event of hyperlipidemia is shown in the table below.

Management of Hyperlipidemia

Grade	Description	Treatment	TAK-228 Dose Modification
1	Cholesterol: > ULN - 300 mg/dL Triglycerides: > 150 - 300 mg/dL	None.	None.
2	Cholesterol: > 300 – 400 mg/dL Triglycerides: > 300 - 500 mg/dL	Treat hyperlipidemia according to standard guidelines. Triglycerides ≥ 500 mg/dl should be treated urgently due to risk of pancreatitis.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt TAK-228 dosing until recovery to ≤ Grade 1. Reinitiate at same dose.
3	Cholesterol: > 400 - 500 mg/dL Triglycerides: > 500 - 1000 mg/dL	Same as for Grade 2.	Hold dose until recovery to ≤ Grade 1, then restart at a dose reduction
4	Cholesterol: > 500 mg/dL Triglycerides:	Same as for Grade 2.	Same as for grade 3

Management of Hyperlipidemia

Grade	Description	Treatment	TAK-228 Dose Modification
	> 1000 mg/dL		
Prevention/Prophylaxis			
Life-style modifications, as appropriate (balanced diet, limit consumption of alcoholic beverages, increase physical activity).			

Abbreviations: dL = deciliters; mg = milligrams; ULN = upper limit of normal.

6.3.4 Management of Oral Mucositis

Guidance for TAK-228 dose management in the event of oral mucositis is provided in the table below.

Management of Oral Mucositis

Grade	Description	Treatment	TAK-228 Dose Modification
1	Asymptomatic or mild symptoms	Non-alcoholic mouth wash or 0.9% salt water rinse; Consider topical corticosteroids at earliest signs of mucositis.	None.
2	Moderate pain, not interfering with oral intake Modified diet indicated	Topical analgesic mouth treatments; Topical corticosteroids; Initiate antiviral or antifungal therapy, if indicated.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt TAK-228 dosing until recovery to ≤ Grade 1. Reinitiate at same dose.
3	Severe pain, interfering with oral intake	Same as for Grade 2; Consider intra-lesional corticosteroids.	Hold dose until recovery to ≤ Grade 1, then restart TAK-228 at a dose reduced by 1 level
4	Life-threatening consequences	Same as for Grade 2. Consider intra-lesional corticosteroids.	Discontinue treatment.

Prevention/Prophylaxis

- Consider initiation of a non-alcoholic mouthwash or 0.9% salt water rinses 4-6 times daily with start of therapy before signs of mucositis develop.
- Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

6.3.5 Management of Rash

Guidance for TAK-228 dose adjustment for the event of rash is provided in the table below.

Management of Rash

Grade	Description	Treatment	TAK-228 Dose Modification
≤ 2	Macules/papules covering ≤ 30% body surface area with or without symptoms	Consider treatment with topical steroid cream/ointment and/or oral anti-histamines or antibiotics.	None.
≥ 3	Macules/papules covering	Consider treatment with	Hold until ≤ Grade 2;

	> 30% body surface area with or without symptoms	topical steroid cream/ointment, oral antihistamines or antibiotics and/or pulsed steroids.	Resume TAK-228 based on timing of recovery: ≤ 3 weeks: reduce dose ; > 3 weeks: stop TAK-228 and discontinue subject from the study.

Prevention/Prophylaxis:

- Rash should be managed aggressively. The investigator should consider consulting a dermatologist or other specialist, if needed.
- A skin biopsy at the site of rash should be considered as soon as possible after the initial episode.

6.3.6 Management of Nausea and/or Vomiting

Guidance for TAK-228 dose adjustment for the event of nausea and/or vomiting is provided in the table below.

Management of Nausea and/or Vomiting

Grade	Description	Treatment	TAK-228 Dose Modification
≤ 2	Loss of appetite with or without decreased oral intake; 1-5 episodes of vomiting within 24 hours	Maximize anti-emetic therapy; Consider IV fluid hydration.	None.
≥ 3	Inadequate oral intake; ≥ 6 episodes of vomiting within 24 hours	Maximize anti-emetic therapy; Initiate tube feeding, IVF, or TPN.	Hold until ≤ Grade 1; Resume TAK-228 without dose modification.
Prevention/Prophylaxis Prophylactic use of anti-emetic, anti-nausea, and anti-diarrheal medications are encouraged and may be used before each dose of TAK-228 as needed throughout the study.			

Abbreviations: IV = intravenous; IVF = intravenous fluids; TPN = total parenteral nutrition

6.3.7 Management of Cardiac Events

6.3.7.1 Management of Cardiac Instability

For subjects showing signs of cardiac instability after TAK-228 dosing, additional monitoring onsite before clinic discharge should be considered.

6.3.7.2 Management of Left Ventricular Dysfunction

Guidance for TAK-228 dose adjustment for the event of left ventricular dysfunction is provided in the table below.

Management of Left Ventricular Dysfunction

Grade	Description	TAK-228 Dose Modification
1	Asymptomatic decline in LVEF > 15% from baseline values OR; LVEF > 10%-15% from baseline values and is below institution's LLN	No change; continue TAK-228 at same dose and schedule.

≥ 2	Symptomatic cardiac dysfunction/congestive heart failure	Discontinue treatment.

Abbreviations: LLN = lower limit of normal; LVEF = left ventricular ejection fraction.

6.3.7.3 Management of QTc Prolongation

Guidance for TAK-228 dose adjustment for the event of QTc prolongation is provided in the table below.

Management of QTc Prolongation

Grade	Description	Treatment	TAK-228 Dose Modification
2	480 ms < QTc < 501 ms	Evaluate for other possible causes (e.g., electrolyte disturbance, concomitant medication, etc.)	None; continue TAK-228 at the same dose and schedule.
≥ 3	QTc ≥ 501 ms	Evaluate for other possible causes (e.g., electrolyte disturbance, concomitant medication)[a]; Consider a formal consult by a cardiologist; Contact the BTCRC project manager who will notify the sponsor-investigator; Additional ECGs may be performed at intervals that the treating physician deems clinically appropriate until repeated QTc measurements fall or are below the threshold interval that triggered the repeat measurement.	Hold TAK-228 The decision whether to reinitiate TAK-228 with or without dose reduction and additional monitoring in those subjects who had asymptomatic prolonged QTc ≥501 msec (Grade 3) that has reverted to an acceptable interval, have previously tolerated TAK-228, and appear to have benefitted from treatment with either disease control or response, will be agreed to by the sponsor-investigator and the treating physician on a case-by-case basis.

Abbreviations: ECG = electrocardiogram; IV = intravenous; ms = milliseconds; QTc = QT interval corrected for heart rate

a A list of medications known to prolong QTc can be found at www.torsades.org and www.QTdrugs.org.

6.3.8 Management of Other Non-hematologic Toxicities (Including Asthenia, Weakness and Fatigue)

Guidance on dose adjustment for subjects with other non-hematologic toxicities is provided below

Management of Other Non-hematologic Toxicities (Including Asthenia, Weakness, and Fatigue)

Grade	Description	Treatment	Dose Modification
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Initiate appropriate medical therapy and monitor.	If tolerable, then no adjustment is required.
2	Moderate; minimal, local or noninvasive intervention indicated.	Initiate appropriate medical therapy and monitor.	• If tolerable, no adjustment required. • If toxicity becomes intolerable, hold TAK-228(s)

Management of Other Non-hematologic Toxicities (Including Asthenia, Weakness, and Fatigue)

Grade	Description	Treatment	Dose Modification
			until recovery to ≤Grade 1, then reinitiate at same dose.
≥ 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated		Hold TAK-228(s) until recovery to ≤ Grade 1. Reinitiate TAK-228 at dose reduced by 1 level

6.3.9 Management of Aspartate Aminotransferase/Alanine Aminotransferase Elevations

Guidance on dose adjustment for subjects with AST/ALT elevations is provided below

Management of Aspartate Aminotransferase/Alanine Aminotransferase Elevations

Grade	Description	Treatment	Dose Modification
1	>ULN to 3×ULN	None	None
2	Asymptomatic with levels 3 to 5×ULN; >3×ULN with the appearance of worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.	• Closely monitor LFTs at least weekly or more frequently as indicated. • Assess subjects for other causes of transaminitis (eg, past medical history, concomitant medications).	None
3	>5 to 20×ULN; >5×ULN for >2 weeks	Same as for Grade 2.	Hold TAK-228(s) until ≤Grade 1; Restart TAK-228 at the same dose;
4	>20×ULN	Same as for Grade 2.	Stop TAK-228 and discontinue subjects from the study
Prevention/Prophylaxis: Ensure proper screening of subjects for study participation.			

LFTs=liver function tests, ULN=upper limit of normal.

6.4 Sorafenib Dose Modifications

Dose adjustment for sorafenib will be per standard of care.

Table of Dose Adjustments for Sorafenib Dosing on a BID Scheduling

Dose Level	Sorafenib Dose
1	400mg PO BID
-1	400mg PO QD (once a day)
-2	400mg PO QOD (every other day)
-3	Discontinue

Level 1 is the starting dose.

6.5 Management of Sorafenib Clinical Events

6.5.1 Sorafenib Dose Modifications for Skin Toxicity

Dose modifications for Rash (Maculopapular) or Palmar-Plantar Erythrodysesthesia (Hand-Foot Syndrome; HFSR)		
Grade	**Appearance**	**Sorafenib Dose Modification**
Grade 2	1st	Interrupt sorafenib until skin toxicity improves to ≤ grade 1, then resume sorafenib at the previous dose level.
	2nd or 3rd	Interrupt sorafenib until skin toxicity improves to ≤ grade 1, then resume sorafenib at one reduced dose level
	4th	Discontinue all protocol therapy
Grade 3	1st or 2nd	Interrupt sorafenib until skin toxicity improves to ≤ grade 1, then resume sorafenib at one reduced dose level
	3rd	Discontinue all protocol therapy

If sorafenib is interrupted for more than 3 weeks for skin toxicity, discontinue all protocol therapy.

Following a full cycle of reduced dose sorafenib with no rash (maculopapular) or HFSR of ≥ grade 1 severity, the dose of sorafenib may be re-escalated to the prior dose level.

6.5.1.1 Management of Skin Toxicity:
At first occurrence of HFSR, independent of grade, supportive measures such as topical emollients, low potency steroids, or urea-containing cream should be administered.

6.5.2 Sorafenib Dose Modifications for Hypertension

Description	Sorafenib Dose Modification
> 140/90 and ≤ 160/100	Continue sorafenib. Consider adding or adjusting anti-hypertensive medications.
persistent (> 160/100) or symptomatic hypertension	Interrupt sorafenib. Resume when blood pressure improves to ≤ 160/100.

If sorafenib is interrupted for more than 3 weeks, contact the BTCRC Project Manager regarding continuation of therapy.

6.5.3 Other Non-hematologic toxicities

Grade 3: For other grade 3 toxicity considered at least possibly related to sorafenib, interrupt sorafenib until toxicity improves to ≤ grade 1.
If sorafenib is interrupted for more than 3 weeks, discontinue all protocol therapy.

Grade 4: Discontinue all protocol therapy

6.5.4 Hematology toxicities

Grade 4 neutropenia, thrombocytopenia, neutropenic fever: Interrupt sorafenib until ≤ grade 2, and then resume with one dose level reduction of sorafenib for all subsequent doses.

7 STUDY CALENDAR & EVALUATIONS

Study Day	Prior to registration	Cycle 1 (±3) Cycle = 28 days[3]				Cycle 2 (±3)				Cycle 3+ (±3)	Every 2 cycles	End of treatment	Follow Up
	-28 days	D 1[5]	D 8	D 15	D 22	D 1	D 8	D 15	D 22	Day 1	Day 1 (±7) C3, 5, 7 . . .	30 days (±7) post Tx	(±14)
TESTS AND OBSERVATIONS													
Medical History	X												
Physical Exam	X	X	X	X	X	X		X		X		X	
Height, SpO_2[1]	X												
Vital Signs[2]	X	X	X	X	X	X		X		X		X	
ECOG Performance Status	X	X	X	X	X	X		X		X		X	
Adverse Events		X	X	X	X	X		X		X		X	
Concomitant Medication Log	X	X	X	X	X	X		X		X			
Drug Diary Review		X	X	X	X	X		X		X			
12 Lead ECG	X												
LABORATORY ASSESSMENTS[3]													
Complete Blood Count + Differential[4]	X	X		X		X		X		X			
Comprehensive Metabolic Panel[5]	X	X		X		X		X		X			
Urinalysis	X	X				X				X			
LDH	X					X				X			
Calculated Creatinine Clearance	X					X				X			
HBsAg, HBcAb, HCVAb[18]	X												
PT, INR, PTT	X					X				X			
TSH	X					X				X			
Alpha-fetoprotein	X					X				X			
Child Pugh Score (see SPM)	X					X				X			
Pregnancy test (WOCBP)[19]	-7days	X				X				X			
HbA1c	X												
Fasting Lipid Profile[6]	X												
TAK-228 SUBJECTS ONLY													
12 Lead ECG[17]		X				X						X	
HbA1c										q3 cycles			
Fasting serum glucose[16]		X[16]	X	X	X	X[16]		X		X			
At-home fasting blood glucose monitoring		X, daily throughout treatment											
Fasting Lipid Profile[6]						X				X			
DISEASE ASSESSMENT													
CT (arterial, venous phase of liver)[7] or MRI	X										X	None	[X][15]

Study Day	Prior to registration	Cycle 1 (±3) Cycle = 28 days[3]				Cycle 2 (±3)				Cycle 3+ (±3)	Every 2 cycles	End of treatment	Follow Up
	-28 days	D 1[5]	D 8	D 15	D 22	D 1	D 8	D 15	D 22	Day 1	Day 1 (±7) C3, 5, 7 . . .	30 days (±7) post Tx	(±14)
TREATMENT													
TAK-228[8] (all Phase I; Phase II Arm A)		X	X	X	X	X	X	X	X	D1, 8, 15, 22			
Sorafenib (Phase II Arm B)		X →											
CORRELATIVE STUDIES: PHASE II SUBJECTS ONLY													
Pharmacokinetics[9] (1st 10 pts. in Arm A)		D1 D2				D1 D2							
HCC unstained slides or new biopsy[10]	X												
Central analysis of CT/MRI images[11]	X										Best Resp.	At PD	
BANKING SAMPLES: PHASE II SUBJECTS ONLY													
Whole Blood[12]		X											
Unstained slides from HCC tumor[13]		X											
Serum and plasma[14]		X										X	
FOLLOW-UP[15]													
Survival													X

Footnotes:

1: Subjects with O_2 saturation < 90% by ABG (Arterial Blood Gas) analysis or pulse oximetry on room air are excluded. See section 3.2.11.3.

2: Vital signs to include: pulse, blood pressure and weight.

3: C1D1 labs must be verified before subject begins study drug. For subsequent cycles, labs may be obtained up to 3 days prior to day of treatment. Screening labs performed within 7 days of C1D1 do not need to be repeated.

4: Complete Blood Count with differential to include: absolute neutrophil count (ANC), platelet and hemoglobin.

5: Comprehensive Metabolic Panel to include: Na, K, Cl, CO_2, total bilirubin, direct bilirubin, total protein, albumin, alk phos, AST, ALT, creatinine, BUN, calcium, Mg, Phos, and glucose.

6: Fasting lipid profile to include: total cholesterol, LDL, HDL, total triglycerides

7: Preferably CT chest/abdomen/pelvis with triphasic liver scan. If CT contrast is contraindicated despite the use of antihistamines and steroids, CT chest without contrast and MRI of abdomen and pelvis is allowed.

8: TAK-228 will be administered only to eligible subjects under the supervision of the investigator or identified sub-investigator(s) during Cycle 1 for all TAK-228 subjects and during Cycle 2 Day 1 for the first 10 subjects randomized to Phase II arm A; subsequent doses may be taken at home. Sorafenib will be taken at home twice daily.

9: Phase II Arm A subjects only: Pharmacokinetic sampling will be performed on the first 10 subjects randomized to Arm A. PKs will be collected on C1D1-2 and C2D1-2 at the following time points: pre-dose, 0.5, 1, 2, 4, 6, 8, and 24 hours post-dose. See Clinical Laboratory Manual (CLM) for collection, processing, labeling and shipping instructions.

10: Phase II subjects only: Unstained slides will be collected and evaluated for mTOR and PI3K/Akt expression and phosphoproteins via immunohistochemistry (IHC) and oncogene expression affecting mTOR activation via targeted deep sequencing assay. If the subject does not have an

HCC archived tumor tissue block available, the subject must have a biopsy prior to registration to obtain tumor tissue for correlative studies. See CLM for collection, labeling and shipping instructions.

11: Phase II subjects only: CT/MRI images from baseline, best response and disease progression scans will be submitted for central analysis to assess tumor necrosis and modified RECIST (mRECIST) criteria.

12: Phase II subjects only: Submission of whole blood for banking is to be collected at Pre-Treatment Cycle 1 Day 1. See CLM for collection, processing, labeling and shipping instructions.

13: Phase II subjects only: Submission of unstained slides from an archived FFPE tumor block for banking is requested. See CLM for collection, labeling and shipping instructions.

14: Phase II subjects only: Submission of serum and plasma are to be collected at Pre-Treatment Cycle 1 Day 1 and at the End of Treatment visit. See CLM for collection, labeling, processing and shipping instructions.

15: Post treatment follow up: If treatment ended for reasons other than disease progression: every 3 months for 1 year, then every 6 months until progression. After disease progression, report survival status every 6 months until 2 years after progression.

16: TAK-228 subjects only: Fasting serum glucose testing will be performed at each clinic visit. In addition, the first 10 subjects randomized to Phase II Arm A will have fasting serum glucose testing on Cycle 1 Days 1 and 2 and Cycle 2 Days 1 and 2.

17: TAK-228 subjects only: 12-lead ECGs will be collected at pre-dose Cycle 1 Day 1, pre-dose Cycle 2 Day 1, and during the EOT visit. When the timing of an ECG coincides with blood samples for PK or tumor biopsy, the ECG should be completed first.

18: Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), Hepatitis C antibody (HCVAb).

19: Pregnancy test for women of childbearing potential at screening and prior to starting each cycle. Serum pregnancy test at screening; urine pregnancy test is acceptable for all other time points. A positive urine test should be confirmed with a serum test.

7.1 Screening

7.1.1 Within 28 days prior to registration for protocol therapy unless otherwise specified:

- Medical history
- Physical exam
- Pulse, blood pressure, height, weight, O_2 saturation
- ECOG performance status
- Concomitant medications
- 12-lead ECG
- Complete blood count with differential and platelets (absolute neutrophil count (ANC), platelets and hemoglobin)
- Comprehensive metabolic panel (Na, K, Cl, CO_2, total bilirubin, direct bilirubin, total protein, albumin, alk phos, AST, ALT, creatinine, BUN, calcium, Mg, Phos, and glucose)
- Urinalysis
- LDH
- Calculated creatinine clearance (Cockcroft Gault)
- Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibody
- PT, INR, PTT
- TSH
- Alpha-fetoprotein
- Child-Pugh Score (see SPM)
- Serum pregnancy test for females of childbearing potential (within 7 days prior to registration)
- HbA1c
- Fasting lipid profile (total cholesterol, LDL, HDL, total triglycerides)
- CT or MRI
  - Preferably CT chest/abdomen/pelvis with triphasic liver scan. If CT contrast is contraindicated despite the use of antihistamines and steroids, CT chest without contrast and MRI of abdomen and pelvis is allowed. The same imaging modality should be used throughout the study.
- Phase II subjects only:
  - An archived HCC tumor tissue block must be identified prior to registration. If an archived HCC tumor tissue block is not available, the subject must have a biopsy performed prior to registration to obtain HCC tumor tissue for correlative analysis.

7.2 On Treatment

7.2.1 Cycle 1 Day 1:

Note: Cycle 1 Day 1 lab testing need not be repeated if completed within 7 days of starting protocol therapy.

- Physical exam
- Pulse, blood pressure, weight
- ECOG performance status

- Baseline signs/symptoms
- Concomitant medications
- Drug diary distribution/education
- Complete blood count with differential (absolute neutrophil count (ANC), platelets and hemoglobin)
- Comprehensive metabolic panel
- Urinalysis
- Drug administration as outlined in Section 6 and Study Calendar
- Phase II subjects only:
  - Correlative and banking samples. See section 9.0 and CLM for specific instructions.
- TAK-228 subjects only:
  - 12-lead ECG at pre-dose. When the timing of an ECG coincides with blood samples for PK, the ECG should be completed first.
  - Fasting serum glucose will be performed at each clinic visit.
    - Cycle 1 Days 1 and 2: Fasting serum glucose (first 10 Phase II Arm A subjects only).
  - At-home fasting blood glucose monitoring will occur daily.
  - Cycle 1 Day 1-2: PK sampling (first 10 Phase II Arm A subjects only). See section 9.0 and CLM for specific instructions.

7.2.2 Cycle 1 Day 8 (±3 days):

- Physical exam
- Pulse, blood pressure, weight
- ECOG performance status
- Adverse event assessment
- Concomitant medications
- Drug diary review
- Drug administration as outlined in Section 6 and Study Calendar
- TAK-228 subjects only:
  - Fasting serum glucose will be performed at each clinic visit.
  - At-home fasting blood glucose monitoring will occur daily.

7.2.3 Cycle 1 Day 15 (±3 days):

- Physical exam
- Pulse, blood pressure, weight
- ECOG performance status
- Adverse events
- Concomitant medications
- Drug diary review
- Complete blood count with differential (absolute neutrophil count (ANC), platelets and hemoglobin)
- Comprehensive metabolic panel
- Drug administration as outlined in Section 6 and Study Calendar
- TAK-228 subjects only:

- Fasting serum glucose will be performed at each clinic visit.
- At-home fasting blood glucose monitoring will occur daily.

7.2.4 Cycle 1 Day 22 (±3 days):

- Physical exam
- Pulse, blood pressure, weight
- ECOG performance status
- Adverse event assessment
- Concomitant medications
- Drug diary review
- Drug administration as outlined in Section 6 and Study Calendar
- TAK-228 subjects only:
  - Fasting serum glucose will be performed at each clinic visit.
  - At-home fasting blood glucose monitoring will occur daily.

7.2.5 Cycle 2 Day 1 (±3 days):

- Physical exam
- Pulse, blood pressure, weight
- ECOG performance status
- Adverse Events
- Concomitant medications
- Drug diary review
- Complete blood count with differential (absolute neutrophil count (ANC), platelets and hemoglobin)
- Comprehensive metabolic panel
- Urinalysis
- LDH
- Calculated creatinine clearance (Cockcroft Gault)
- PT, INR, PTT
- TSH
- Alpha-fetoprotein
- Child-Pugh Score (see SPM)
- Urine pregnancy test for women of childbearing potential.
- Drug administration as outlined in Section 6 and Study Calendar
- TAK-228 subjects only:
  - 12-lead ECG at pre-dose. When the timing of an ECG coincides with blood samples for PK, the ECG should be completed first.
  - Fasting serum glucose will be performed at each clinic visit.
    - Cycle 2 Days 1 and 2: Fasting serum glucose (first 10 Phase II Arm A subjects only).
  - At-home fasting blood glucose monitoring will occur daily.
  - Fasting lipid profile Cycle 2 Day 1
  - Cycle 2 Day 1-2: PK sampling (first 10 Phase II Arm A subjects only). See section 9.0 and CLM for specific instructions.

7.2.6 Cycle 2 Day 8 (±3 days):

- Drug administration as outlined in Section 6 and Study Calendar

7.2.7 Cycle 2 Day 15 (±3 days):

- Physical exam
- Pulse, blood pressure, weight
- ECOG performance status
- Adverse events
- Concomitant medications
- Drug diary review
- Complete blood count with differential (absolute neutrophil count (ANC), platelets and hemoglobin)
- Comprehensive metabolic panel
- Drug administration as outlined in Section 6 and Study Calendar
- TAK-228 subjects only:
  - Fasting serum glucose will be performed at each clinic visit.
  - At-home fasting blood glucose monitoring will occur daily.

7.2.8 Cycle 2 Day 22 (±3 days):

- Drug administration as outlined in Section 6 and Study Calendar

7.2.9 Cycle 3+ Day 1 (±3 days):

- Physical exam
- Pulse, blood pressure, weight
- ECOG performance status
- Adverse Events
- Concomitant medications
- Drug diary review
- Complete blood count with differential (absolute neutrophil count (ANC), platelets and hemoglobin)
- Comprehensive metabolic panel
- Urinalysis
- LDH
- Calculated creatinine clearance (Cockcroft Gault)
- PT, INR, PTT
- TSH
- Alpha-fetoprotein
- Child-Pugh Score (see SPM)
- Urine pregnancy test for women of childbearing potential.
- Drug administration as outlined in Section 6 and Study Calendar
- TAK-228 subjects only:
  - Fasting serum glucose will be performed at each clinic visit.
  - At-home fasting blood glucose monitoring. If no irregularities in the fasting blood glucose level are observed during a minimum of two consecutive months, the

frequency of in-home fasting blood glucose testing may be reduced to a minimum frequency of once weekly if the investigator approves. See section 6.3.1.
- Fasting lipid profile Day 1 of each cycle
- **Every 3 cycles** (C3, 6, 9, etc.): HbA1c

7.2.10 Day 1 of every 2 cycles (±7 days) (C3, 5, 7, etc.):

- CT (arterial and venous phase of liver) or MRI
  - Preferably CT chest/abdomen/pelvis with triphasic liver scan. If CT contrast is contraindicated despite the use of antihistamines and steroids, CT chest without contrast and MRI of abdomen and pelvis is allowed.

7.3 Off Treatment

7.3.1 Protocol therapy discontinuation:

A subject will be discontinued from the protocol therapy under the following circumstances:

- If there is evidence of disease progression
- If the treating physician thinks a change of therapy would be in the best interest of the subject
- If the subject requests to discontinue protocol therapy
- If the protocol therapy exhibits unacceptable toxicity
- If a female subject becomes pregnant
- If protocol therapy is interrupted for ≥ 28 days for TAK-228, or ≥ 21 days for sorafenib due to a treatment-related adverse event.
- If the subject demonstrates serious or continuing non-compliance

Subjects can stop study participation at any time. However, if they decide to stop, subjects will continue to be followed per section 7.4, Follow-Up, unless the subject has also withdrawn consent for further follow-up.

7.3.2 End of Treatment 30 days (±7 days) after final protocol therapy dose

At the time of protocol therapy discontinuation, all study procedures outlined for the End of Treatment visit should be performed. The primary reason for subject's discontinuation should be recorded in the source documents and eCRF.

- Physical exam
- Pulse, blood pressure, weight
- ECOG performance status
- Adverse Events
- CT/MRI images from baseline, best response and disease progression scans will be submitted for central analysis to assess tumor necrosis and modified RECIST (mRECIST) criteria
- TAK-228 subjects only:
  - 12 lead ECG
- Phase II subjects only:
  - Banking samples. See section 9.0 and CLM for specific instructions.

7.4 Follow-up (±14 days)

If treatment ended for reasons other than disease progression, subjects will be followed for disease progression and survival every 3 months for 1 year, then every 6 months until progression.

After disease progression, survival status should be reported every 6 months until 2 years after progression.

8 CRITERIA FOR DISEASE EVALUATION

8.1 Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [*Eur J Ca* 45:228-247, 2009].

8.1.1 ***Measurable disease***: The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

8.1.2 ***Measurable lesions:*** 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).

Non-measurable lesions: 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 subject, these are preferred for selection as target lesions.

8.1.3 ***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.

8.1.4 ***Baseline documentation of "Target" and "Non-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.

8.2 Response Criteria

8.2.1 *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

8.2.2 *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 subject 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 Sponsor-Investigator.

8.3 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 PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
	Not evaluated	No	PR
PR	Non-CR/ Non-PD/ not evaluated	No	PR
SD	Non-CR/ Non-PD/ not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that

the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

8.4 Definitions for Response Evaluation –RECIST version 1.1

8.4.1 First Documentation of Response:

The time between initiation of therapy and first documentation of PR or CR.

8.4.2 Confirmation of Response:

To be assigned a status of complete or partial response, changes in tumor measurements must be confirmed by repeat assessments performed no less than four weeks after the criteria for response are first met.

8.4.3 Duration of Response:

Duration of overall response – the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

8.4.4 Duration of Overall Complete Response:

The period measured from the time that measurement criteria are met for complete response until the first date that progressive disease is objectively documented.

8.4.5 Objective Response Rate:

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST v1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

8.4.6 Disease Control Rate:

The disease control rate is the proportion of all subjects with stable disease (SD) for 8 weeks, or partial response (PR), or complete response (CR) according to RECIST v1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

8.4.7 Time To Progression:

A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1. Subjects who have not progressed or have died due to any cause will be right-censored at the date of the last disease evaluation or date of death.

8.4.8 Progression Free Survival:

A measurement from the date of randomization until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

8.4.9 Overall Survival:

Overall Survival is defined by the date of randomization to date of death from any cause.

8.5 Methods of Measurement

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 28 days before the beginning of the treatment.

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. The same imaging modality must be used throughout the study to measure disease.

8.5.1 CT and MRI:

CT and MRI are the best currently available and most reproducible methods for measuring target lesions. 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.

8.5.2 Chest X-Ray:

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by an aerated lung (CT is preferable).

8.5.3 Clinical Examination:

Clinically detected lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.

8.5.4 Cytology and Histology:

Cytologic and histologic techniques can be used to differentiate between complete and partial responses in rare cases (e.g. after treatment to differentiate residual benign lesions and residual malignant lesions in germ cell tumors). Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

8.6 mRECIST for HCC: Assessment of Tumor Lesions at Baseline

According to RECIST, tumor lesions are categorized at baseline as follows: measurable (lesions that can be accurately measured in at least one dimension as ≥1 cm with a spiral CT scan) or nonmeasurable [all other lesions, including small lesions (longest diameter <1 cm with spiral CT scan) and truly nonmeasurable lesions]. The original RECIST publication states that all measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. The recent 1.1 release of RECIST has reduced the number of lesions to select as target lesions to a maximum of two lesions per organ and five lesions in total.[42] In fact, analyses on a large prospective database has shown that assessment of five versus 10 lesions per patient did not affect the overall response rate, and that progression-free survival was only minimally affected.[43] Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements. All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

It is our understanding that the measurement of the longest viable tumor diameter for the assessment of response according to mRECIST[44] can be only applied in case of typical lesions. Conversely, for non- enhancing atypical lesions, as well as for any extrahepatic neoplastic niches, the measurements of the longest overall tumor diameter as per conventional RECIST should prevail.

To be selected as a target lesion using mRECIST, an HCC lesion should meet all the following criteria:

- The lesion can be classified as a RECIST measurable lesion (i.e., the lesion can be accurately measured in at least one dimension as 1 cm or more).
- The lesion is suitable for repeat measurement.
- The lesion shows intratumoral arterial enhancement on contrast-enhanced CT or MRI.

It is important to point out that only well-delineated, arterially enhancing lesions can be selected as target lesions for mRECIST. This may not be the case of infiltrative-type HCC. Infiltrative-type HCC should be considered as a nontarget lesion when the mass shows ill-

defined borders and therefore does not appear to be suitable for accurate and repeat measurements. HCC lesions previously treated with locoregional or systemic treatments may or may not be considered as suitable to be selected as target lesions for mRECIST: if the lesion shows a well-delineated area of viable (contrast enhancement in the arterial phase) tumor that is at least 1 cm in longest diameter, then it can be selected as a target lesion. In contrast, if the lesion is poorly demarcated or exhibits atypical enhancement as a result of the previous intervention, then it cannot be selected as a target lesion for mRECIST.

8.7 mRECIST: Defining Treatment Response and Tumor Progression

8.7.1 Target Lesions Response

According to RECIST, complete response is the disappearance of all target lesions; partial response is at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease is at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since when treatment started or the appearance of one or more new lesions; stable disease is neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

The mRECIST for HCC has introduced the following amendments to RECIST in the determination of tumor response for target lesions (see table below):

- Complete response: the disappearance of any intratumoral arterial enhancement in all target lesions
- Partial response: at least a 30% decrease in the sum of diameters of viable (contrast enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
- Progressive disease: an increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since the treatment started
- Stable disease: any cases that do not qualify for either partial response or progressive disease

Assessment of Target Lesion Response: Conventional RECIST and mRECIST Assessment for HCC Following the AASLD-JNCI Guideline	
RECIST	mRECIST for HCC
CR = Disappearance of all target lesions	CR = Disappearance of any intratumoral arterial enhancement in all target lesions
PR = At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of the diameters of target lesions	PR = At least a 30% decrease in the sum of diameters of viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
SD = Any cases that do not qualify for either partial response or progressive disease	SD = Any cases that do not qualify for either partial response or progressive disease
PD = An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	PD = An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started
AASLD, American Association for the Study of Liver Diseases; JNCI, Journal of the National Cancer Institute; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.	

The measurement of the longest diameter of the viable tumor may be challenging in lesions showing partial internal necrosis (Fig. 1). The following points should be taken into account in such cases:

- The measurement of the viable tumor should be performed on CT or MRI obtained in the arterial phase, when the contrast between viable vascularized tumor tissue and nonenhancing necrotic tissue is the highest.
- The longest diameter of the viable tumor is not necessarily located in the same scan plane in which the baseline diameter was measured: a thorough careful evaluation of the CT or MRI scans is required.
- The measurement of the viable tumor diameter should not include any major intervening areas of necrosis.

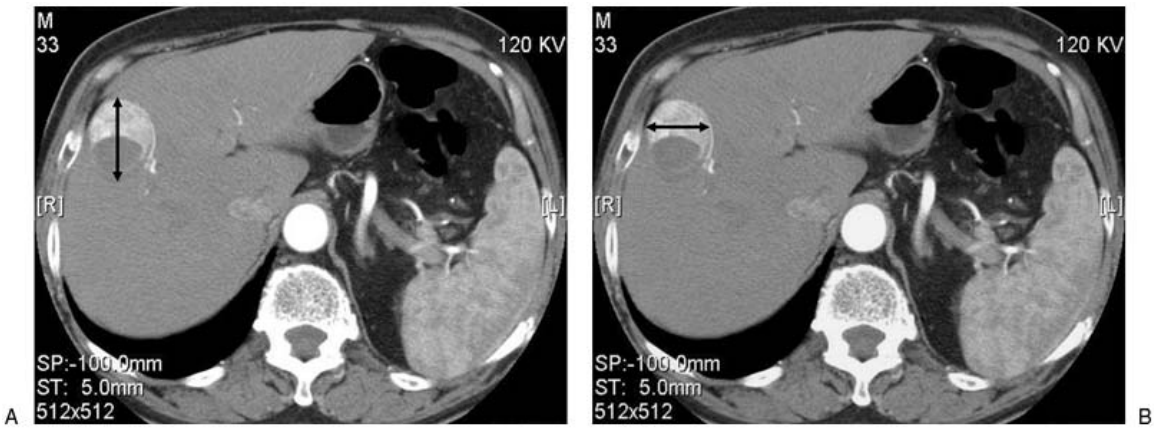


Figure 1 Application of mRECIST assessment for hepatocellular carcinoma (HCC). Target tumor response measurements on arterial-phase computed tomography (CT) scans. (A) Measurement of longest overall tumor diameter according to conventional RECIST, and (B) measurement of longest viable tumor diameter according to mRECIST for HCC.

It is important to point out that a reduction of at least 30% in the diameter of the viable tumor (the threshold required to declare partial response according to mRECIST) corresponds to a decrease of 65% in viable tumor volume. In contrast, an increase of at least 20% in the diameter of the viable tumor (the threshold required to declare progressive disease according to mRECIST) corresponds to an increase of at least 73% in viable tumor volume. The panel acknowledged that direct volumetric measurement to identify partial response and progression should be a priority in future clinical trial research.

8.7.2 Non-Target Lesions Response

The RECIST guideline provides the following definitions of the criteria used to determine the objective tumor response for nontarget lesions: complete response is the disappearance of all nontarget lesions; incomplete response/stable disease is the persistence of one or more nontarget lesions; and progressive disease is the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

According to mRECIST for HCC, tumor necrosis should be taken into account when assessing the response of nontarget lesions. The disappearance of intratumoral arterial enhancement in nontarget lesions should be considered equivalent to the disappearance of nontarget lesions, and therefore, should declare complete response of nontarget lesions. The persistence of intratumoral arterial enhancement in one or more nontarget lesions should be considered equivalent to persistence of one or more nontarget lesions, and therefore, should declare incomplete response / stable disease. The appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions should declare progressive disease.

Special recommendations for the assessment of tumor response in nontarget lesions in subjects with HCC and cirrhosis can be made regarding the following points:

1. Portal vein thrombosis. Malignant portal vein thrombosis should be considered a nonmeasurable lesion due to the difficulty in performing consistent measurements of the malignant thrombus during the course of the treatment. Measurements of the extent

of the malignant thrombus may be impaired by the possible presence of a bland component of the thrombosis.

2. Porta hepatis lymph node. Lymph nodes detected at the portal hepatis can be considered as malignant if the lymph node short axis is at least 20 mm. Evidence of reactive lymph nodes at the porta hepatis, in fact, is a common finding in patients with cirrhosis regardless of the presence of an HCC. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor.
3. Pleural effusion and ascites. The original RECIST publication specifies that cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease (if the neoplastic origin of the fluid is confirmed). The mRECIST for HCC panel of experts considered this issue to be of high importance in the setting of HCC in cirrhosis. The emergence or the increase in ascites is a common event during the course of treatment in a cirrhotic patient, which may be due to worsening of the underlying chronic liver disease and be unrelated to cancer progression.[45] Other effusions, such as pleural effusion, may also be unrelated to cancer progression and be caused by the liver insufficiency. Thus, the mRECIST for HCC emphasizes that cytopathologic confirmation of the neoplastic nature of any effusion (particularly ascites) that appears or worsens during treatment is required when the measurable tumor has met criteria for response or stable disease. It has to be underlined that peritoneal carcinomatosis is a very rare event in HCC.

8.7.3 New Lesions

Characterization of a newly detected focal liver lesion as true HCC is a challenging issue in the setting of cirrhosis because pathologic abnormalities related to cirrhosis changes—such as large regenerative nodules and dysplastic nodules—may be indistinguishable from a small tumor. Moreover, the clear-cut separation of the hepatic phases of liver enhancement routinely achieved by state-of-the-art CT or MRI creates additional problems in a cirrhotic liver, mostly related to the presence of perfusion abnormalities resulting in areas of abnormal liver enhancement. In most cases, such perfusion abnormalities are detected as arterially hyperenhancing areas caused by a selective impairment of the portal venous feeding. Such perfusion abnormalities may ultimately mimic or conceal focal liver lesions; hence, they represent an additional major source for interpretation errors.

The AASLD practice guideline for the clinical management of HCC has recommended strict criteria for the imaging diagnosis of HCC in cirrhosis.[46] Noninvasive diagnostic criteria of HCC can be made without histology in lesions of at least 1 cm in diameter showing characteristic vascular features of HCC—arterial hypervascularization with washout in the portal venous or the late phase—at dynamic imaging studies. For diagnostic purposes, two imaging techniques—CT and MRI—are required for such a confirmation in tumors of 1 to 2 cm in diameter, and one imaging technique in tumors beyond 2 cm in cirrhotic patients.

In the assessment of tumor progression, these concepts have been adopted by the mRECIST assessment proposal, considering some specificities for the frame of progression mode (Fig. 2):

- A newly detected hepatic nodule will be classified as HCC—and therefore will be declared as evidence of progression—when its longest diameter is at least 1 cm and the nodule shows the typical vascular pattern of HCC on dynamic imaging, that is, hypervascularization in the arterial phase with washout in the portal venous or late venous phase.
- Liver lesions larger than 1 cm that do not show a typical vascular pattern can be diagnosed as HCC by evidence of at least 1-cm-interval growth in subsequent scans.
- An individual radiologic event will be adjudicated in retrospect as progression at the time it was first detected by imaging techniques, even if strict criteria were fulfilled only on subsequent radiologic testing.

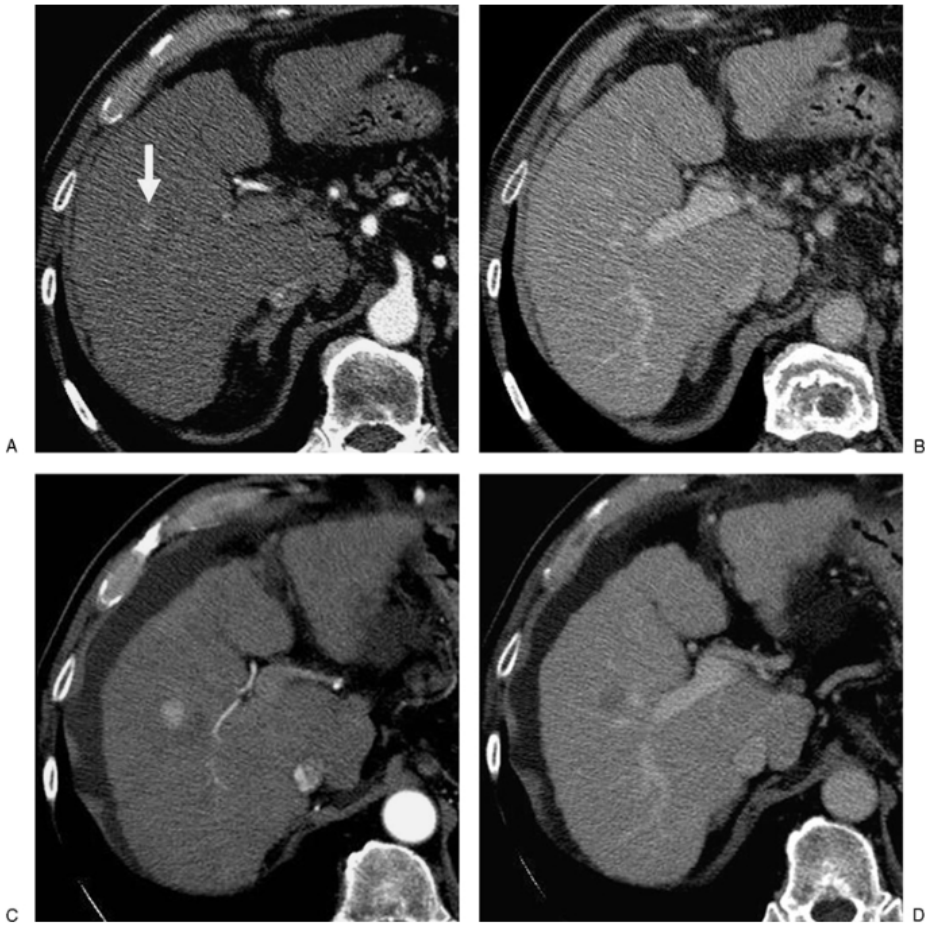


Figure 2 Application of mRECIST assessment for hepatocellular carcinoma (HCC). New lesion. Computed tomography (CT) scans obtained in an HCC patient's follow-up after treatment (main tumor not shown). On scans obtained at time point 1 (A, arterial phase; B, venous phase), a new lesion is identified (arrow). The tiny lesion is smaller than 1 cm; therefore, it must be considered equivocal. On CT scans obtained at time point 2 (C, arterial phase; D, venous phase), the tumor has become larger than 1 cm and shows the characteristic vascular pattern of HCC (arterial hypervascularization with venous washout). Although the criteria for diagnosing the lesion as HCC were fulfilled only at time point 2, progression must be declared in retrospect at time point 1, that is at the time the lesion was first detected.

8.8 mRECIST: Overall Response Assessment

In mRECIST for HCC, identical to conventional RECIST, overall subject response is a result of the combined assessment of target lesions, nontarget lesions, and new lesions (table below). It is important to point out that appearance of one or more new lesions declares progression whatever the response of target and nontarget lesions. Overcalling of equivocal lesions as new HCC, therefore, has a major impact on the outcome of studies with a radiologic endpoint, such as tumor response or time to progression. Hence, any newly detected focal liver lesion that does not meet the criteria reported above should be considered equivocal and not conclusive for disease progression.

Overall Response Assessment in mRECIST: Responses for All Possible Combinations of Tumor Responses in Target and Nontarget Lesions with or without the Appearance of New Lesions

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	IR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

mRECIST, modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; IR, incomplete response; SD, stable disease; PD, progressive disease.

9 BIOLOGICAL CORRELATIVES

Biological correlatives will be performed on Phase II subjects only. Refer to the Correlative Laboratory Manual associated with this protocol for collection, processing, labeling and shipping instructions of biological correlatives.

An archived HCC tumor tissue block must be identified prior to registration. If an archived HCC tumor tissue block is not available, the patient must have a biopsy performed prior to registration to obtain HCC tumor tissue for correlative analysis.

9.1 Evaluate mTOR and PI3K/Akt expression and phosphoproteins via immunohistochemistry (IHC) of phosphorylated Akt, 4EBP1, S6 kinase, and ERK1/2.

Immunohistochemical studies will be performed on unstained slides from an archived formalin-fixed/paraffin-embedded archival tumor tissue. The presence of tumor tissue will be confirmed.. IHC will be performed per standardized protocols including the use of phospho-Akt (Ser473) (1:100, #4060, Cell SignalingTechnology), phospho-4EBP1 (Thr37/46) (1:800, #2855, Cell Signaling Technology), phospho-S6 (Ser235/236) (1:50, #4858, Cell Signaling Technology) and phosphor-ERK1/2 (1:400, #4695, Cell Signaling Technology). Omission of the primary antibody will be used as a negative control along with

positive control tissue. Semi-automated quantitative brightfield assessment of expression will be performed using the Vectra imaging system (PerkinElmer) and inForm analysis software system. A scanning protocol will be generated based on the tissue size and location of the cancer within the sample. Biomarker quantification will be calculated as a continuous variable (mean optical density) and also as quartiles (ex. 0, 1+, 2+, or 3+). Biomarker quantification will then be correlated with treatment response.

In total, 10 unstained slides (FFPE) will be required for all biologic correlatives. See also section 9.4 regarding additional tissue requirements for tissue banking for future studies.

9.2 Characterize oncogene expression affecting mTOR activation via targeted deep sequencing assay designed to interrogate genes commonly mutated in human cancers.
Unstained slides from an archived formalin-fixed paraffin embedded archival tumor specimen for each subject will be obtained. The presence of tumor tissue will be confirmed. Pathology will guide isolation of DNA. Genomic DNA will be prepared from an unstained slide using the Maxwell system as previously described by the manufacturer [Promega, Madison, WI] and stored. Typically, the amount of DNA extracted from tumor specimens range from 1000 to 5000ng from a single slide. Targeted sequencing will be performed using the Ion AmpliSeq Cancer Panel® (Life Sciences). The Ion AmpliSeq Cancer Hotspot Panel v2 is designed to rapidly survey key cancer genes; including ABL1, AKT1, ALK, APC, ATM, BRAF, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, FBXW7, FGFR1-3, FLT3, GNAS, HNF1A, HRAS, IDH1, JAK2, JAK3, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, MARCB1, SMO, SRC, STK11, TP53, VHL for targeted mutations using the Ion Torrent PGM system and commercially available analysis software, such as NextGEN (Softgenetics, LLC). The mutation profiles of the tumors investigated will then be correlated with treatment response to TAK-228.

In total, 10 unstained slides (FFPE) will be required for all biologic correlatives. See also section 9.4 regarding additional tissue requirements for tissue banking for future studies.

9.3 Assess tumor necrosis and modified RECIST (mRECIST) criteria
De-identified images will be stored centrally, and central image analysis performed including tumor necrosis and mRECIST quantification.

9.4 Samples for future studies
Subject consent will be obtained for additional samples collected for future Big Ten Cancer Research Consortium studies. Hoosier Cancer Research Network, as Administrative Headquarters for the BTCRC, will manage the banked samples.

- Central image analysis and storage of de-identified images. These central images will be stored at Northwestern for future use after the planned analysis for this trial.

The following samples will be banked indefinitely in the Hoosier Cancer Research Network biorepository.

- Whole blood:
  - Whole blood will be collected prior to treatment on Cycle 1 Day 1.

- Pre- and Post-treatment plasma:
  - Whole blood for plasma will be collected prior to treatment on Cycle 1 Day 1 and at End of Treatment.
- Pre- and Post-treatment serum:
  - Whole blood for serum will be collected prior to treatment on Cycle 1 Day 1 and at End of Treatment.
- Unstained slides:
  - Unstained slides will be obtained from the subject's archived formalin fixed paraffin embedded tumor sample.

Please refer to the Clinical Laboratory Manual for all sample collection, processing, labeling and shipping instructions.

10 DRUG INFORMATION

10.1 TAK-228

10.1.1 Classification

TAK-228 selectively and potently inhibits mTOR kinase (the concentration inhibiting 50% of enzyme activity [IC50] is 1.1 nM), inhibits mTORC1/2 signaling, and prevents cellular proliferation.

TAK-228 inhibited phosphorylation of downstream modulators of mTORC1and mTORC2 in human U87 glioblastoma tumor xenograft models in mice and showed strong tumor growth inhibition (TGI) at tolerable oral (PO) doses in all 8 xenograft models tested.

10.1.2 Mechanism of Action

TAK-228 selectively and potently inhibits mTOR kinase (IC_{50} = 1.1 nM), inhibits mTORC1/2 signaling, and prevents cellular proliferation. The mTOR is a kinase that regulates cell growth, translational control, angiogenesis, and cell survival by integrating nutrient and hormonal signals. mTOR kinase plays a key role in several pathways that are frequently dysregulated in human cancer.[36] mTORC1 is best known as a key regulator of protein translation through phosphorylation of 4EBP1 (the eukaryotic translation Initiation Factor 4E-binding Protein 1) and ribosomal protein S6 (known as S6) kinase. mTORC2 is best known for its ability to fully activate protein kinase B (Akt) by phosphorylation on the S473 site, which regulates proliferation and survival pathways.[37]

10.1.3 Availability

TAK-228 will be supplied by Millennium Pharmaceuticals as capsules for oral administration. The TAK-228 capsule contains milled active pharmaceutical ingredient (API). The study drug is available in 3 dose strengths, 1 mg, 3 mg, and 5 mg, each containing 1 mg, 3 mg, and 5 mg of TAK-228, respectively, in addition to the following inactive ingredients: microcrystalline cellulose (solid filler/diluents), magnesium stearate (lubricant), and hard gelatin capsule. All 3 dose strengths are formulated into size 2 capsules, and each dose strength is differentiated by color, as listed below:

- TAK-228 capsules, 1 mg – white opaque color
- TAK-228 capsules, 3 mg – orange opaque color; and/or
- TAK-228 capsules, 5 mg – grey opaque color

10.1.4 Storage, Handling and Accountability

TAK-228 should be stored at controlled room temperature 15°C to 30°C (59°F to 86°F). All study supplies must be kept in a restricted access area.

Because TAK-228 is an investigational agent, it should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (e.g., from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Accountability for TAK-228 at all study sites is the responsibility of the sponsor-investigator.

10.1.5 Preparation, Reconstitution, and Dispensing

TAK-228 study drug will be provided in 60 cc high-density polypropylene (HDPE) bottles with polypropylene, child-resistant caps and induction seal. Study drug will be dispensed with dosing instructions for home use, including the requirement that capsules are stored in their original containers and that capsules be swallowed whole and not opened, chewed, or manipulated in any way. Materials provided by the sponsor should be dispensed to subjects with clear administration instructions from the investigator.

TAK-228 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling TAK-228 capsules.

Study drug will be administered or dispensed only to eligible subjects under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

10.1.6 Interactions with Other Medicaments and Other Forms of Interaction

Clinical drug-drug interaction studies have not been conducted with TAK-228. At this time, there are no known drug interactions. In vitro data, including cytochrome P450 induction/inhibition and transporter inhibition studies conducted for TAK-228, suggest a low risk for TAK-228 to precipitate a drug-drug interaction. Although potential drug-drug interactions with TAK-228 cannot be ruled out based on the known metabolism characteristics of TAK-228, the potential risk is considered low.

10.1.7 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints,
call MedComm Solutions at
Phone: 1-866-VELCADE (1-866-835-2233)
E-mail: ***GlobalOncologyMedinfo@takeda.com***
Millennium study number: IISR-2014-100530 (Bert O'Neil, MD)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to BTCRC Administrative Headquarters (See Section 11.3).

10.1.8 Special Warnings and Special Precautions for Use

Insulin and Glucose Levels

Hyperglycemia and hyperinsulinemia are known toxicities associated with inhibition of mTOR (mechanistic [formerly mammalian] target of rapamycin) and related pathways based on nonclinical studies.

A rise in fasting plasma glucose has been observed as early as 1 to 2 days following oral administration of TAK-228. Daily in-home glucose monitoring and early initiation of treatment of the hyperglycemia are essential. For subject self-monitoring of blood glucose, a finding of fasting blood glucose ≥ 150 mg/dL measured by glucometer would initiate closer monitoring of serum glucose and possible intervention. Subjects with Grade 1 hyperglycemia (fasting serum glucose [FSG] > the upper limit of the normal range ≤ 160 mg/dL) are treated with oral hypoglycemic agents (e.g., metformin), and subjects with ≥ Grade 2 hyperglycemia (FSG > 160 mg/dL) are treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated. Daily home monitoring and early treatment, as noted previously, have resulted in good control of glucose levels for the majority of TAK-228-treated subjects who developed hyperglycemia.

Cardiac Effects

Cardiac events (including QT interval corrected for heart rate prolongation and arrhythmias) have been infrequently observed in clinical studies of TAK-228. As of 9December 2015, there has been 1 report of ventricular fibrillation and cardiac arrest post-dose that had a fatal outcome and was assessed as related to TAK-228. Routine cardiac monitoring with baseline and on-study electrocardiograms (ECGs) and physical examination constitute the core cardiac safety monitoring in all TAK-228 studies.

Preliminary results from a dedicated study of the effects of TAK-228 on the QTc interval (study C31002) show lack of clinically relevant effects on QTc interval, PR and QRS intervals, minimal effects on heart rate, and absence of treatment-emergent ECG morphology findings and therefore the treatment with TAK-228 is not associated with clinically meaningful effects on the overall electrocardiographic safety profile (further details available in the current IB version).

For subjects showing any signs of cardiac instability after TAK-228 dosing, additional monitoring onsite before clinic discharge should be considered.

Renal Function
Elevations in creatinine (regardless of causality) have been observed in subjects receiving TAK-228, all of which have been reversible with drug interruption and/or supportive care with intravenous (IV) hydration. Further evaluation of the renal insufficiency with urine electrolytes suggested a pre-renal etiology with a low fractional excretion of sodium < 1%. However, the adverse event cases were confounded by multiple factors such as nausea, vomiting, hyperglycemia, concomitant medications with GI side effects such as metformin, and hydronephrosis, any of which may have also contributed to dehydration and elevated creatinine. Subjects should be encouraged to drink at least 20 ounces of fluids a day, especially on days requiring fasting (per protocol), with administration of IV fluids in the clinic as indicated to avoid dehydration.

Baseline macroscopic urinalysis and routine serum chemistries along with other safety laboratory assessments are performed in all TAK-228 studies. Additionally, microscopic urinalysis, a 12-hour urine collection, spot urine electrolytes, protein and creatinine, and serum chemistry should be collected at any time when the serum creatinine is ≥ Grade 1, according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4, to further evaluate possible etiologies for the renal dysfunction.

Rash
Rash observed in clinical studies of TAK-228 tends to be maculopapular and pruritic and has ranged from Grade 1 to 3. For the most part, rash and pruritus improve with antihistamines, topical steroid creams, and/or dose interruption. Some subjects have required pulse systemic steroids, dose reduction, and/or study treatment discontinuation.

Pneumonitis
Pneumonitis is a known potential risk of mTOR inhibitors. Early recognition, prompt intervention, and a conservative risk management approach are recommended due to pneumonitis that has been observed with rapalog therapy and with TAK-228 administration. Symptoms of pneumonitis will be closely monitored in all TAK-228 study subjects.

Please reference the current TAK-228 Investigator's Brochure for a complete list of adverse reactions.

10.2 Sorafenib

10.2.1 Classification
Kinase inhibitor (Raf, VEGFR, and PDGFR)

10.2.2 Mechanism of Action
Sorafenib is a kinase inhibitor that decreases tumor cell proliferation *in vitro*.

Sorafenib was shown to inhibit multiple intracellular (c-CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT-3, RET, RET/PTC, VEGFR-1, VEGFR-2, VEGFR-3, and PDGFR-ß). Several of these kinases are thought to be involved in tumor cell signaling, angiogenesis and apoptosis. Sorafenib inhibited tumor growth of HCC, RCC, and DTC human tumor xenografts in immunocompromised mice. Reductions in tumor angiogenesis were seen in models of HCC and RCC upon sorafenib treatment, and increases in tumor apoptosis were observed in models of HCC, RCC, and DTC.

10.2.3 Availability
Sorafenib tablets are supplied as round, biconvex, red film-coated tablets, debossed with the "Bayer cross" on one side and "200" on the other side, each containing sorafenib tosylate equivalent to 200 mg of sorafenib.

Commercial supplies of sorafenib will be used in this study and billed to third party payers or the subject.

10.2.4 Storage
Store at 25° C (77° F); excursions permitted to 15–30° C (59–86° F) (see USP controlled room temperature). Store in a dry place.

10.2.5 Administration
Following oral administration, sorafenib's mean relative bioavailability is 38-49%. When given with a moderate fat meal, bioavailability was similar to that in the fasted state. With a high fat meal, sorafenib's bioavailability was reduced by 29% compared to administration in the fasted state. Thus, it is recommended that sorafenib be taken on an empty stomach (at least 1 hour before or 2 hours after eating) and with at least 250 mL of water.

10.2.6 Drug Interactions
Sorafenib is neither a clinically meaningful inhibitor nor a clinically meaningful inducer of CYP2C19, CYP2D6, and CYP3A4 isoenzymes and is not expected to significantly increase or decrease the exposure of co-administered compounds metabolized by these pathways. However, concomitant administration of sorafenib and CYP3A4 inducers, such as phenytoin, carbamazepine, phenobarbital, rifampin, or St. John's wort, should be avoided. Co-administration with doxorubicin or docetaxel leads to a moderate increases in doxorubicin exposure and docetaxel AUC, respectively. Co-administration with irinotecan leads to a significant increase in SN-38 (i.e., the active metabolite of sorafenib, which is eliminated by UGT1A9) exposure.

10.2.7 Side Effects

The following additional drug-related adverse reactions and laboratory abnormalities were reported from clinical trials of sorafenib (*very common* 10% or greater, *common* 1 to less than 10%, *uncommon* 0.1% to less than 1%):

Cardiovascular: *Common*: congestive heart failure*†, myocardial ischemia and/or infarction *Uncommon*: hypertensive crisis* *Rare*: QT prolongation*

Dermatologic: *Very common*: erythema *Common*: exfoliative dermatitis, acne, flushing *Uncommon*: folliculitis, eczema, erythema multiforme, keratoacanthomas/squamous cell cancer of the skin

Digestive: *Very common*: increased lipase, increased amylase *Common*: mucositis, stomatitis (including dry mouth and glossodynia), dyspepsia, dysphagia *Uncommon*: pancreatitis, gastrointestinal reflux, gastritis, gastrointestinal perforations*, cholecystitis, cholangitis

Note that elevations in lipase are very common (41%, see below); a diagnosis of pancreatitis should not be made solely on the basis of abnormal laboratory values

General Disorders: *Very common*: hemorrhage (including gastrointestinal* & respiratory tract* and uncommon cases of cerebral hemorrhage*), asthenia, pain (including mouth, bone, and tumor pain) *Common*: decreased appetite, influenza-like illness, pyrexia *Uncommon*: infection

Hematologic: *Very common*: leukopenia, lymphopenia *Common*: anemia, neutropenia, thrombocytopenia *Uncommon*: INR abnormal

Hypersensitivity: *Uncommon*: hypersensitivity reactions (including skin reactions and urticaria)

Metabolic and Nutritional: *Very common*: hypophosphatemia *Common*: transient increases in transaminases, hypocalcemia, hypokalemia *Uncommon*: dehydration, hyponatremia, transient increases in alkaline phosphatase, increased bilirubin (including jaundice), hypothyroidism, hyperthyroidism

Musculoskeletal: *Common*: arthralgia, myalgia

Nervous System and Psychiatric: *Common*: depression *Uncommon*: tinnitus, reversible posterior leukoencephalopathy*

Renal and Genitourinary: *Common*: renal failure, proteinuria *Rare*: Nephrotic syndrome

Reproductive: *Common*: erectile dysfunction *Uncommon*: gynecomastia

Respiratory: *Common*: hoarseness *Uncommon*: rhinorrhea, interstitial lung disease-like events (includes reports of pneumonitis, radiation pneumonitis, acute respiratory distress, interstitial pneumonia, pulmonitis and lung inflammation)

In addition, the following medically significant adverse reactions were uncommon during clinical trials of sorafenib: transient ischemic attack, arrhythmia, and thromboembolism. For these adverse reactions, the causal relationship to sorafenib has not been established.

*adverse reactions may have a life-threatening or fatal outcome.
†reported in 1.9% of subjects treated with sorafenib (N= 2276).

10.2.8 Warnings and Precautions

Risk of Cardiac Ischemia and/or Infarction
In the HCC study, the incidence of cardiac ischemia/infarction was 2.7% in sorafenib-treated subjects compared with 1.3% in the placebo-treated group and in RCC Study 1, the incidence of cardiac ischemia/infarction was higher in the sorafenib-treated group (2.9%) compared with the placebo-treated group (0.4%). Subjects with unstable coronary artery disease or recent myocardial infarction were excluded from this study. Temporary or permanent discontinuation of sorafenib should be considered in subjects who develop cardiac ischemia and/or infarction.

Risk of Hemorrhage
An increased risk of bleeding may occur following sorafenib administration. In the HCC study, an excess of bleeding regardless of causality was not apparent and the rate of bleeding from esophageal varices was 2.4% in sorafenib-treated subjects and 4% in placebo-treated subjects. Bleeding with a fatal outcome from any site was reported in 2.4% of sorafenib-treated subjects and 4% in placebo-treated subjects. In RCC Study 1, bleeding regardless of causality was reported in 15.3% of subjects in the sorafenib-treated group and 8.2% of subjects in the placebo-treated group. The incidence of CTCAE Grade 3 and 4 bleeding was 2% and 0%, respectively, in sorafenib-treated subjects, and 1.3% and 0.2%, respectively, in placebo-treated subjects. There was one fatal hemorrhage in each treatment group in RCC Study 1. If any bleeding necessitates medical intervention, permanent discontinuation of sorafenib should be considered.

Risk of Hypertension
Monitor blood pressure weekly during the first 6 weeks of sorafenib, in accordance with standard medical practice. Thereafter, monitor blood pressure and treat hypertension, if required, in accordance with standard medical practice. In the HCC study, hypertension was reported in approximately 9.4% of sorafenib-treated subjects and 4.3% of subjects in the placebo-treated group. In RCC Study 1, hypertension was reported in approximately 16.9% of sorafenib-treated subjects and 1.8% of subjects in the placebo-treated group. Hypertension was usually mild to moderate, occurred early in the course of treatment, and was managed with standard antihypertensive therapy. In cases of severe or persistent hypertension despite institution of antihypertensive therapy, consider temporary or permanent discontinuation of sorafenib. Permanent discontinuation due to hypertension occurred in 1 of 297 sorafenib-treated subjects in the HCC study and 1 of 451 sorafenib-treated subjects in RCC Study 1.

Risk of Dermatologic Toxicities
Hand-foot skin reaction and rash represent the most common adverse reactions attributed to sorafenib. Rash and hand-foot skin reaction are usually CTCAE Grade 1 and 2 and generally appear during the first six weeks of treatment with sorafenib. Management of dermatologic toxicities may include topical therapies for symptomatic relief, temporary treatment interruption, and/or dose modification of sorafenib, or in severe or persistent cases, permanent discontinuation of sorafenib. Permanent discontinuation of therapy due to

hand-foot skin reaction occurred in 4 of 297 sorafenib-treated subjects with HCC and 3 of 451 sorafenib-treated subjects with RCC.
There have been reports of severe dermatologic toxicities, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These cases may be life threatening. Discontinue sorafenib if SJS or TEN are suspected.

Risk of Gastrointestinal Perforation
Gastrointestinal perforation is an uncommon adverse reaction and has been reported in less than 1% of patients taking sorafenib. In some cases, this was not associated with apparent intra-abdominal tumor. In the event of a gastrointestinal perforation, discontinue sorafenib.

Warfarin
Infrequent bleeding or elevations in the International Normalized Ratio (INR) have been reported in some patients taking warfarin while on sorafenib. Monitor subjects taking concomitant warfarin regularly for changes in prothrombin time (PT), INR, or clinical bleeding episodes.

Wound Healing Complications
No formal studies of the effect of sorafenib on wound healing have been conducted. Temporary interruption of sorafenib is recommended in subjects undergoing major surgical procedures. There is limited clinical experience regarding the timing of reinitiation of sorafenib following major surgical intervention. Therefore, the decision to resume sorafenib following a major surgical intervention should be based on clinical judgment of adequate wound healing.

Please reference the current US prescribing information for a complete list of sorafenib adverse reactions.

10.2.9 Nursing Considerations

- Monitor for jaundice.
- Evaluate subject for GI intolerance.
- Sorafenib should be taken on an empty stomach (at least 1 hour before or 2 hours after eating) and with at least 250 mL of water.

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse Event (AE):

Any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with the treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

11.1.2 Serious Adverse Event (SAE):

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Serious vs. Severe:

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous.

The general term ***severe*** is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as ***serious***, which is based on subject/event outcome or action criteria described above, and is usually associated with events that pose a threat to a subject's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of $1000/mm^3$ to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

11.1.3 Unexpected Adverse Event:

An adverse event not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the Investigator's Brochure or package insert.

11.1.4 Causality

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	The Adverse Event is *clearly not related* to the study drug(s)
Unlikely	The Adverse Event is *doubtfully related* to the study drug(s)
Possible	The Adverse Event *may be related* to the study drug(s)
Probable	The Adverse Event is *likely related* to the study drug(s)
Definite	The Adverse Event is *clearly related* to the study drug(s)

11.2 Reporting

AEs may be spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Adverse events (AEs) will be recorded from the time of consent and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications.

All AEs considered related to study drug(s) will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

11.3 Serious Adverse Event (SAE) Reporting

11.3.1 Site Requirements for Reporting SAEs to BTCRC AHQ:

Adverse Events which are serious must be reported from the initiation of study drug(s) and for 30 days after administration of the last dose of study drug(s). Any SAE that occurs at any time after treatment discontinuation or after the designated follow-up period that the site investigator and/or sub-investigator considers to be related to any study drug must be reported. Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the trial are not to be considered SAEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). Deaths due to unequivocal progression are not SAEs. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

Investigators and other site personnel must report any SAE within **one business day** of discovery of the event. This includes events both related and unrelated to the investigational product.

The completed SAE Submission Form (see SPM) must be faxed (317-921-2053) or e-mailed (SAFETY@hoosiercancer.org) to Big Ten Cancer Research Consortium (BTCRC) Administrative Headquarters (AHQ) within one business day of discovery of the event. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

The SAE report must include at minimum:

- Event term(s)
- Serious criteria
- Intensity of the event(s): site investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- Causality of the event(s): site investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration. Relationship to all study drugs for each SAE will be determined by the site investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

A copy of the SAE Submission Form can be found in the Study Procedures Manual (SPM).The original SAE report along with e-mail correspondence and/or the fax confirmation sheet must be kept within the study file at the study site.

SAE follow-up information must be submitted via e-mail or faxed to BTCRC AHQ, using the SAE Submission Form. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable), and whether the subject continued or withdrew from study participation.

11.3.2 Site Procedures for Reporting Drug Exposure during Pregnancy and Birth Events to BTCRC AHQ

If a female subject becomes pregnant or suspects that she is pregnant while participating in this study (i.e. from the initiation of study drug(s) through 90 days after the last dose of study drug), she must inform the investigator immediately and permanently discontinue study drug. The site investigator must fax a completed Clinical Pregnancy Report (see SPM) to BTCRC AHQ within 1 business day. BTCRC AHQ will submit the form to the Millennium Department of Pharmacovigilance or designee. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male subject becomes pregnant during the male subject's participation in this study (i.e. from the initiation of study drug(s) through 120 days after the last dose of study drug), the site investigator must also immediately fax a completed

Clinical Pregnancy Report to BTCRC AHQ within 1 business day. BTCRC AHQ will submit the form to the Millennium Department of Pharmacovigilance or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11.3.3 BTCRC AHQ Requirements for Reporting SAEs to Millennium Pharmacovigilance: BTCRC AHQ will report all SAEs, regardless of expectedness or causality, to Millennium Pharmacovigilance.

- Fatal and Life Threatening SAEs: within 1 business day of awareness of the event.
- All other serious (non-fatal/non-life threatening) events: within 4 calendar days of awareness of the event. See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

Since this is a multisite study, the sponsor-investigator has delegated responsibility to BTCRC AHQ to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Site investigators must centrally report all SAEs to BTCRC AHQ so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance.

SAE and Pregnancy Reporting Contact Information

US and Canada
Fax Number: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com

BTCRC AHQ will fax or email the SAE Submission Form or MedWatch to Cognizant and will provide follow-up information as reasonably requested.

11.4 BTCRC AHQ Requirements for Reporting SAEs to FDA

BTCRC AHQ has been designated to manage the Investigational New Drug Application (IND) associated with this protocol on behalf of Bert O'Neil, M.D., sponsor-investigator. BTCRC AHQ will cross-reference this submission to Millennium/ Takeda's parent IND at the time of submission. Additionally, HCRN will submit a copy of these reports to Millennium/ Takeda at the time of submission to FDA.

BTCRC AHQ will report to the FDA any AE that is serious, unexpected and reasonably related (i.e., possible, probably, definite) to the study treatment.

7-day Reporting:
According to CFR 312.32, unexpected fatal or life-threatening events possibly related with the use of the study drug (drugs) will be reported to the FDA by fax or by phone as soon as possible, but in no event later than 7 calendar days after the initial receipt of the information regarding the event. The fax should be sent to the FDA project manager assigned to the IND. A comprehensive

written report will be submitted as an amendment to the IND within an additional 8 days (15 calendar days total).

15-day Reporting:
All other serious unexpected events associated with the use of the study drug will be reported to FDA as an amendment to the IND as soon as possible, but in no event later than 15 calendar days after initial receipt of the information regarding the event.

BTCRC AHQ will be responsible for all communication with the FDA including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally, BTCRC AHQ will submit a copy of these reports to Millennium Pharmacovigilance at the time of submission to FDA.

11.5 IND Safety Reports Unrelated to This Trial

Millennium Pharmacovigilance will send IND safety reports not occurring on this trial but involving the study intervention (outside SAEs) to BTCRC AHQ (SAFETY@hoosiercancer.org). BTCRC AHQ will forward the safety reports to the sponsor-investigator who will review the reports and determine if any revisions are needed to the protocol or consent. BTCRC AHQ will make the reports available to participating sites via OnCore.

Upon receipt from BTCRC AHQ, site investigators (or designees) are responsible for submitting the safety reports to their Institutional Review Boards per their local guidelines.

12 STATISTICAL CONSIDERATIONS

12.1 General Considerations

Statistical analysis of this study will be the responsibility of Biostatistics and Data Management Core at Indiana University Melvin and Bren Simon Cancer Center (IUSCC). Parameter estimates and relevant summary statistics will be reported where appropriate. For continuous variables, summary statistics will include number of subjects, mean, median, standard deviation, minimum and maximum. Categorical endpoints will be summarized using number of subjects, frequency, and percentages. Missing data will not be imputed. Data analysis will be performed in SAS Version 9.3.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Changes from this analysis plan will not require an amendment to the protocol unless it changes a significant feature of the protocol.

12.2 Study Design

This will be an open-label Phase I/II study. Phase I is a traditional 3+3 design with three dose levels (15, 20, and 30 mg QW). See Section 5.4.2 for specific details. This will be followed by a randomized phase II clinical trial. Eligible subjects will be 1:1 randomized to either TAK-228 or sorafenib. Block randomization stratified by CP score (5-6 vs. 7) will be adopted with varying block sizes.

12.3 Analysis Datasets

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Efficacy	This will comprise all subjects who have a baseline disease evaluation, have received at least one dose of study drug and have had at least one post-baseline disease evaluation. All subjects will be analyzed in the group to which they were randomized, regardless of which treatment was administered.
Safety	This will comprise all subjects who received at least 1 dose of study drug.
Pharmacokinetic	This will comprise the first 10 subjects in TAK-228 study arm who will undergo PK data collection.

12.4 Sample Size/Accrual/Study Duration/Replacement Rules

The sample size for Phase I will depend on the DLTs observed and could range from 3 to 18.

For the Phase II study, therapy with sorafenib in subjects with CPA cirrhosis was associated with a median TTP of 5.5 months. Given inclusion of CP 7 subjects (technically CPB), we would anticipate a median TTP of 12-week for sorafenib. In this Phase II study, we assume that TAK-228 will increase TTP from 50% to 70% at week 12. A 10% dropout rate is expected for the sorafenib arm and a similar dropout pattern is expected for the TAK-228 arm. Enrollment is expected to be completed in 24 months. Subjects will be followed for a total of 2 years after progression. Two-sided log-rank test will be used to compare TTP at type I error level 0.05. Consequently, N=44 subjects per group are required to obtain a power level of 0.80. Subjects not evaluable for response will be replaced, so we further adjust the sample size to N=50 per group to account for potentially unevaluable subjects.

The expected accrual rate is 5 subjects/month. The accrual is based on an initial estimate reflecting accrual of previous phase II studies in HCC conducted by different groups, and upon the participation of additional groups within the BTCRC. Total expected accrual is 88 minimum, and 100 maximum. We do not expect any differences in accrual compared to historical controls.

12.5 Subject Characteristics and Significant Protocol Violations

Subject demographics and subject baseline characteristics will be listed and summarized for all subjects enrolled, including age, gender, and race by phase. Counts, means, medians, standard deviation, minimum and maximum values will be presented. For Phase II, the treatment groups will be compared using either Student's *t*-test or Pearson's chi-square test. Significant protocol violations will be listed.

12.6 Concomitant Medication

Concomitant medication use will be tabulated by phase and by treatment group for Phase II.

12.7 Disposition

Subject disposition will be tabulated by phase and treatment group for Phase II and will show the number of subjects enrolled, and the number of subjects completing the study. All reasons for discontinuation will be listed and summarized.

12.8 Exposure/Compliance

Pill counts/missed doses will be obtained at each visit in order to assess compliance. Cumulative dose will be calculated for each subject and descriptive statistics will be presented by phase and treatment group for Phase II.

12.9 Analysis of Primary Objectives/Aims

This will be done in the Efficacy population following the intent-to-treat principle (analyze as randomized). The primary objective in the Phase I cohort is to determine the maximum tolerated dose, and the primary objective in the Phase II cohort is time to progression (TTP). For Phase I, we will count the number of subjects and DLTs per dose cohort. For the Phase II cohort, Kaplan-Meier curves will be plotted for each treatment group. Median TTP times will be computed, and TTP rate at 4 months +/- 1 week will be calculated with associated 95% confidence intervals. Survival curves will be compared using the log-rank test.

12.10 Analysis of Secondary Objectives/Aims

Phase I:
All analyses of secondary objectives will be by listings/tabulations only and reported by dose cohort.

Phase II:
OS and PFS will be analyzed similarly to the primary outcome. For OS, Cox regression will be used to evaluate the effects of oncogenic abnormalities on survival times.

Preliminary information will be collected for treatment related toxicity and tolerance in the safety population. Toxicity will be graded using the NCI's Common Terminology Criteria for Adverse Events version 4 (CTCAE v4). Treatment tolerance will be based on the number of treatment delays and dose reductions. Information will be presented in a tabular and descriptive manner. Proportion of subjects with each grade of toxicity will be computed along with 95% confidence intervals, and reported in a tabular and descriptive manner. Toxicity will be compared by treatment group using chi-square or Fisher's exact tests.

Objective Response rate (ORR) and Disease control rate (DCR) will be estimated by proportions with 95% confidence intervals by treatment group and reported graphically via waterfall plot.

12.11 Tertiary/Exploratory/Correlative Endpoints (Phase II subjects only)

Pharmacokinetics
Pharmacokinetics (PK) will be evaluated in first 10 subjects in TAK-228 arm at predose, 0.5, 1, 2, 4, 6, 8, and 24 hours on C1D1 and C2D1. An exploratory analysis will be assessed and correlated with clinical outcomes. The pharmacokinetic parameters for TAK-228 will be expressed by descriptive statistics (geometric mean, median, standard deviation, and coefficient of variation). The primary pharmacokinetic parameters investigated for each compound will be AUC_{0-t}, $AUC_{0-\infty}$, C_{max} and λ_z. Descriptive statistics will be calculated for the demographic data. Graphs and Pearson or Spearman correlations will be used to examine the distribution of values and bivariate relationships.

Evaluate mTOR and PI3K/Akt expression and phosphoproteins via immunohistochemistry (IHC) of phosphorylated Akt, 4EBP1, S6 kinase, and ERK1/2.
Immunohistochemical studies will be performed on formalin-fixed/paraffin-embedded archival tumor tissue. Biomarker quantification will be calculated as a continuous variable (mean optical density) and also as quartiles (ex. 0, 1+, 2+, or 3+). Biomarker quantification will then be correlated with treatment response. All correlative studies are considered exploratory. Descriptive statistics will primarily be generated to summarize the above data. For continuous variables, descriptive statistics may include the number of subjects (n), mean, standard deviation, median, minimum, and maximum; frequencies and percentages may be displayed for categorical data. Data summaries will be presented by experimental cohort. Statistical significance will be determined by students t-test for normally distributed data. If data distributions are not normal, a non-parametic test will be used (Wilcoxon rank sum test).

Characterize oncogene expression affecting mTOR activation via targeted deep sequencing assay designed to interrogate genes commonly mutated in human cancers.
Formalin-fixed paraffin embedded archival tumor specimens for each subject will be obtained. The presence of tumor tissue will be confirmed by a central surgical pathologist. Targeted sequencing will be performed using the Ion AmpliSeq Cancer Panel® (Life Sciences). The Ion AmpliSeq Cancer Hotspot Panel v2 is designed to rapidly survey key cancer genes for targeted mutations using the Ion Torrent PGM system and commercially available analysis software, such as NextGEN (Softgenetics, LLC). The mutation profiles of the tumors investigated will then be correlated with treatment response to TAK-228. Descriptive statistics will be used to summarize the data and a logistic regression will be performed to correlate mutation prolife to treatment response.

Assess tumor necrosis and modified RECIST (mRECIST) criteria.
De-identified images will be sent to Northwestern's Quantitative Imaging Core Lab for analysis. Three imaging time points will be collected: baseline, at best response, at upon progression of disease. Images will be stored centrally, and image analysis performed including tumor necrosis and modified RECIST (mRECIST) criteria. Percent necrosis will be describe graphically and by mean, SD, median, minimum and maximum. Frequency of response per mRECIST will tabulated.

12.12 Interim Analysis

No formal interim analyses are planned.

13 TRIAL MANAGEMENT

13.1 Quality Controls and Quality Assurance

13.1.1 Study Monitoring:

BTCRC AHQ staff will conduct at least one routine on-site monitoring visit per year per accruing trial site during the trial to ensure all aspects of the protocol are followed. Source documents will be reviewed for verification of agreement with data entered into OnCore. The investigator/ institution guarantee access to source documents by BTCRC AHQ or its designee and appropriate regulatory agencies.

It is important for the site investigator and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

The trial site may also be subject to quality assurance audit by Millennium Pharmaceuticals or its designee as well as inspection by appropriate regulatory agencies.

13.1.2 Data and Safety Monitoring Plan:

The study will be conducted in accord with the Indiana University Simon Cancer Center's DSMP, and the Indiana University Simon Cancer Center's Data and Safety Monitoring Committee (DSMC).

BTCRC AHQ facilitated oversight activities include:

- Review and processing of all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information, and data summary reports to the sponsor-investigator
- Notify participating sites of adverse events potentially requiring expedited reporting and subsequent DSMC recommendations for study modifications
- Investigators will conduct continuous review of data and patient safety.
- BTCRC AHQ will coordinate weekly review meetings for the phase I portion of the trial and then monthly meetings during the phase II portion. These meetings will include each accruing site's principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion).
- Meeting summaries from the above meetings should include review of data, the number of patients, significant toxicities as described in the protocol, SAEs, and responses observed. Summaries will be submitted and reviewed monthly by the DSMC. Submit to DSMC@iupui.edu.
- Submit data summary reports to the lead institution Data Safety Monitoring Committee according to IUSCC DSMP.

13.1.3 IUSCC Data Safety Monitoring Committee (DSMC) and Protocol Progress Committee (PPC)

The DSMC will review the following:

- Adverse event and serious adverse event summary report
- Site monitoring and/or audit reports, if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The IUSCC DSMC will review the above data semi-annually during the phase I portion of the trial and then annually during the phase II portion. Documentation of DSMC reviews will be provided to sponsor-investigator and HCRN. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with HCRN to address the DSMC's concerns.

Additionally, monthly meeting summaries, including SAE and deviation reports, will be reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review. Furthermore, the monthly meeting summaries will be available for the Protocol Progress Committee (PPC) who reviews study accrual twice per year while the PPC coordinator reviews accrual quarterly.

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the Data Safety Monitoring Committee. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review of the investigator reports.

13.2 Data Handling and Record Keeping

13.2.1 Data Management

This study will utilize electronic case report forms (eCRFs) in the OnCore® database. The OnCore® database is a comprehensive database used by BTCRC AHQ and properly used is compliant with Title 21 CFR Part 11. Access to the data through OnCore® is restricted by user accounts and assigned roles. Once logged into the OnCore® system with a user ID and password, OnCore® defines roles for each user, which limits access to appropriate data. User information and passwords can be obtained by contacting BTCRC AHQ at 317-921-2050.

13.2.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in OnCore® and correlative results will be captured in OnCore® or other secure database. If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in OnCore®, according to study-specific objectives. Please see the eCRF completion guidelines for further details.

The completed dataset is housed at BTCRC AHQ and is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and BTCRC AHQ. After the initial publication, the complete data set will be available to all BTCRC institutions.

13.2.3 Record Retention:

To enable evaluations and/or audits from Health Authorities/BTCRC AHQ, the site investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the investigator in compliance with local and federal regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRFs will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

13.3 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Samples that are collected will be identified by a subject study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject study number.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, BTCRC AHQ, Millennium Pharmaceuticals, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

13.4 Changes to the Protocol and Informed Consent

Study procedures will not be changed without the mutual agreement of the sponsor-investigator, BTCRC AHQ, and Millennium Pharmaceuticals.

If it is necessary for the study protocol and/or the informed consent to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by BTCRC AHQ and must be approved by the sponsor-investigator, Millennium Pharmaceuticals, the FDA (if applicable) and each site's IRB. Local requirements must be followed.

The site investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center.

Millennium Pharmaceutical's willingness to supply study drug is predicated upon the review of the protocol. BTCRC AHQ agrees to provide written notice to Millennium of any modifications to the protocol or informed consent.

13.5 Ethics

13.5.1 Institutional Review Board (IRB) Review:

The final study protocol, including the final version of the Written Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB. The investigator must submit written approval to the BTCRC AHQ office before he or she can enroll any subject into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of adverse events will be provided to the IRB according to local regulations and guidelines.

13.5.2 Ethical Conduct of the Study:

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH Good Clinical Practice, and applicable regulatory requirements.

13.5.3 Written Informed Consent:

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The investigator must store the original, signed Written Informed Consent Form. A copy of the signed Written Informed Consent Form must be given to the subject.

13.5.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. The sponsor-investigator has delegated responsibility to BTCRC AHQ for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

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