CLINICAL STUDY PROTOCOL

Protocol #X31025

A Phase 1 Evaluation of the Safety and Tolerability of TAK-228 in Combination with TAK-117 and Paclitaxel in Advanced Solid Tumors

Indication: Advanced solid tumors

Phase: 1

Protocol History

Original	March 6, 2017
Amendment 1	March 26, 2018
Amendment 2	May 1, 2019
Amendment 3	January 24, 2020

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This is an investigator-initiated study. The principal investigator Dr. Casey Williams, (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

PROTOCOL SUMMARY

Study Title: A Phase 1 Evaluation of the Safety and Tolerability of TAK-228 in Combination with TAK-117 and Paclitaxel in Advanced Solid Tumors

Phase: 1

Number of Patients: 2-30

Study Objectives

Primary

- To determine the maximum tolerated dose of the combination of TAK-228, TAK-117 and paclitaxel for the treatment of patients with advanced solid tumors

Secondary

- To determine the objective response rate (according to RECIST 1.1 response criteria)

Tertiary/Exploratory

- To describe symptom occurrence and severity and Health Related Quality of Life (HRQOL) as measured by the TRSC and HRQOL-LASA respectively
- To assess whether patients with specific alterations respond more favorably to the combination

Overview of Study Design:

Phase 1 trial. 3 + 3 design to determine the safety and tolerability of the combination of TAK-228, TAK-117 and paclitaxel in patients with advanced solid tumors. The maximum tolerable dose (MTD) will be assessed, which is the dose level at which less than one-third of patients will experience a dose limiting toxicity.

Study Population: The study population will consist of patients with advanced solid tumors.

Inclusion Criteria:

- Male or female patients 18 years or older
- Patients must have a diagnosis of an advanced solid tumor malignancy and must be refractory to or intolerant of existing therapies known to provide a clinical benefit
- Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status of 0-2
- Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential must have a negative pregnancy test and agree to practice one effective method of pregnancy prevention contraception and one additional effective (barrier) method, at the same time, from the time of signing the informed consent through 90 days (or longer as mandated by local labeling [e.g., USPI, SmPC, etc.,]) after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, sympto- thermal and post ovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Male patients, even if surgically sterilized (i.e., status post-vasectomy), who:
    - Agree to practice highly effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, sympto- thermal and post ovulation methods for the female partner], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
    - Agree not to donate sperm during the course of this study or within 120 days after receiving their last dose of study drug
- Screening clinical laboratory values as specified below:
    - Bone marrow reserve consistent with: absolute neutrophil count (ANC) ≥1.5 x 109/L; platelet count ≥100 x 109/L; hemoglobin ≥9 g/dL without transfusion within 1-week preceding study drug administration
    - Hepatic: total bilirubin ≤1.5 x upper limit of normal (ULN), transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase- AST/SGOT and alanine aminotransferase/serum glutamic pyruvic transaminase-ALT/SGPT) ≤2.5 x ULN (≤5 x ULN if liver metastases are present)
    - Renal: creatinine clearance ≥50 mL/min based either on Cockcroft-Gault estimate or based on urine collection (12 or 24 hour)
    - Metabolic: Glycosylated hemoglobin (HbA1c) <7.0%, fasting serum glucose (≤ 130 mg/dL) and fasting triglycerides ≤300 mg/dL
- Ability to swallow oral medications
- Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that the patient may withdraw consent at any time without prejudice to future medical care
- Patients who have a history of brain metastasis are eligible for the study provided that all the following criteria are met:

- Brain metastases which have been treated
- No evidence of disease progression for ≥3 months before the first dose of study drug
- No hemorrhage after treatment
- Off-treatment with dexamethasone for 4 weeks before administration of the first dose of TAK-228
- No ongoing requirement for dexamethasone or anti-epileptic drugs

Exclusion Criteria:

- Active central nervous system (CNS) metastasis
- Other clinically significant co-morbidities, in the opinion of the investigators, such as uncontrolled pulmonary disease, active central nervous system disease, active infection, or any other condition that could compromise the patient's participation in the study
- Known human immunodeficiency virus infection
- Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.
- Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol
- Diagnosed or treated for another malignancy within 2 years before administration of the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
- Breast feeding or pregnant
- Treatment with any investigational products within 30 days before the first dose of study drug
- Previous treatment with PI3K, AKT, dual PI3K/mTOR inhibitors, TORC1/2 inhibitors (prior treatment with everolimus is allowed)
- Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of TAK-228. In addition, patients with small bowel or jejunal stomata are also excluded.

- History of any of the following within the last 6 months before administration of the first dose of the drug:
    - Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures
    - Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures
    - Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation or ventricular tachycardia)
    - Placement of a pacemaker for control of rhythm
    - New York Heart Association (NHYA) Class III or IV heart failure (See Appendix B)
    - Pulmonary embolism
- Significant active cardiovascular or pulmonary disease including:
    - Uncontrolled hypertension (i.e., systolic blood pressure >180 mm Hg, diastolic blood pressure >95 mm Hg). Use of anti-hypertensive agents to control hypertension before Cycle1 Day 1 is allowed.
    - Pulmonary hypertension
    - Uncontrolled asthma or O2 saturation <90% by arterial blood gas analysis or pulse oximetry on room air
    - Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention, or history of valve replacement
    - Medically significant (symptomatic) bradycardia
    - History of arrhythmia requiring an implantable cardiac defibrillator
    - 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)
- Poorly controlled diabetes mellitus defined as glycosylated hemoglobin (HbA1c) >7%; patients with a history of transient glucose intolerance due to corticosteroid administration may be enrolled in this study if all other inclusion/exclusion criteria are met
- Treatment with strong inhibitors and/or inducers of cytochrome P450 (CYP) 3A4, CYP2C19 or CYP2C19 within 1 week preceding the first dose of study drug
- Patients receiving systemic corticosteroids (either IV or oral steroids, excluding inhalers or low-dose hormone replacement therapy – doses of prednisone $\leq$ 10mg or equivalent are allowed) within 1 week before administration of the first dose of study drug
- Daily or chronic use of a proton pump inhibitor (PPI) and/or having taken a PPI within 7 days before receiving the first dose of study drug

Duration of Study: Patients will complete 3 cycles within their cohort and will be followed until disease progression. Patients that have stable disease or better after 3 cycles can continue therapy until progression.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
AKT	Protein kinase B
ALP/ SGPT	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
AST/ SGOT	aspartate aminotransferase
BCRP	breast cancer resistance protein
BID	bis in die; twice a day
CBC	complete blood count
CL	clearance, IV dosing
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CRM	continual reassessment method
CV	cardiovascular
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	electrocardiogram; electrocardiography
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	End of Study (visit)
EOT	End of Treatment (visit)
EU	European Union
FDA	United States Food and Drug Administration
FSG	Fasting serum glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice

Abbreviation	Term
Hb	Hemoglobin
HbA1c	Glycosylated hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
Hy's Law	Drugs that conform to Hy's Law have a high potential for severe liver injury
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous; intravenously
IVRS	interactive voice response system
K_i	inhibition constant
LDH	lactate dehydrogenase
LFT	liver function test(s)
LLN	Lower limit normal
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MOA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
mTOR	mechanistic target of rapamycin
mTOR[1] or [2]	target of rapamycin complex [1 or 2]
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NPO	nothing by mouth
NYHA	New York Heart Association
PD	progressive disease (disease progression)
PK	pharmacokinetic(s)
PGx	Pharmacogenomic(s)

Abbreviation	Term
PO	*per os*; by mouth (orally)
PPI	Protein pump inhibitor
PR	partial remission or partial response *choose one*
PRO	patient-reported outcome
PSA	prostate-specific antigen
QD	*quaque die*; each day; once daily
QID	*quater in die;* 4 times a day
QOD	*quaque altera die*; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisecond) of electrocardiograph
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
TGI	tumor growth inhibition
T_{max}	single-dose time to reach maximum (peak) concentration
TIA	Transient ischemic attack
TPN	Total parental nutrition
UK	United Kingdom
ULN	upper limit of the normal range
US	United States
V_z	volume of distribution in the terminal phase
WBC	white blood cell
WM	Waldenström macroglobunemia

1. INTRODUCTION

1.1 Disease Under Treatment

The treatment of patients with advanced solid tumors remains unsatisfactory. New combinations are needed to improve the outcomes for patients with advanced disease. Thus, successful treatment of advanced solid tumors represents a great challenge. The optimal combination, sequencing of treatment, and schedule for targeted drugs and chemotherapy has not been established. Little is also known regarding the unique molecular characteristics and patterns of each individual's cancer tumor cells. New pathway-driven molecular subtypes are just now being elucidated[1] and clinical trials with molecularly targeted therapy, for example, in the different types of advanced solid tumors are urgently needed using theragnostic information[2, 3].

Therapies are being developed to primarily reduce signaling via oncogenic intracellular pathways and thereby change transcriptional events that take place within the cancer cell nucleus. These novel therapies may potentially benefit cancer patients with all different tumor types and at all stages in the cancer process. Previously, factors used to make traditional chemotherapy decisions were based on the tissue of origin or histological subtype. But now, in the era of precision medicine, therapeutic strategies must be based on the degree of addiction of an individual tumor to the pathway being targeted. Identifying the oncogenic drivers of solid tumors and having drugs that target these drivers and/or pathways are the keys to the successful treatment of cancer in the future.

There were approximately 14.1 million new cases of cancer globally in 2012 (not including skin cancer other than melanoma), which resulted in nearly 8.2 million deaths[4], and rates are increasing as more people live to an old age and as lifestyle changes occur in the developing world[5]. The most common types of cancer in males are lung, prostate, colorectal and stomach, and in females, breast, colorectal, lung and cervical[4]. The addition of skin cancer, other than melanoma, would account for around 40% of cases in the total number of new cancers each year[6, 7]. The financial costs of cancer are also staggering and have been estimated at $1.16 trillion US dollars per year as of 20104. Although, for the most part, cancer is a disease of old age, children are not immune to this disease. In 2012, about 165,000 children under 15 years of age were diagnosed with cancer and in children, acute lymphoblastic leukemia and brain tumors are most common[4].

As an example of solid tumors in women, ovarian cancer is the seventh most common cancer (and the 18th most common cancer overall) worldwide. Approximately 239,000 cases were

recorded in 2012, accounting for nearly 4% of all new cases of cancer in women (2% overall). This cancer is usually fatal, and is the eighth most common cause of cancer death in women worldwide (14th overall)[8]. Cancers of the ovary, fallopian tube, and peritoneal origin exhibit similar behaviors and clinical and molecular characteristics. As such, these are often combined together and define epithelial ovarian cancer (EOC). About 85–90% of ovarian cancers are epithelial carcinomas.

1.2 Study Drugs

1.2.1 TAK-228

Millennium has developed TAK-228 (formerly INK128 and MLN0128), 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 targets two distinct mTOR complexes, TORC1 and TORC2.

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 antihormonal agents.

1.2.2 TAK-117

TAK-117 (formerly MLN1117/INK1117) is an investigational, orally (PO) available, selective small molecule inhibitor of the Class I phosphoinositide 3-kinase (PI3K) alpha isoform (PI3Kα).

Pharmacological data obtained to date suggest that TAK-117 may have therapeutic potential as an orally administered PI3Kα inhibitor for the treatment of cancers associated with dysregulated activation of the PI3K pathway such as breast, lung, endometrial, colon, gastroesophageal, gastric, and bladder cancers, among others.

TAK-117 is being developed for the treatment of advanced solid tumors, both as a single agent and in combination with chemotherapy, such as paclitaxel and docetaxel, or other targeted therapies such as the investigational agents MLN8237 (alisertib) and TAK-659.

TAK-117 is also being investigated in combination with the investigational agent TAK-228.

2. SUMMARY OF NONCLINICAL EXPERIENCE

2.1 TAK-228

The mammalian mTOR serine/threonine kinase has a central role in regulating cellular growth and metabolism in response to external environmental factors[9, 10]. The mTOR kinase binds with other proteins to form two distinct multiprotein complexes, TORC1 and TORC2. The TORC1 complex is stimulated by growth factors and amino acids and regulates cell growth by controlling the activity of the ribosomal protein S6 kinase (S6K) and eukaryotic initiation factor 4-binding protein (4E-BP1)[11]. The TORC2 complex is activated by growth factors and promotes cell survival, proliferation, and actin cytoskeleton organization by phosphorylating and activating kinases, such as serine/threonine-specific protein kinase (AKT) kinase (also known as protein kinase B), which is a regulator of apoptosis[12, 13].

Two major classes of mTOR inhibitors are under development, allosteric inhibitors and ATP-competitive inhibitors. The first-generation, or allosteric, inhibitors include rapamycin and the related analogs or rapalogs temsirolimus, everolimus and ridaforolimus. The rapalogs effectively inhibit phosphorylation of S6K but only partially inhibit the phosphorylation of 4E-BP1, which regulates cap-dependent translation of transcripts for cell survival, proliferation and angiogenesis[10]. Thus, rapamycin and the rapalogs are only partial inhibitors of TORC1[10].

The ATP-competitive inhibitors, such as TAK-228, bind to the catalytic domain of mTOR and thus inhibit both TORC1 and TORC2 complexes, including the rapamycin-insensitive or resistant actions of TORC1, such as phosphorylation of 4E-BP1[14-16].

The rapalogs, temsirolimus and everolimus, have been approved by the US Food and Drug Administration (FDA) as monotherapy for patients with advanced renal cell carcinoma (temsirolimus and everolimus), advanced pancreatic neuroendocrine tumors (everolimus), and subependymal giant cell astrocytoma associated with tuberous sclerosis (everolimus). However, resistance to single-agent rapalog therapy occurs and may be related to either incomplete inhibition of the targeted pathway or loss of S6K-mediated feedback inhibition of growth factor receptor signaling leading to paradoxical hyperactive signaling. The normal feedback loop involves activated S6K, which phosphorylates and inactivates insulin receptor substrate-1 and inhibits signaling through the PI3K pathway[17, 18]. In the presence of rapalogs, the feedback loop is abrogated, leading to continued PI3K signaling, TORC2 activation, and subsequent phosphorylation of AKT at threonine-308 and serine-473, which markedly enhances the activity of AKT[10, 13, 19, 20].

In vitro studies have demonstrated that TAK-228 selectively and potently inhibits the mTOR kinases with an IC50 of 1.1 nM. Relative to mTOR inhibition, TAK-228 has >100-fold less potency on class I (PI3K isoforms α, β, γ, δ), class II (PI3KC2α and PI3K2Cβ) and class III (VPS34) PI3K family members as well as PI4Kα and PI4Kβ.

TAK-228, administered orally in multiple human tumor xenograft mouse models, can inhibit angiogenesis and tumor growth by inhibiting mTOR signaling at plasma concentrations associated with in vitro inhibition of mTOR in a dose- and time-dependent manner. These effects display a clear pharmacokinetic (PK)-to-pharmacodynamic relationship[21]. TAK-228 inhibits both the phosphorylation of S6 and 4E-BP1, the downstream substrates of TORC1, and selectively inhibits AKT phosphorylation at serine-473 (S473), as evidenced by decreased pAKT, the downstream substrate of TORC2[18, 21, 22]. Dual TORC1/2 inhibition mitigates the feedback activation of AKT, which is known to facilitate resistance to TORC1- only inhibitors such as rapamycin[17]. TAK-228 inhibits mTOR signaling and has demonstrated anticancer activity against a number of human solid tumor cell-line xenograft mouse models, including phosphatase and tensin homolog (PTEN) mutant endometrial, breast and renal cell carcinomas.

For detailed information regarding the nonclinical pharmacology and toxicology of TAK-228 please refer to the Investigator's Brochure (IB).

2.1.1 TAK-228 in Combination with Paclitaxel

Paclitaxel is an anti-mitotic chemotherapeutic agent that interferes with spindle assembly or disassembly, thereby increasing mitotic arrest and inducing cancer cell death. Cancer cells, however, have the ability to evade mitotic arrest prior to cell death, a mechanism that inevitably reduces the efficacy of these anti-mitotic drugs[23]. The mTORC1 inhibitor rapamycin was reported to synergistically enhance the activity of paclitaxel in breast cancer cells24. In an AN3-CA endometrial tumor xenograft model, TAK-228 in combination with paclitaxel exhibited stronger antitumor efficacy compared to paclitaxel alone. TAK-228 has been shown to induce G1 cell cycle arrest. Paclitaxel is known to block the progression of cells through G2 into mitosis and this G2-M arrest has been proposed to be a prerequisite step for apoptosis induced by paclitaxel[25]. Pretreatment of mTOR inhibitors will arrest cells in G1 phase and may potentially antagonize the toxic effect of paclitaxel[26]. Therefore, TAK-228 should be given after paclitaxel administration in order not to interfere with the mechanism of paclitaxel.

2.2 Nonclinical Experience with TAK117

Activating somatic missense mutations (e.g., E542K, E545K and H1047R) in the phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) gene encoding the p110α catalytic subunit of PI3Kα have been identified as a major mechanism for PI3K-dependent malignant transformation, proliferation and survival. PIK3CA mutations have been reported to occur in various solid tumors with the highest rates in breast (27%), endometrial (24%), bladder (23%), colon (15%) and ovarian (10%) cancers[27-29]. In addition to direct mutations of PI3Kα, the pathway may also be activated by mutations or overexpression of upstream effectors such as receptor tyrosine kinases (RTKs) including human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR) and insulin-like growth factor receptor (IGFR). PIK3CA is also amplified in several tumor types including the squamous type of NSCLC[30].

TAK-117, a selective, small molecule inhibitor of PI3K, has demonstrated greatest antiproliferative activity in cell lines harboring PIK3CA activating mutations and/or HER2 overexpression. TAK-117 inhibited the *in vitro* biochemical activity of human recombinant PI3Kα enzyme with an average IC_{50} of 21.4 nM and shown similar potency against PIK3CAs with hotspot mutations at E545K and H1047R. TAK-117 was shown to be 50- to 600-fold less potent against the remaining Class I PI3K isoforms (PI3Kβ, δ and γ) and mTOR.

2.3 TAK-228 in Combination with TAK-117 (PIKTOR)

The nonclinical antitumor activity of TAK-228 in combination with TAK-117, known as PIKTOR, has been explored in a number of experimental *in vitro* and *in vivo* tumor models. To investigate the effect of PIKTOR on the downstream cellular signaling of the PI3K/AKT/mTOR pathway, western blot analysis was performed using a diverse group of human tumor cell lines treated with PIKTOR as a single agent or in combination. The treatment of PIKTOR resulted in greater inhibition of these targets than either single agent. Additionally, treatment with PIKTOR induced greater apoptosis, as indicated by decreased levels of total PARP (poly ADP ribose polymerase). Further, the antiproliferative effect of PIKTOR was determined against a diverse group of human tumor cell lines *in vitro* and *in vivo*. The combination exhibited at least additive activity in all other cell lines tested (HCC1419, HCC1954, MDA-MB-468, MDA-MB-436 [breast tumor], A549, NCI-H460 and NCI-H596 [lung carcinoma]). The level of inhibition observed was greater for PIKTOR than for either single agent alone. Antitumor activity of PIKTOR was assessed in three xenograft models in mice: two breast cancer cell line models, HCC70 (triple negative breast cancer, PTEN null) and MDA-MB-361 (HER2 amplified breast

cancer with mutated PIK3CA), and one colorectal cancer model, HCT-116 (KRAS and PIK3CA mutations). The treatment of PIKTOR was tolerated and resulted in a statistically significant ($p<0.001$) increase in antitumor effects when compared with single-agent treatment in multiple treatment schedules in these xenograft models.

The principal adverse effects associated with the administration of each agent are consistent with their respective mechanisms of action. Based on the available single-agent nonclinical and clinical safety data for PIKTOR, the expected overlapping nonclinical combination toxicities (including bone marrow and lymphoid depletion, effects on glucose/insulin homeostasis including hyperglycemia, and potential effects on chloride and cholesterol levels) can be monitored with routine clinical hematology and serum chemistry evaluations, and are expected to be reversible and manageable in the clinic. Results from *in vitro* drug metabolism and pharmacokinetic studies suggest that the potential for DDIs between PIKTOR in humans is low.

For detailed information regarding the nonclinical pharmacology of PIKTOR please refer to the PIKTOR IB.

3. SUMMARY OF CLINICAL EXPERIENCE

3.1 Clinical Experience with TAK-228

TAK-228 is in clinical development as a single agent in 3 phase 1 studies including study INK128-01 in patients with advanced solid malignancies[31], study INK128-002 in patients with multiple myeloma, non-Hodgkin lymphoma and Waldenström macroglobulinemia[32] and study C31002 to measure the effect of TAK-228 on QTc interval in patients with advanced solid malignancies. It is also being investigated in combination with paclitaxel (with or without trastuzumab) in patients 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 in these studies included QD, QW, QD×3 days per week (once daily for 3 consecutive days followed by a 4-day dosing holiday every week), and QD×5 days per week (once daily for 5 consecutive days followed by a 2-day dosing holiday every week).

A new TAK-228 capsule containing milled active pharmaceutical ingredient (API) was

developed to allow scaled-up production. The milled API, could result in a faster absorption profile with possibly higher maximum concentration (Cmax), which could present a different safety profile compared to the previous unmilled API capsules. Therefore, an additional study: 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 patients with advanced non-hematological malignancies (study TAK-228-1004), was designed to determine the recommended phase 2 dose (RP2D) for single agent milled 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.

The following Table summarizes TAK-228 doses, schedules, active pharmaceutical ingredient (API) and PK population investigated in all studies. Details on PK and safety information for each study are available in the current IB edition.

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]).

3.2 Clinical Experience with TAK-117

TAK-117 is currently being investigated both as a single agent and in combination with chemotherapy or other targeted therapies for the treatment of advanced solid tumors. As of the clinical data cutoff date (22 June 2015), the safety, tolerability, and PK data of single- agent TAK-117 evaluated in one FIH, dose-finding study in patients with advanced non-hematologic malignancies (Study INK1117-001) is available in the IB. Three additional clinical studies (MLN1117-1002, MLN1117-1003 and MLN1117-1501) are ongoing. A tabular summary of the studies is presented below.

TAK-117 is also being investigated in combination with TAK-228 in study C32001as described in the following section.

Summary of TAK-117 Clinical Studies

Study No.	Study Design/Population	Dosing Regimen / Dose (Number of patients)	Status
INK1117-001 Phase 1	Open-label, multicenter, dose-escalation / Adult patients (aged ≥18 years) with advanced solid tumors	*Process A capsules:* • QD: 100, 150, 200, 300 mg (n=24) • MWF QW: 200, 300, 400, 600, 900, 1200 mg (n=27) • MTW QW: 200, 400, 600, 900 mg (n=20) *Process B capsules:* • MWF QW: 600, 900, 1200 mg (n=13) • MTW QW: 600, 900, 1200, 1500 mg (n=15) • BID on MWF QW: 300, 400, 500, 600 mg (n=22)	Enrolling
MLN1117-1003 Phase 1b	Open-label, multicenter, 4-arm combination, dose- escalation/ Adult patients (aged ≥18 years) with advanced or metastatic gastric or gastroesophageal adenocarcinoma • Part 1: lead-in dose escalation in patients with advanced solid tumors, including gastric cancer • Part 2: expansion at MTD or RP2D	*CohortsA-C(28-daycycles):* o TAK-659 (PO QD each week) +MLN1117 (MTW QW) o Alisertib (40 mg PO BID MTW, Wks 1-3) +MLN1117 (MTW QW) o Paclitaxel (80 mg/m^2 IV M QW, Wks 1-3) +MLN1117 (TWTh QW) *Cohort D (21-day cycles):* o MLN1117 (MTW QW) +docetaxel (75 mg/m^2 IV M, Wk 1 only)	Enrolling
MLN1117-1501 Phase 1b/2	Adaptive, open-label 2-arm dose-escalation / Adult patients (aged ≥18 years) with advanced or metastatic NSCLC • Part 1: dose escalation • Part 2: sequential, multistage, adaptive, randomized phase 2 expansion at MTD or RP2D	*21-day cycles:* • Escalation: MLN1117 (TWTh QW) +docetaxel (36 mg/m^2 IV M, Wks 1-2) • Expansion (2 treatment arms): o MLN1117 (TWTh Wks 1-3) +docetaxel (36 mg/m^2 IV M, Wks 1-2) o Docetaxel single agent (75 mg/m^2 IV M, Wk 1 only)	Enrolling
C32001 Phase 1b	Multicenter, open-label, safety, and PK. Adult patient (aged ≥ 18 years) with advanced nonhematologic malignancies • Dose escalation (3+3) • Expansion (mutual PK DDI; tumor-specific cohorts)	*28-day cycles:* o Escalation: (includes milled TAK-228) o Arm A: TAK-228 QD+TAK-117 QD x3d (MWF) QW o Arms B & C: TAK-228+TAK-117 QDx3d (MTW) QW o Expansion: (2 arms) o TBD per escalation	Enrolling

Abbreviations: BID=twice daily, EU=European Union, IV=intravenous, M=Monday, MTD=maximum tolerated dose, MTW=Monday, Tuesday and Wednesday, MWF=Monday, Wednesday and Friday, NSCLC=non-small cell lung cancer, PO=orally, QD=once daily, QD=once daily, QW=each week, RP2D=recommended phase 2 dose, TWTh=Tuesday, Wednesday and Thursday, UK=United Kingdom, US United States, Wk(s)=week(s).

3.3 Clinical Experience with TAK-228 + TAK-117 (PIKTOR; study C32001)

As of the clinical safety data cutoff date (10 March 2015), PIKTOR was being investigated in 1 phase 1b study (Study C32001). This study is a multicenter, open-label, phase 1b trial of PIKTOR administered to adult patients with advanced non-hematologic malignancies for whom standard, curative, or life-prolonging anticancer treatment does not exist or is no longer effective.

PIKTOR is being administered in 28-day dosing cycles, in weekly regimens of TAK-228 QD+TAK-117 QDx3d (MWF) (Arm A) and TAK-228+TAK117 QDx3d (MTuW) (Arms B and C).

As of the data cutoff, a total of 44 patients had received at least 1 dose of TAK-228 or TAK-117 in Study C32001 and are included in the Safety Population.

3.3.1 Pharmacokinetics

Preliminary PK data from study C32001 suggests that TAK-228 exposures increase with dose in the 2 to 8 mg dose range and appear variable across the various cohorts (%CV range across all cohorts: 16-90%). TAK-228 in combination with TAK-117 did not accumulate to any meaningful extent in plasma and PK appeared broadly consistent with single agent TAK-228 PK and TAK-117 in studies INK128-001 and INK1117-001 respectively.

Although a formal drug interaction evaluation between TAK-228 and TAK-117 has not been performed yet in study C32001, these initial findings suggest a lack of a readily apparent effect of these agents on each other's PK when combined.

Please refer to the TAK-228 IB and (TAK-117 IBs for detailed information on the clinical PK of the individual molecules.

3.3.2 Pharmacodynamics

To date, skin samples collected from a total of 34 patients in Study C32001 have been analyzed. Expression of all markers (pS6, p4EBP1 and pNDRG1) in skin was suppressed >50% compared to the pre-dose level in a majority of patients in all treatment arms with >80% suppression of markers in a subset of patients when measured approximately 2 hours post-dose on Cycle 1 Day 24. Based upon the time course of PD data available there appeared to

be a more sustained PD effect (up to 8 hours post-dose) at TAK-117 doses of 200 mg or greater in combination with TAK-228 when both given in a MTuW schedule.

3.3.3 Safety

TAK-228 and TAK-117 are being investigated as single agents in clinical trials for the treatment of advanced malignancies. To date, the principal TEAEs associated with the administration of each single agent are consistent with their respective MOAs. Clinical safety information for TAK-228 and TAK-117 administered as single agents is summarized in their respective single-agent IBs.

As of the clinical data cutoff for the most recent IB (10 March 2015), the two agents had been co-administered in a single open-label, phase 1b study (Study C32001) in patients with advanced non-hematologic malignancies. A total of 44 patients had been treated; 11 were ongoing. One on-study death was reported in a patient with a fatal event of dyspnea, which was considered by the investigator as not related to study drug. A total of 12 treatment-emergent SAEs were reported for 9 patients (20%); all SAEs were classified as unrelated with the exception of 1 related SAE of Grade 3 enterocolitis. Five patients had discontinued due to TEAEs (three with related AEs). The most frequently reported TEAEs, regardless of causality, were nausea, fatigue, diarrhea, vomiting, decreased appetite, increased aspartate aminotransferase, stomatitis, ALT, constipation and maculopapular rash.

3.3.4 Potential Risks

The most common TEAEs observed with TAK-228 are consistent with the pharmacodynamic mechanism of mTOR inhibition that is also seen with rapalogs (TORC1 inhibition) or other dual mTORC1/2 inhibitors. The TEAEs observed across the TAK-228 single-agent studies include diarrhea, fatigue, vomiting, rash, mucosal inflammation, asthenia, dysgeusia, thrombocytopenia, stomatitis, blood creatinine increased, hyperglycemia, nausea, anorexia, and decreased appetite.

The identified and potential risks of TAK-228 and TAK-117, including data from nonclinical and clinical studies for each product, as well as more detailed information on the identified and potential risks of both drugs is included in the individual single-agent IBs and in the PIKTOR IB.

Potential overlapping toxicities associated with TAK-228 and TAK-117 include:

- Dermatologic disorders (pruritus and rash)
- Gastrointestinal disorders (diarrhea, mucosal inflammation, nausea, stomatitis and vomiting)
- Generalized disorders (anorexia, asthenia, decreased appetite and fatigue)
- Hematologic disorders (lymphoid and bone marrow depletion)
- Metabolic disorders (decreased blood chloride, hypercholesterolemia and hyperglycemia)

On the basis of current clinical experience and the previous list of potential overlapping toxicities, hyperglycemia, diarrhea, nausea, vomiting, fatigue, and rash are the most anticipated TEAEs associated with the TAK-228 + TAK-117 combination regimen. These events are expected to be manageable.

During this study, risk mitigation strategies include, but are not limited to, strict application of the study inclusion and exclusion criteria, frequent monitoring of clinical and laboratory results, guidelines for management and prophylaxis of potential toxicities, criteria for dose modification, and regular monitoring of TEAEs and serious adverse events (SAEs) by the sponsor.

4. SPECIAL WARNINGS AND PRECAUTIONS

4.1 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 (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 have resulted in good control of glucose levels for the majority of TAK-228-treated subjects who developed hyperglycemia. Guidelines

for monitoring and treating hyperglycemia are provided in all clinical protocols administering TAK-228.

4.2 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 one report of ventricular fibrillation and cardiac arrest post dose that had a fatal outcome and was assessed as related to TAK-228 (see IB for further details).

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 (for further details refer to 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.

4.3 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. Patients 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 4.0, to further evaluate possible etiologies for the renal dysfunction.

4.4 Rash

Rash observed in clinical studies of TAK-228 tends to be maculopapular and pruritic and has ranged from Grade 1–3. 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.

4.5 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.

4.6 Interactions

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.

5. RATIONALE FOR THE RP2D FOR PIKTOR (TAK-228 + TAK-117)

Study C32001 is an ongoing open-label study designed to determine the MTD and DLTs for oral administration of milled TAK-228 given in combination with TAK-117 and was designed to characterize the safety and tolerability of escalating doses of TAK-228 and/or TAK-117 in patients with advanced solid tumors. The study features a dose-escalation phase evaluating 3 dosing schedules. A favorable tolerability profile was observed when increasing doses of TAK-228 (3–8 mg) were administered with a fixed dose of TAK-117 (both given QD × 3QW). The MTD for TAK-228 in combination with TAK-117 both given QD × 3 QW was 6 mg TAK-228 + 200 mg TAK-117.

Table Dose Limiting Toxicity Observed with TAK-228 + TAK-117 (3 Days Per Week) in Study C32001

Dose of Milled MLN0128 + MLN1117	Number of Evaluable Patients	DLTs Observed in Cycle 1
6 mg + 200 mg QD × 3 QW	6	1 patient experienced DLT of AST/ALT elevation
4 mg + 200 mg QD × 3 QW	8	None

Abbreviations: DLT = dose-limiting toxicity; QD × 3 QW = once daily for 3 days each week.

While both combination dose levels were considered safe based on 3+3 rules, the lower dose level of 4 mg + 200 mg QD × 3 QW was chosen as the RP2D for milled TAK228 + TAK-117 for further development.

6. STUDY RATIONALE

Activation of the PI3K/AKT/mTOR axis (Figure 1; slide 9 in ref. [33]) has been implicated as playing an important role in the tumorigenesis process in many malignancies[34]. Activation of this pathway through mutation of various genes directly involved in pathway activation or through mutation of the suppressor PTEN result in activation of this signaling axis. We propose that inhibitors of this pathway in combination with chemotherapy might be efficacious in the treatment of advanced solid tumors.

It is hypothesized that blocking both TORC1 and TORC2 complexes is more effective at preventing activation of AKT than inhibiting AKT through TORC1 complex inhibition alone[33]. In this regard, TAK-228 is a selective mTOR inhibitor that blocks both TORC1/TORC2-complex activity. In a clear-cell Renal Cell Carcinoma (ccRCC) xenograft model, TAK-228 was more effective than everolimus, a TORC1 complex inhibitor, at inhibiting tumor growth *in vivo* (slide 3 in ref. [33]). However, it was also shown that TAK-228 inhibition of TORC1/TORC2 resulted in a rapid but transient inhibition of AKT phosphorylation and AKT signaling. Inhibition of PI3Kα with TAK-117 in combination with TAK-228 led to a more sustained inhibition of TORC1 and TORC2 complexes that resulted in a more complete inhibition of tumor growth in the ccRCC xenograft model than with TAK-228 alone (slides 8–10 in ref. [33]).

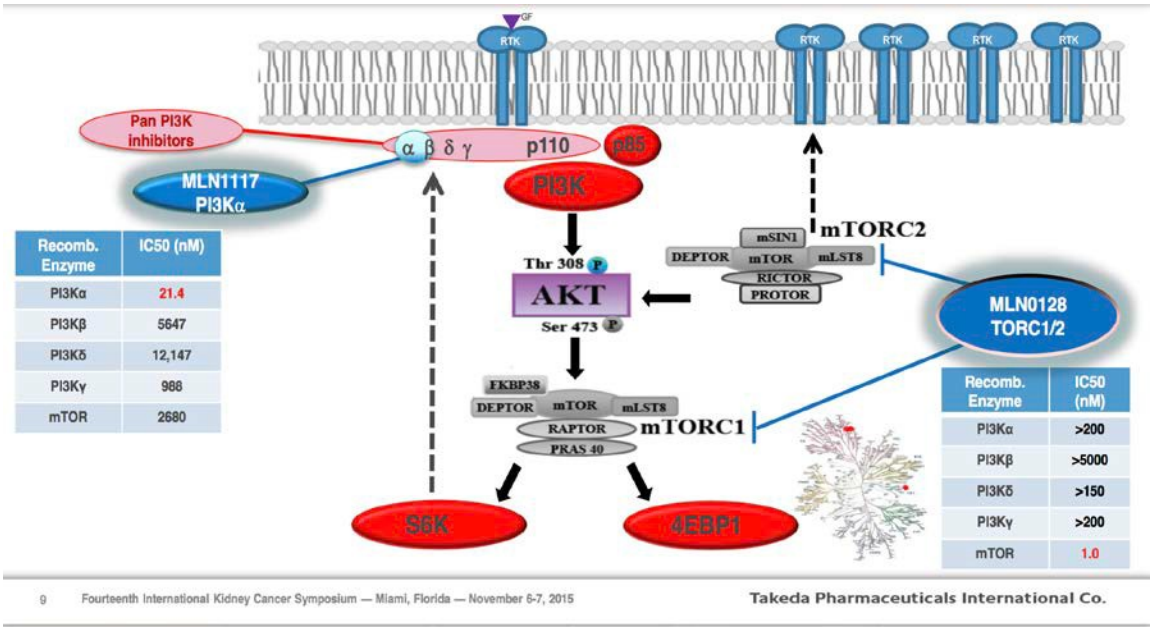

Figure 1. Sustained inhibition of PI3Ka, TORC1 and TORC2 may be required to be more effective than sustained TORC1 and TORC2 inhibition to maximize cancer growth inhibitory effects.

The mechanisms by which cells develop resistance to taxanes are not entirely understood. Evidence suggests, however, that activation of the PI3K/AKT/mTOR pathway by paclitaxel may play a role[35-37]. Conversely, PI3K inhibitors have been shown to sensitize tumors to the effects of paclitaxel[37-39]. In one study by Hou *et al.*[40], they found that by inhibiting PI3Ks they could regulate mitotic progression and prevent mitotic cell death. Therefore, the link between taxane resistance and activation of the PI3K/AKT/mTOR signaling pathway suggests that by inhibiting this axis in combination with anti-mitotic drugs like paclitaxel may also improve treatment outcomes in advanced solid tumors.

Therefore, the rationale for using this combination is that TAK-228 plus TAK-117 will exert antitumor effects against advanced solid tumors and enhance the effects of paclitaxel through inhibition of cell proliferation and more complete blockade of the PI3K/AKT/mTOR pathway. This approach may represent a promising combination to employ as targeted therapy in the treatment of advanced solid tumors. We propose to combine TAK-228 with TAK-117 and paclitaxel in a phase I trial to determine the safety profile of this combination in advanced solid tumors.

Exploratory Studies

Treatment-Related Symptom Checklist

Symptom occurrence and severity of therapy-related symptoms and health-related quality of life (HRQOL) will be described for patients undergoing the treatment regimen described on this study.

The Therapy-Related Symptom Checklist (TRSC) is a patient self-report tool that allows for the subjective measurement of therapy-related symptom severity[41]. Patients rate 25 symptoms on severity using a five-point scale; other symptoms may be added and rated as well. A higher total score on the TRSC indicates greater frequency and severity of symptoms. Prior studies have indicated that TRSC scores correlate inversely with the Karnofsky Performance Scale (KPS) and have led to improved symptom documentation and management, thereby affecting patients' quality of life[42]. The TRSC has shown good internal consistency and reliability with a Cronbach's alpha of at least 0.70 in prior studies[41]. Construct validity is evidenced by previous correlations between TRSC scores and clinician-rated Karnofsky scale, as well as scores on a quality of life index.

Patient health-related quality of life (HRQOL) will be assessed using the Health-Related Quality of Life Linear Analogue Self-Assessment (HRQOL-LASA). The HRQOL-LASAS measures six items on a 10-point scale from 0 (as bad as can be) to 10 (as good as can be). These items have been validated as measures of global QOL constructs in numerous settings[43-47].

Potential Biomarkers

Most patients who enter this study will have had or will have genomic sequencing performed. For patients who have had sequencing completed and for whom results are available, correlations with response and presence of the genomic alterations will be assessed.

7. STUDY OBJECTIVES

7.1 Primary Objective

- The primary objective is to determine the maximum tolerated dose of the combination of TAK-228, TAK-117 and paclitaxel for the treatment of patients with advanced solid tumors

7.2 Secondary Objective

- To determine the objective response rate (according to RECIST 1.1 response criteria)

7.3 Tertiary/Exploratory Objectives

- To assess whether patients with genomic alterations responded more favorably to the combination
- To describe symptom occurrence and severity of therapy-related symptoms and Health Related Quality of Life (HRQOL) as measured by the TRSC and HRQOL - LASA respectively

8. STUDY ENDPOINTS

8.1 Primary Endpoints

- Safety evaluation
- Patient tolerance

8.2 Secondary Endpoint

- Objective tumor response (according to RECIST 1.1 response criteria)

8.3 Tertiary/Exploratory Endpoints

- Symptom occurrence and severity of therapy-related symptoms and Health Related Quality of Life (HRQOL) as measured by the TRSC and HRQOL-LASA, respectively
- To assess whether patients with genomic alterations respond more favorably to the combination

9. STUDY DESIGN

9.1 Overview of Study Design

This is an open-label, cohort study to determine the feasibility and tolerability of the combination of TAK-228 and TAK-117 given on days 2-4, 9-11, 16-18, and 23-25 with paclitaxel on days 1, 8, and 15 for one 28-day cycle in patients with advanced solid tumors.

In Amendment 3, only cohort 4 will be used and no DLT criteria will be utilized. After enrolling 3 patients in cohort 5, there was a noticeable increase in toxicity that suggests we have exceeded the recommended phase 2 dose (R2PD). No MTD was established, but the dramatic reduction in tolerability makes this dose and schedule unsuitable for long-term use. Thus, it was determined to proceed with a dose expansion of cohort 4 to further evaluate if this dose and schedule would be the eventual RP2D.

Dosing schema: (3–6 pts. per cohort)

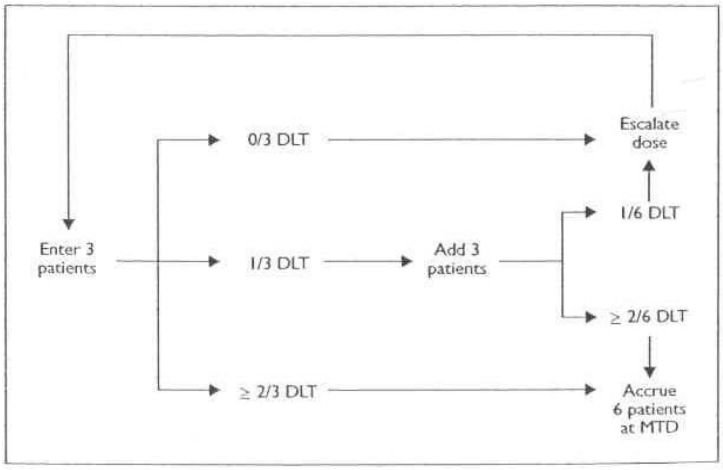

FIGURE 1: Standard phase I trial
DLT = dose-limiting toxicity, MTD = maximum tolerated dose

The goal of this study is to determine a tolerated dose of the combination of TAK-228, TAK-117 and paclitaxel. To do this, we will estimate the maximum tolerated dose (MTD) that is defined as the dose level at which less than one-third of patients will experience a dose-limiting toxicity (DLT). A traditional dose escalation design will be used, beginning with the lowest dose level and escalating to the maximum allowable dose level as specified in the protocol. Three patients will be treated one at a time at a given dose level. A maximum of 5 dosing levels results in a maximum sample size of n=30 subjects. Adverse events will be defined using the Common Toxicity Criteria v. 4.0.

Cohort 1	**Cycle 1**						
Study Day	1	2-4	8	9-11	15	16-18	23-25
Paclitaxel 60mg/m2	X		X		X		
TAK-228 2mg		X		X		X	X
TAK-117 100mg		X		X		X	X

Cohort 2	**Cycle 1**						
Study Day	1	2-4	8	9-11	15	16-18	23-25
Paclitaxel 60mg/m2	X		X		X		
TAK-228 2mg		X		X		X	X
TAK-117 200mg		X		X		X	X

Cohort 3	**Cycle 1**						
Study Day	1	2-4	8	9-11	15	16-18	23-25
Paclitaxel 80mg/m2	X		X		X		
TAK-228 2mg		X		X		X	X
TAK-117 200mg		X		X		X	X

Cohort 4	**Cycle 1**						
Study Day	1	2-4	8	9-11	15	16-18	23-25
Paclitaxel 80mg/m2	X		X		X		
TAK-228 3mg		X		X		X	X
TAK-117 200mg		X		X		X	X

Cohort 5	**Cycle 1**						
Study Day	1	2-4	8	9-11	15	16-18	23-25
Paclitaxel 80mg/m2	X		X		X		
TAK-228 4mg		X		X		X	X
TAK-117 200mg		X		X		X	X

DLT is defined as:

- Any death not clearly due to underlying disease or extraneous causes
- Hy's Law
    - Subjects with AST or ALT elevations > 3 x ULN and total bilirubin elevation >2 x ULN without initial findings of cholestasis (elevated serum alkaline phosphatase)
- Grade 3 or higher non-hematologic toxicity, despite adequate treatment, except for the following:
    - Grade 3 hyperglycemia lasting ≤14 days (all patients should receive optimal antiglycemic treatment, including insulin, as clinically indicated)
    - Grade 3 rash lasting ≤3 days (all patients should receive topical steroid treatment, oral antihistamines, and oral steroids, if necessary)
    - Inadequately treated Grade 3 nausea and/or vomiting and Grade 3 diarrhea (all

patients should receive optimal antiemetic and/or antidiarrheal prophylaxis and/or treatment)

- Patients experiencing any Grade 3 or more hematologic toxicity attributed to the treatment will hold all therapy until resolution of the toxicity to Grade 1 or baseline levels. If toxicity persists, the patients will be removed from the study. Upon resolution of the toxicity, the patient will restart treatment at the original dose at the discretion of the investigators. No dose adjustments are allowed during the DLT phase of the study.
- Grade 4 neutropenia lasting >7 days in the absence of growth factor support
- Grade 4 neutropenia of any duration accompanied by fever ≥38.5°C and/or systemic infection
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia > 7 days
- Any other ≥Grade 4 hematologic toxicity
- Inability to administer at least 75% of planned doses of TAK-228 within Cycle 1, due to study drug-related toxicity
- Any clinically significant occurrence that the investigator and sponsor agree would place patients at an undue safety risk

Patients experiencing any adverse event that requires drug to be held should return to Grade 1 or baseline before resuming therapy at the current or a reduced dose. Rash and hyperglycemia are permitted exceptions in which therapy may be resumed at Grade 2 or less.

One of the following outcomes will determine the treatment of subsequent patients:

- If none of the three patients experiences a DLT, the next group of patients will be entered in the next higher dose cohort. All patients within a cohort must have completed at least once cycle (28 days) prior to initiation of the next cohort of patients.
- If one of the three patients experiences a DLT, three more patients will be accrued at the current dose level. Subsequently, if only one of the six patients treated at this level experiences a DLT, the dose will be escalated to the next higher dose in the next group of patients. If two or more of the six patients experiences a DLT, the MTD has been exceeded and is defined as the previous dose at which no more than 1/3 experienced a DLT.
- If at least two of the three experience a DLT, the MTD has been exceeded and is defined as the previous dose at which no more than 1/3 experienced a DLT

If the lowest allowable dose level exceeds the MTD, the study will be terminated and the

combination will not be deemed safe for use in this population. Additionally, the highest dose level will not be exceeded, even if no DLTs are experienced at that dose.

The adverse events overall and by individual AE categories will be summarized. Serious adverse events will be summarized in a similar manner. These summaries will be performed overall and for each dose cohort. We will summarize all events as well as the highest grade for a given subject. We will summarize the number of subjects that exhibit a DLT at each dose cohort and describe the DLT for each subject, if applicable.

Growth factor support may be utilized at the discretion of the PI, but may not be used prophylactically in cycle 1. All other routine supportive care may be used in Amendment 3.

9.2 Study Procedures

Screening Procedures/Enrollment

All subjects must have signed and dated the informed consent and HIPAA Authorization prior to any study specific screening procedures being performed. Pre-enrollment screening test and evaluations will be used to determine the eligibility of the patient for study inclusion. All screening tests and procedures must be completed within 30 days prior to study registration and include the following:

1) Demography and Medical History including documentation of prior regimen
2) Physical exam including height and weight
3) Vital signs including: temperature, BP, pulse, respiration rate
4) Concomitant medications
5) Performance Status–-ECOG
6) CBC with differential and platelet count (CBCD)
7) Coagulation Panel (PT/INR, aPTT)
8) Urinalysis (UA)
9) Comprehensive Metabolic Panel (CMP): ALT/SGPT, AST/SGOT, LDH, phosphorus, magnesium, calcium, total protein, alkaline phosphatase, total bilirubin (direct and indirect bilirubin if total bili is abnormal), HbA1C, fasting glucose, fasting lipid panel (Total cholesterol, HDL-C, LDL-C, triglycerides), creatinine clearance (calculated using the Cockcroft formula) or creatinine and albumin
10) Serum pregnancy test, required only for women of child-bearing potential
11) Electrocardiogram
12) Tumor Assessment

Baseline

The following baseline assessments are to be performed within 14 days prior to starting recommended treatment. Screening clinical evaluations and laboratory assessments may be used as the baseline evaluations if they are done within 14 days prior to starting recommended treatment.

The investigator/treating physician will need to ensure that the patient's baseline evaluations still meet eligibility criteria or will report any exclusionary criteria to a Clinical Principal Investigator for review prior to starting the patient on the recommended treatment.

- Physical exam including height and weight
- Vital signs including: temperature, BP, pulse, respiration rate
- Concomitant medications
- TRSC (see Appendix 5)
- HRQOL-LASA (see Appendix 6)
- Performance Status-ECOG
- CBC with differential and platelet count (CBCD)
- Comprehensive Metabolic Panel (CMP): ALT/SGPT, AST/SGOT, Alkaline Phosphatase, Total Bilirubin, HbA1C, fasting glucose, lipid panel, Creatinine Clearance (calculated using the Cockcroft formula) or Creatinine, and Albumin. All additional labs are at the discretion of the treating physician.
- Baseline Tumor Assessment according to RECIST
    - Scans must be performed within the 30 days prior to starting recommended treatment
- Pregnancy Test – to be performed ≤72 hours prior to the first dose of study drug
-

On-Study

For the purposes of this study the following evaluations will be performed:

- Physical Exam
- Vital Signs
- ECOG performance status
- CBC with differential
- Coagulation Panel (PT/INR, aPTT)
- Urinalysis
- Fasting lipid profile every 3 cycles
- HgbA1C every 3 cycles
- Home glucose monitoring if required, per Table 1 Schedule of Study Assessments

- Fasting serum glucose on days patient receives paclitaxel (prior to treatment only)
- Comprehensive Metabolic Panel to include full electrolyte panel with calcium, phosphate, and magnesium, LFTs, kidney function tests, total bilirubin (direct bilirubin if total bili is abnormal), total protein
- ECG
- Tumor Assessment according to RECIST 1.1 will be performed at the end of the third cycle, and then every 12 ± 1 week until study discontinuation or disease progression, whichever is later. (See Section 7.2)
- TRSC and HRQOL-LASA
- Adverse events will be assessed at every visit. Adverse events will be graded according to NCI-CTCAE, version 4. For the purposes of this study only the following adverse events will be reported:
    - Any grade ≥3 adverse event
    - Any adverse event resulting in treatment dose reduction or discontinuation
    - Any adverse event considered by the treating investigator/treating physician to be medically significant
    - Any serious adverse event

End of Treatment

At the time the patient discontinues the recommended treatment for disease progression or any other reason the following assessments are to be performed within 30 days of last dose of treatment:

- Physical exam
- CMP and CBCD (labs as described previously)
- Urinalysis (UA)
- Fasting lipid profile
- Fasting serum glucose
- Tumor Assessment according to RECIST 1.1 (see Section 7)
- ECG
- Coagulation Panel (PT/INR, aPTT)
- Tumor markers for those patients who had elevated tumor markers on last prior regimen
- Concomitant medications
- TRSC
- HRQOL-LASA
- Assessment of adverse events ongoing at study discontinuation. Adverse events will be graded according to NCI-CTCAE, version 4. For the purposes of this study only the

following adverse events will be reported:

- Any grade ≥3 adverse event
- Any adverse event resulting in treatment dose reduction or discontinuation
- Any adverse event considered by the treating investigator/treating physician to be medically significant
- Any serious adverse event

- Reason for discontinuation is to be documented in patient source documents and recorded on CRF
- Any new primary malignancies must be reported to Takeda if occurring within 3 years from study initiation

Follow-Up

All patients will be contacted for survival status following study discontinuation at 4, 8, 12, 18 and 24 months. For those patients without disease progression at the end of therapy, tumor assessments will be undertaken every 3 months until either disease progression is observed or further anti-cancer treatment is initiated.

Table 1. Schedule of Study Assessments

		Cycle 1				Cycle 2				Cycle 3-8		Subsequent cycles	
Assessments[1]	Screening Day -30 to Day -1	C1D1	C1D8	C1D15	C1D22	C2D1	C2D8	C2D15	C2D22	D1	D15	D1	Termination
Demographics and Medical	X												
Physical Exam[2]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG PS	X	X				X				X			
Vitals	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology[3]	X	X	X	X		X	X	X		X		X	X
Chemistry[3]	X	X	X	X		X	X	X		X		X	X
Serum pregnancy	X	X											
Coagulation Panel	X	X				X				X			X
ECG[5]	X												X
HbA1c	X	X								C3D1		C6 and q3 cycles	
In home fasting		Daily pre-dose from cycle 1 Day 2 through last dose of study drug (may be decreased to once a week after the first 2 cycles, as detailed in Management of Hyperglycemia – section 12.3.1)											
Urinalysis	X	X		X		X				X		X	X
TRSC		X				X				X		X	X
HRQOL-LASA		X				X				X		X	X
AE assessment		X	X	X	X	X	X	X	X	X	X	X	X

		Cycle 1				Cycle 2				Cycle 3-8	Subsequent cycles	
Tumor Assessment[7] (per RECIST 1.1) and/or tumor	X									To be completed prior to cycle 4 and then every 12 weeks	Every 3 cycles at the discretion of the investigators	

[1] With the exception of ECGs, assessments may be done within 24-48 hours of dosing with drug administration.

[2] Symptom directed.

[3] Labs as listed in the protocol (section 9.2.1). Labs that are drawn on clinic days should be drawn while fasting. Patients are required to fast overnight prior to all chemistry panels and must include a blood glucose.

[4] Pregnancy test will be performed for females that are of childbearing potential, and will need to be performed ≤72 hours prior to the first dose of study drug

[5] Single, 12-lead ECG will be collected at screening (within 30 days of first dose), EOT and as clinically indicated while on protocol therapy.

[6] Patients will be given a glucometer to monitor fasting glucose levels at home collected daily, pre-dose only on dosing days of the TAK 228 and TAK 117, at approximately the same time each day and will be instructed to notify the study staff any time the fasting glucose is abnormal (≥150mg/dL and <160 mg/dL). In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic. For further instruction see Management of Hyperglycemia section (section 12.3.1).

[7] Tumor assessment per RECIST 1.1 will be performed at baseline (within 30 days before entering the study), at the end of the third cycle, and then every 12 ±1 week until study discontinuation or disease progression, whichever is later.

9.3 Number of Patients

Total number of patients to be enrolled, 2–30. A patient is considered enrolled on the first day of paclitaxel treatment.

9.4 Duration of Study

Each patient will have a disease evaluation after the completion of three cycles. Patients with a minimum response of stable disease or better, may continue study therapy until disease progression. They may then be followed up for a period of 24 months.

10. STUDY POPULATION

10.1 Inclusion Criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. The Principal Investigator or his designee must review results of all baseline evaluations prior to enrollment of that patient, to assure all inclusion and exclusion criteria have been satisfied. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule, required evaluations, and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

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

1. Male or female patients 18 years or older
2. Patients must have a diagnosis of an advanced solid tumor malignancy that is refractory to or intolerant of existing therapy(ies) known to provide clinical benefit for their condition
3. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status of 0-2
4. Female patients who:
    a. Are postmenopausal for at least 1 year before the screening visit, OR
    b. Are surgically sterile, OR
    c. If they are of childbearing potential must have a negative pregnancy test and agree to practice one effective method of pregnancy prevention contraception and one additional effective (barrier) method, at the same time, from the time of signing the informed consent through 90 days (or longer as

mandated by local labeling [e.g., USPI, SmPC, etc.,]) after the last dose of study drug, OR

d. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, sympto-thermal and post ovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

5. Male patients, even if surgically sterilized (i.e., status post-vasectomy), who:
    a. Agree to practice highly effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
    b. Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, sympto-thermal and post ovulation methods for the female partner], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
    c. Agree not to donate sperm during the course of this study or within 120 days after receiving their last dose of study drug
6. Screening clinical laboratory values as specified below:
    a. Bone marrow reserve consistent with: absolute neutrophil count (ANC) ≥1.5 x 109/L; platelet count ≥100 x 109/L; hemoglobin ≥9 g/dL without transfusion within 1 week preceding study drug administration
    b. Hepatic: total bilirubin ≤1.5 x upper limit of normal (ULN), transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase-AST/SGOT and alanine aminotransferase/serum glutamic pyruvic transaminase-ALT/SGPT) ≤2.5 x ULN (≤5 x ULN if liver metastases are present);
    c. Renal: creatinine clearance ≥50 mL/min based either on Cockcroft-Gault estimate or based on urine collection (12 or 24 hour);
    d. Metabolic: Glycosylated hemoglobin (HbA1c) <7.0%, fasting serum glucose (≤ 130 mg/dL) and fasting triglycerides ≤300 mg/dL
7. Ability to swallow oral medications
8. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that the patient may withdraw consent at any time without prejudice to future medical care
9. Patients who have a history of brain metastasis are eligible for the study provided

that all the following criteria are met:

a. Brain metastases which have been treated
b. No evidence of disease progression for ≥3 months before the first dose of study drug
c. No hemorrhage after treatment
d. Off-treatment with dexamethasone for 4 weeks before administration of the first dose of TAK-228
e. No ongoing requirement for dexamethasone or anti-epileptic drugs

10.2 Exclusion Criteria

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

1. Active central nervous system (CNS) metastasis
2. Other clinically significant co-morbidities, in the opinion of the investigators, such as uncontrolled pulmonary disease, active central nervous system disease, active infection, or any other condition that could compromise the patient's participation in the study
3. Known human immunodeficiency virus infection
4. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection
5. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol
6. Diagnosed or treated for another malignancy within 2 years before administration of the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection
7. Breast feeding or pregnant
8. Treatment with any investigational products within 30 days before the first dose of study drug
9. Previous treatment with PI3K, AKT, dual PI3K/mTOR inhibitors, TORC1/2 inhibitors (prior treatment with everolimus is allowed)
10. Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of TAK-228. In addition, patients with small bowel or jejunal stomata are also excluded.
11. History of any of the following within the last 6 months before administration of the

first dose of the drug:

a. Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures
b. Ischemic cerebrovascular event, including transient ischemic attack and artery revascularization procedures
c. Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation or ventricular tachycardia)
d. Placement of a pacemaker for control of rhythm
e. New York Heart Association (NYHA) Class III or IV heart failure (See Appendix B)
f. Pulmonary embolism

12. Significant active cardiovascular or pulmonary disease including:
    a. Uncontrolled hypertension (i.e., systolic blood pressure >180 mm Hg, diastolic blood pressure >95 mm Hg). Use of anti-hypertensive agents to control hypertension before Cycle1 Day 1 is allowed.
    b. Pulmonary hypertension
    c. Uncontrolled asthma or O_2 saturation <90% by arterial blood gas analysis or pulse oximetry on room air
    d. Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention, or history of valve replacement
    e. Medically significant (symptomatic) bradycardia
    f. History of arrhythmia requiring an implantable cardiac defibrillator
    g. 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)
13. Poorly controlled diabetes mellitus defined as glycosylated hemoglobin (HbA1c) >7%; patients with a history of transient glucose intolerance due to corticosteroid administration may be enrolled in this study if all other inclusion/exclusion criteria are met
14. Treatment with strong inhibitors and/or inducers of cytochrome P450 (CYP) 3A4, CYP2C19 or CYP2C19 within 1 week preceding the first dose of study drug

15. Patients receiving systemic corticosteroids (either IV or oral steroids (doses of prednisone ≤ 10mg or equivalent are allowed), excluding inhalers or low-dose hormone replacement therapy) within 1 week before administration of the first dose of study drug
16. Daily or chronic use of a proton pump inhibitor (PPI) and/or having taken a PPI within 7 days before receiving the first dose of study drug

11. STUDY DRUG

11.1 Study Drug Administration

All protocol-specific criteria for administration of TAK-228 + TAK-117 must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator.

TAK-228 + TAK-117 will be administered on an empty stomach. It is recommended that each dose of TAK-228 + TAK-117 be given PO with 8 ounces (240 mL) of water. Patients 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.

Patients must 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. TAK-228 and TAK-117 must always be taken together in this order, at the same time, when dosed on the same day. Patients must swallow the study medication whole and not chew it, open it, or manipulate it in any way before swallowing. If a patient does not take their TAK-228 + TAK-117 doses within the time frame specified (±24 hours of the QW scheduled dosing time, or ± 12 hours of the QD or QD×3days per week schedule), then the doses will be skipped and considered missed doses. Patients will record any missed doses in their diary and resume drug administration at the next scheduled time with the prescribed dosage. Under no circumstance will a patient repeat a dose or double-up doses.

If severe emesis or mucositis prevents the patient from taking scheduled doses, that dose will be skipped. If emesis occurs after study medication ingestion, the dose will not be re-administered, and patients should resume dosing at the next scheduled time with the prescribed dosage. Patients will record the occurrence of the emesis in their dosing diaries. Under no circumstance will a patient repeat a dose or double-up doses.

Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

Cycles consist of 28 days for all treatment arms. Paclitaxel will be administered once weekly for 3 consecutive weeks (on Days 1, 8, and 15 of a 28-day treatment cycle) and TAK-228 and TAK-117 will be administered together, 3 days per week (on Days 2–4, 9–11, 16–18, and 23–25 of a 28-day treatment cycle) in all 5 cohorts. Paclitaxel will be administered intravenously per its package insert or Summary of Product Characteristics (SmPC)[48, 49].

11.2 Definitions of Dose-Limiting Toxicity (DLT)

Dose limiting toxicities are defined according to the AE profile observed during the first 28 days of study drug administration in phase 1 or 1b of the study and as described below. All AEs should be considered possibly related to the study drug unless such relationship can be definitively excluded. It is thought that the RP2D is the cohort 4 dosing and have not seen any dose-limiting toxicity in the 6 patients who have received this dose and schedule.

Toxicity will be evaluated according to NCI CTCAE version 4.0. A DLT will be defined as any of the following events that are considered by the investigator to be at least possibly related to treatment with study drug:

- Any death not clearly due to underlying disease or extraneous causes
- Hy's Law
    - Subjects with AST or ALT elevations > 3 x ULN and total bilirubin elevation >2 x ULN without initial findings of cholestasis (elevated serum alkaline phosphatase)
- Grade 3 or higher non-hematologic toxicity, despite adequate treatment, except for the following:
    - Grade 3 hyperglycemia lasting ≤14 days (all patients should receive optimal antiglycemic treatment, including insulin, as clinically indicated)
    - Grade 3 rash lasting ≤3 days (all patients should receive topical steroid treatment, oral antihistamines, and oral steroids, if necessary)
    - Inadequately treated Grade 3 nausea and/or vomiting and Grade 3 diarrhea (all patients should receive optimal antiemetic and/or antidiarrheal prophylaxis and/or treatment)
- Patients experiencing any Grade 3 or more hematologic toxicity attributed to the treatment will hold all therapy until resolution of the toxicity to Grade 1 or baseline

levels. If toxicity persists, the patients will be removed from the study. Upon resolution of the toxicity, the patient will restart treatment at the original dose at the discretion of the investigators. No dose adjustments are allowed during the DLT phase of the study.

- Grade 4 neutropenia lasting >7 days in the absence of growth factor support
- Grade 4 neutropenia of any duration accompanied by fever ≥38.5°C and/or systemic infection
- Grade 3 thrombocytopenia with bleeding
- Grade 4 thrombocytopenia > 7 days
- Any other ≥Grade 4 hematologic toxicity
- Inability to administer at least 75% of planned doses of TAK-228 within Cycle 1, due to study drug-related toxicity
- Any clinically significant occurrence that the investigator and sponsor agree would place patients at an undue safety risk

Patients who experience an AE that meets the definition of a DLT during or after completing Cycle 1 should have their study drug treatment interrupted. If the event resolves to Grade 1 or Grade 2 for hyperglycemia or rash or baseline values within 3 weeks of interrupting planned therapy, and in the opinion of the investigator the benefits of continuing treatment outweigh the risks posed by the toxicity, patients may continue study treatment with TAK-228 dose reduction.

11.3 Dose-Modification Guidelines for all Cycles

The primary principle for dose reduction in TAK-228 + TAK-117 is to maintain the 200-mg dose of TAK-117, which is considered a minimally efficacious dose in the combination of TAK-228 + TAK-117. Thus, the dose of TAK-228 will be reduced if necessary while the dose and schedule of TAK-117 is maintained when study drug administration is resumed (see tables below).

If the Grade 3 or greater event that led to dose interruption resolves to Grade 1 or baseline value within 3 weeks of interrupting treatment, then the patient may resume combination study treatment if treatment with study drug is thought to be beneficial for the patient by the investigator and with the sponsor's approval. In this case, the patient may resume study treatment with TAK-117 at 200 mg QD x 3 days and TAK-228 reduced by 1 dose level.

TAK-228 and TAK-117 should be administered in continuous cycles, which should continue

unless the patient has a Grade 3 or greater TAK-228 and/or TAK-117 related event.

Management of neutropenia and thrombocytopenia may be done at the discretion of the investigators. Please see Appendix 5 for guidance.

11.3.1 Criteria for Dose Interruption during a Cycle

Administration of TAK-228 + TAK-117 should be withheld for treatment-related toxicities that are Grade 3 or higher, despite supportive treatment per standard clinical practice. The following non-hematologic toxicities attributed to TAK-228 and/or TAK-117 would not require dose interruption:

- Grade 3 or higher nausea and/or emesis in the absence of optimal anti-emetic prophylaxis. (Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs both a 5-HT3 antagonist and a corticosteroid given in standard doses and according to standard schedules.)
- Grade 3 or higher diarrhea that occurs in the absence of optimal supportive therapy
- Grade 3 fatigue

Table Dose Reduction Schedule for TAK-228 and TAK-117

Cohort	TAK-228 Dose	TAK-117 Dose	TAK-228 # of Capsules and Strength
1	1 mg QD x 3	100 mg	One 1 mg capsule
2	1 mg QD x 3	200 mg	One 1 mg capsule
3	1 mg QD x 3	200 mg	One 1 mg capsules
4	2 mg QD x 3	200 mg	Two 1 mg capsules
5	3 mg QD x 3	200 mg	Two 1 mg capsules

11.3.2 Criteria for Discontinuation of Study Drugs

In general, TAK-228 + TAK-117 dosing should be withheld for ≥Grade 3 TAK-228 and/or TAK-117-related non-hematologic toxicities. If TAK-228 + TAK-117 dosing is delayed because of TAK-228 and/or TAK-117-related toxicities for > 21 consecutive days despite supportive treatment per standard clinical practice or if >3 TAK-228 dose reductions are required, stop TAK-228 + TAK-117, discontinue the subject from the study, and complete the EOT visit within 30 days of the last administration of TAK-228 + TAK-117 whichever is discontinued last.

11.3.3 Recommended Dose Modifications for Paclitaxel Treatment Associated Toxicity

Paclitaxel dose modifications may be done at the discretion of the investigators. Please see

Appendix 5 for guidance.

12. EXCLUDED CONCOMITANT MEDICATIONS AND PROCEDURES

Based on in vitro drug metabolism studies, TAK-117 is primarily metabolized by CYP3A4 (72%), with minor contributions from CYPs 1A2 (12%), 2C9 (9%), and 2C8 (6%); whereas, TAK-228 is metabolized by enzymes CYP2C19 (35%), CYP3A4 (28%), and 2C9 (28%). Consequently, induction of CYP3A, 2C19, and 2C9 enzymes by co-administered drugs can potentially result in decreased TAK-117 and TAK-228 exposures with the associated risk of decreased efficacy of TAK-117 and TAK-228. Conversely, inhibition of these enzymes can potentially result in increased TAK-117 and TAK-228 exposures and thus increase the risk for toxicity. Therefore, use of strong CYP3A4, CYP2C9, and CYP2C19 inhibitors and clinically significant enzyme inducers are not permitted within 1 week prior to administration of the first dose of TAK-228 and/or TAK-117. During the study, strong CYP3A4, CYP2C9, and CYP2C19 inhibitors and clinically significant enzyme inducers should only be administered with caution at the discretion of the investigator.

There is potential for TAK-117 to affect the PK of breast cancer resistance protein (BCRP) substrates (e.g., methotrexate, imatinib, topotecan, lapatinib, rosuvastatin, etc.) and organic cation transporter protein 1 or 2 (OCT1 or OCT2) substrates (e.g., metformin, cimetidine, amantadine, famotidine, pindolol, etc.). If patients require treatment with medications that are known substrates of these transporters, then these agents should be administered with caution or alternative treatment options should be considered. It is recommended that patients requiring metformin for treatment of hyperglycemia resulting from TAK-228 + TAK-117 administration should begin treatment with the lowest effective dose of metformin and have their blood or serum glucose closely monitored.

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, i.e., rash or other emergent conditions that require intervention. Pre-medication for paclitaxel is allowed
- Anti-epileptic drugs for subjects with treated brain metastasis
- Concomitant administration of any PPI is not permitted during the study. Patients

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.

- Consumption of grapefruit or grapefruit juice is not permitted during the study. Patients should not consume food or beverages containing the fruit or juice of grapefruits or Seville oranges within 7 days before the first dose of study drug and throughout the study
- See below restrictions that apply to the use of CYP3A4, CYP2C19 and CYP2C9 inhibitors and inducers, histamine H2 receptor antagonists, neutralizing antacids, calcium and anti-gas preparations

12.1 Permitted Concomitant Medications and Procedures

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. Patients 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, nizatidine, and cimetidine.

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 + TAK-117 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 4 hours before until 2 hours after TAK-228 + TAK-117 administration. Some anti-gas preparations may also have antacid properties, and should also not be permitted from 4 hours before until 2 hours after study drug administration.

Strong CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2C9 should only be administered with caution, at the discretion of the investigator. Alternative treatments, if available, should be considered.

Prophylactic use of antiemetic, anti-nausea, and antidiarrheal medications is encouraged and may be used before each TAK-228 and TAK-117 dosing as needed throughout the study.

Other medications considered necessary for the safety and well-being of the patient may be administered at the discretion of the investigator.

12.2 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 (BCG), yellow fever, varicella and TY21a typhoid vaccines.

No dietary restrictions will be imposed on study patients other than avoiding food or beverages containing the fruit or juice of grapefruits or Seville oranges within 7 days before first dose of study drug and throughout the study. Patients are required to fast for glucose monitoring, and refrain from eating or drinking for 2 hours before and 1 hour after each dose.

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

Patients 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.

Pregnancy

It is not known what effects TAK-228 + TAK-117 have on human pregnancy or development of the embryo or fetus. Therefore, women participating in this study should avoid becoming pregnant, and men should avoid impregnating a female partner or donating sperm. Women of childbearing potential and men should use effective methods of contraception during and through 90 days after the last dose of study drug, as specified below.

- Women 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 21 highly effective method of contraception and 1 additional effective (barrier) method, at the same time, from the time of signing the informed consent through 90 days (or longer, as mandated by local labeling [e.g., USPI, SmPC, etc.;]) after the last dose of study drug, OR
  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, sympto- thermal and post ovulation methods], withdrawal, spermicides only

and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

- Male patients, even if surgically sterilized (i.e., status post vasectomy), who:
  - Agree to practice highly effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [e.g., calendar, ovulation, sympto- thermal, post ovulation methods for the female partner], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
  - Agree not to donate sperm during the course of this study or 120 days after receiving their last dose of study drug

12.3 Management of Clinical Events/Dose Modifications

12.3.1 Management of Hyperglycemia

In normoglycemic patients (no previously diagnosed diabetes mellitus, FBG and HbA1c within normal limits at screening), FBG should be checked at the clinic visits, every two weeks during the first cycle of treatment then day 1 of each subsequent cycle. In addition, HbA1c will be measured every 3 cycles.

In patients with prediabetes (FPG 100-125 mg/dL, 2-h plasma glucose 140-199 mg/dL, HbA1c 5.7-6.4% at screening), in addition to obtaining fasting serum glucose levels at the clinic visits as outlined in the SCHEDULE OF EVENTS, patients randomized to receive TAK-228 will be provided with a glucometer and trained in its use to monitor their daily predose fasting blood glucose levels at home. The level should be collected daily, predose on dosing days, and at approximately the same time each day. Patients will be instructed to notify the study staff of any abnormal readings ≥150 mg/dL and <160 mg/dL at the next office visit. Patients will be instructed to notify the study staff immediately with any reading > 160 mg/dL for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia. If no irregularities in the FPG level are observed during a minimum of 2 consecutive cycles, then the frequency of in-home FBG testing can be reduced to a minimum frequency of once weekly (day 4, 11, 18, and 25) depending on the investigator's judgment and approval. Patients will continue to notify the investigator of FBG levels ≥150 mg/dL,

and if blood glucose levels are not well controlled, or if they require either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily and hyperglycemia is managed aggressively as described in Table below.
For the patients with pre-existing diabetes or patients with a HbA1c >7, self-monitoring should be intensified. It is recommended to initiate a treatment with metformin, the first-line drug for management of hyperglycemia, when FBG is above 160 mg/dL, when 2-h plasma glucose is above 200 mg/dl at any time or when HbA1c is above 6.5%. To aggressively manage the hyperglycemia per standard clinical practice, the guidelines are provided to aid the investigator in initiating antiglycemic therapies.

For the patients with known diabetes mellitus, it is recommended to initiate a treatment with metformin, the first-line drug for management of hyperglycemia, when FBG is above 126 mg/dl (7.0 mmol/l), when plasma glucose is above 200 mg/dl at any time or when HbA1c is above 6.5%.

On the basis of the clinical experience in TAK-228 trials, most episodes of hyperglycemia observed occurred within the first 60 days after initiation of treatment with TAK-228, have been Grade 1 or Grade 2, and have responded quickly to oral metformin. Hyperglycemia has not been dose limiting since instituting a standard regimen for early treatment of hyperglycemia. All patients developing hyperglycemia on the study should have their glucose closely monitored by study staff. The investigator may choose either to continue close monitoring of patients who develop Grade 1 hyperglycemia (FBG >ULN ≤160 mg/dL) or consider initiating treatment with an oral hypoglycemic agent, such as metformin. All patients with ≥ Grade 2 hyperglycemia (FBG >160 mg/dL) should be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated while continuing on TAK-228 treatment. The investigator should consult an endocrinologist if needed to aid in optimizing the hyperglycemia treatment plan for the patient.

It is recommended that patients be treated initially with a fast-acting insulin sensitizer, such as metformin at 500 mg orally daily, and titrate up to a maximum of 1000 mg orally twice daily as needed. Concurrent addition to metformin of dipeptidyl peptidase-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 patients. The dose of oral hypoglycemic agents should be adjusted in patients with renal insufficiency. In addition, patients should be encouraged to follow a low-carbohydrate diet once hyperglycemia is first observed.
Guidance on study drug dose modification for patients with hyperglycemia is provided in the

table below:

Table: Management of Hyperglycemia

Grade	Description	Treatment	Dose Modification
1	Fasting blood glucose: FBG >ULN to 160 mg/dL	• Continue close monitoring of blood sugar. • Initiate oral hypoglycemic agent.	None
2	FBG >160 to 250 mg/dL	• Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None
≥3	FBG >250 mg/dL	• Initiate oral hypoglycemic agent and/or insulin.	Hold TAK-228 and TAK-117 until ≤Grade 2. Resume TAK-228 and TAK-117 based on timing of recovery after maximal treatment: • ≤1 week: resume TAK-228 and TAK-117 at same dose and schedule. • >1 but ≤2 weeks: reduce TAK-228 by 1 dose level and resume TAK-117 at same dose and schedule • >2 weeks: discontinue patient from the study.

Prevention/Prophylaxis:
- Follow fasting glucose levels during clinic visits.
- Monitor home glucometer test results.
- Check HbA1c levels every 3 cycles during therapy.
- Recommend life-style modifications, as appropriate (balanced diet, limited alcohol consumption, increased physical activity).
- Most episodes of Grade 1 or 2 hyperglycemia respond quickly to oral metformin. Early initiation of therapy at the lowest therapeutic dose 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.

HbA1c=glycosylated hemoglobin, ULN=upper limit of normal.

12.3.2 Management of Hyperlipidemia

Guidance on study drug dose modification for patients with hyperlipidemia is provided below.

Table: Management of Hyperlipidemia

Grade	Description	Treatment	Dose Modification
1	Cholesterol >ULN to 300 mg/dL OR Triglycerides >150 to 300 mg/dL	None	None
2	Cholesterol >300 to 400 mg/dL OR 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 and TAK-117 until recovery to ≤Grade 1. Re-initiate TAK-228 +TAK-117 at the same dose level
3	Cholesterol >400–500 mg/dL OR Triglycerides >500–1000 mg/dL	Same as for Grade 2	Hold TAK-228 and TAK- 117 until recovery to ≤Grade 1, then reinitiate TAK-228 at a dose reduced by 1 level and resume TAK-117 at same dose and schedule
4	Cholesterol >500 mg/dL OR Triglycerides >1000 mg/dL	Same as for Grade 2	Same as for Grade 3.

Prevention/Prophylaxis:
Life-style modifications, as appropriate (balanced diet, limit alcohol consumption, increase physical activity)

ULN=upper limit ofnormal.

12.3.3 Management of Oral Mucositis

Guidance on study dose modification for patients with oral mucositis is provided below.

Table: Management of Oral Mucositis

Grade	Description	Treatment	Dose Modification
1	Asymptomatic or mild symptoms.	Nonalcoholic mouthwash, 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 TAK-228 and TAK-117 dose if tolerable Hold only TAK-228 and TAK-117 if intolerable until recovery to ≤Grade 1, then restart at same dose.
3	Severe pain, interfering with oral intake.	Same as for Grade 2. Consider intralesional corticosteroids.	Hold all drugs until recovery to ≤Grade 1, then restart TAK-228 at a dose reduced by 1 level and resume TAK-117 at same dose and schedule
4	Life-threatening consequences.	Same as for Grade 2 Consider intra-lesional corticosteroids	Stop all drugs and discontinue patient from the study

Prevention/Prophylaxis:

- Initiation of a nonalcoholic mouth wash, or 0.9% salt water rinses 4–6 times daily is strongly recommended at the 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.

12.3.4 Management of Rash

Guidance on study drug dose modification for patients with rash is provided below.

Table: Management of Rash

Grade	Description	Treatment	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 >30% body surface area with or without symptoms.	Consider treatment with topical steroid cream/ointment, oral anti-histamines, oral antibiotics, and/or pulsed steroids.	Hold TAK-228 and TAK-117 until ≤Grade 2 Resume TAK-228 and TAK-117 based on timing of recovery: • ≤3 weeks: reduce TAK-228 by 1 dose level and resume TAK-117 at same dose and schedule • >3 weeks: stop TAK-228 and TAK-117 and discontinue patient from the study
4	Rash acneiform/ papulopustular with papules and/or pustules covering any % body surface area, which may or may not be associated with symptoms of pruritus or tenderness, and are associated with extensive superinfection with intravenous (IV) antibiotics indicated; life threatening consequences (NCI CTCAE Version 4.03, effective date 14 June 2010).		Permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recover to ≤Grade 1 severity

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 at the discretion of the treating physician and investigators.

12.3.5 Management of Nausea/Vomiting

Guidance for patients with nausea and/or vomiting is provided in the table below.

Table Management of Nausea/Vomiting

Grade	Description	Treatment	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.	If experienced for ≤ 72 hours, hold TAK-228 and TAK-117 until ≤ Grade 1, then resume TAK-228 and TAK-117 without dose modification. If experienced for >72 hours despite optimal therapy, hold TAK-228 and TAK-117 until ≤ Grade 1, then resume treatment with the dose of TAK-228 reduced by 1 level and resume TAK-117 at same dose and schedule.

Prevention/Prophylaxis:
Prophylactic use of antiemetic, anti-nausea, and antidiarrheal medications is encouraged and may be used before each TAK-228 and TAK-117 dosing as needed throughout the study.

IV=intravenous, IVF=intravenous fluids, TPN=total parental nutrition.

12.3.6 Management of Cardiac Abnormalities

Management of Patients with Possible Cardiac Instability

For patients showing signs of cardiac instability after TAK-228 and TAK-117 administration, additional monitoring onsite before clinic discharge should be considered.

Management of Patients with Left Ventricular Dysfunction

Guidance for TAK-228 and TAK-117 dose adjustments for patients with left ventricular dysfunction is provided below.

Table: Management of Left Ventricular Dysfunction

Grade	Description	Dose Modification
1	Asymptomatic decline in: LVEF >15% from baseline values, OR LVEF >10% to 15% from baseline values and is below institution's LLN	No change; continue TAK-228 and TAK-117 at the same dose and schedule
≥2	Symptomatic cardiac dysfunction/congestive heart failure.	Discontinue treatment.

LLN=lower limit of normal, LVEF=left ventricular ejection fraction

12.3.7 Management of Patients with QTc Prolongation

Guidance for TAK-228 and TAK-117 dose adjustments for patients exhibiting a prolonged QTc interval is provided below.

Table Management of QTc Prolongation

Grade	Description	Treatment	Dose Modification
2	480 msec <QTc <501 msec	Evaluate for other possible causes (e.g., electrolyte disturbance, concomitant medication, etc.).	None; continue TAK-228 and TAK-117 at the same dose and schedule.
≥3	QTc ≥501 msec	Evaluate for other possible causes (e.g., electrolyte disturbance, concomitant medication); Consider a formal consult by a cardiologist; Notify the study doctor; 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 all drugs The decision whether to reinitiate TAK-228 and TAK-117 with or without dose reduction and additional monitoring in those patients who had asymptomatic prolonged QTc ≥501 msec (Grade 3) that has reverted to an acceptable interval, have previously tolerated TAK-228 and TAK-117, and appear to have benefitted from treatment with either disease control or response, will be agreed to by the investigator on a case-by-case basis Patients who experience persistent symptomatic Grade 3 or Grade 4 QTc prolongation without another cause should permanently discontinue study treatment.

ECG=electrocardiogram, IV=intravenous, msec=milliseconds, QTc=QT interval corrected for heart rate.
(a) A list of medications known to prolong QTc can be found at https://www.crediblemeds.org/new-drug-list/

12.3.8 Management of Asthenia, Weakness and Fatigue

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

Table Management of 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 and TAK-117 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 all drugs until recovery to ≤ Grade 1. Reinitiate TAK-228 at dose reduced by 1 level and resume TAK-117 at same dose and schedule. Patients who develop Grade 4 non-hematological toxicities (with the exception of isolated non-clinically significant laboratory values) should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose

12.3.9 Management of Asparte Aminotransferase/Alanine Aminotransferase Elevations

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

Table 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 patient for other causes of transaminitis (e.g., past medical history, concomitant medications).	None
3	>5 to 20×ULN; >5×ULN for >2 weeks	Same as for Grade 2.	Hold paclitaxel, TAK-228 and TAK-117 until ≤ Grade 1; Restart all drugs at the same dose. Permanently discontinue study treatment if in combination with Grade 2 total bilirubin elevation when alternative causes cannot be identified (i.e., Hy's Law);
4	>20×ULN	Same as for Grade 2.	Stop paclitaxel, TAK-228 and TAK-117 and discontinue patient from the study. Permanently discontinue study treatment if in combination with Grade 2 total bilirubin elevation when alternative causes cannot be identified (i.e., Hy's Law).
Prevention/Prophylaxis: Ensure proper screening of patients for study participation.			

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

12.3.10 Management of Non-infectious Pneumonitis

Guidance for the management of pneumonitis is provided below.

Table 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 activities of daily living.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤Grade 1.	Hold TAK-228 and TAK-117 When symptoms ≤Grade 1, reinitiate TAK-228 at a dose reduced by 1 level and resume TAK-117 at same dose and schedule. If no recovery within 4 weeks, then discontinue TAK-228 and TAK-117
3	Symptomatic: Interfering with activities of daily living; Requires administration of oxygen.	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤Grade 1.	Hold all drugs until symptoms resolve to ≤Grade 1. Consider reinitiating TAK-228 at a dose reduced by 1 level and resume TAK-117 at same dose and schedule If toxicity recurs at Grade 3, discontinue TAK-228 and TAK-117
4	Life-threatening: Ventilatory support indicated	Rule out infection and consider treatment with corticosteroids	Discontinue all drugs.

12.4 Description of Investigational Agents

TAK-228 will be supplied as capsules for oral administration. 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

TAK-117 will be supplied as 100 mg capsules for oral administration. Each 100 mg capsule contains 100 mg of MLN1117 and the following inactive ingredients: hard gelatin capsule and small amount of colloidal silicon dioxide.

Refer to the MLN0128 (TAK-228), MLN1117 (TAK-117), and MLN0128 + MLN1117 (TAK-228 + TAK-117) IBs for full details.

12.5 Preparation, Reconstitution, and Dispensing

TAK-228 and TAK-117

TAK-228 and TAK-117 study drugs will be provided in labeled bottles in accordance with all applicable regulations. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

TAK-228 and TAK-117 are anticancer drugs and, as with other potentially toxic compounds, caution should be exercised when handling TAK-228 and TAK-117 capsules.

Paclitaxel

Paclitaxel will be diluted prior to infusion in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. At ambient temperature (approximately 25°C /77°F) and room lighting conditions the solution is physically and chemically stable for up to 27 hours.

The diluted product will be prepared and stored in glass, polypropylene, or polyolefin containers; DEHP-containing (polyvinyl chloride (PCV)) containers should not be used.

Paclitaxel will be administered using a vented Paclitaxel set with in-line 0.22-micron filter and run over at least 1 hour.

All patients should be pre-medicated prior to paclitaxel infusion with corticosteroids, diphenhydramine, and H2 antagonists, in order to prevent severe hypersensitivity reactions.

12.6 Packaging and Labeling

TAK-228 and TAK-117 will be provided by Millennium and will be handled at the investigative site as open-label material. Sites must store according to the labeled conditions.

TAK-228 and TAK-117 will be provided in high density polyethylene (HDPE) bottles with polypropylene, child-resistant caps and induction seal. TAK-228 will contain 30 capsules per bottle. TAK-117 will contain 14 capsules per bottle.

TAK-228 and TAK-117 are packaged and labeled in accordance with all applicable regulations.

12.7 Storage, Handling, and Accountability

Upon receipt at the investigative site, drug should be stored in the original bottles until use and stored at room temperature from 15°C to 30°C (59°F to 86°F). All temperature excursions will be reported for assessment and authorization for continued use. All investigational supplies must be stored in a secure area with controlled access and will be stored in original packaging. All drug supplies should be used before the retest expiry date.

Because TAK-228 and TAK-117 are investigational agents, they 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), the 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.

Patients will receive instructions for home storage and administration of TAK-228 and TAK-117.

Accountability for TAK-228 and TAK-117 at all study sites is the responsibility of the sponsor-investigator.

Commercial paclitaxel will be stored per institutional guidelines. Unopened vials of paclitaxel

are stable until the date indicated on the package when stored between 20 to 25°C (68 to 77°F), and protected from light.

12.8 Study Compliance

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

12.9 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Protocol violation
- Lost to follow-up
- Progressive disease
- Study terminated
- Other

Patients who are withdrawn from the study will not be replaced. At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for patient's withdrawal from the study should be recorded in the source documents and CRF.

13. Dose Expansion

After completion of the DLT phase, the projected phase 2 dose and schedule may be expanded to fill any remaining patient slots up to a maximum of 30 patients under amendment 3 of this protocol. There will be no restriction on how many patients can be enrolled concomitantly and all patients may utilize any applicable supportive therapy during the first cycle, including GCSF. Further, all patients will receive modified blood glucose monitoring and be stratisfied based upon their history of hyperglycemia and response to therapy.

14. STATISTICAL AND QUANTITATIVE ANALYSES

14.1 Statistical Methods

The demographic and clinical characteristics of the study patients will be summarized using descriptive statistics

- Primary objective: The maximum tolerable dose (MTD) will be assessed, which is the dose level at which < one-third of patients will experience a dose-limiting toxicity

(DLT)

- Secondary objectives:
  1. Adverse events will be defined according to the CTCAE v. 4.03 and will be summarized with descriptive statistics
  2. Response rate will be determined according to the RECIST 1.1 response criteria. Number and type of responses will be summarized with descriptive statistics
- Exploratory objectives
  1. Response rate and relationship with genomic alterations will be examined by using a two-sided Fisher Exact test due to the small sample sizes
  2. TRSC and HRQOL-LASA scores will be summarized with descriptive statistics

15. ADVERSE EVENTS

15.1 Definitions

15.1.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal 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.

15.1.2 Adverse Drug Reaction

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal 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.

15.1.3 Serious Adverse Event Definition

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 (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

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 patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient'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/mm3 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.

15.2 Procedures for Reporting Serious Adverse Events

Adverse Events may be spontaneously identified by the patient 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 which are serious must be reported to Takeda Pharmacovigilance (or designee) from the time of consent up to and including 30 days after administration of the last dose of TAK-228. Any SAE that occurs at any time after completion of TAK-228 treatment or after the designated follow-up period that the sponsor-investigator and/or sub- investigator considers to be related to any study drug must be reported to Takeda Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up period (up to 24 months) must be reported. All new cases of primary malignancy must be reported to Takeda Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness (es).

Since this is an investigator-initiated study, the principal investigator Dr. Casey Williams, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency, data safety board, or IRB.

Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

The sponsor-investigator or designee will send all SAE reports to Takeda Pharmacovigilance (or designee) within 24 hours but no later than 4 calendar days as per any agreements.

The sponsor-investigator must fax or email the SAE Form per the timelines above. A sample of an SAE Form will be provided.

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Sponsor-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):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration

Follow-up information on the SAE may be requested by Takeda Pharmacovigilance (or designee).

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Takeda Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Takeda Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the 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)?

US and Canada
Toll-Free Fax #: 1-800-963-6290
E-mail: takedaoncocases@cognizant.com

All other countries (Rest of World)
Fax #: 1 202 315 3560
E-mail: takedaoncocases@cognizant.com

Suggested Reporting Form:

- SAE Report Form (a sample will be provided)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the sponsor-investigator

15.3 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee immediately (see Section 8.2). The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Takeda Pharmacovigilance or designee will request this information from the sponsor-investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:
Pregnancy Report Form (a sample will be provided)

16. ADMINISTRATIVE REQUIREMENTS

16.1 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 Takeda (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 Takeda Quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not.

Individuals who identify a potential medication error situation should immediately contact Takeda (see below) and report the event.

For Product Complaints or Medication Errors, call

For ADCETRIS or PIPELINE Products: Phone: 1-844-ONC-TKDA (1-844-662-8532)
Email: GlobalOncologyMedInfo@takeda.com
Fax: 1-800-881-6092, Hours Mon – Fri, 9 a.m. – 7 p.m. ET

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 Takeda Pharmacovigilance (refer to Section 8.2).

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Appendix 1: Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[50]

Appendix 2: Cockcroft-Gault Equation

For men:

$$\text{Creatinine Clearance} = \frac{(140 - \text{age [years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

OR

$$\text{Creatinine Clearance} = \frac{(140 - \text{age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

For women:

$$\text{Creatinine Clearance} = \frac{0.85 \quad (140 - \text{age [years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine [mg/dL]})}$$

OR

$$\text{Creatinine Clearance} = \frac{0.85 \quad (140 - \text{age [years]}) \times \text{weight [kg]}}{0.81 \times (\text{serum creatinine [µmol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41 [32].

Appendix 3: New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of	No objective evidence of physical activity. Ordinary physical activity does not cause cardiovascular disease. Undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of	Objective evidence of minimal physical activity. They are comfortable at rest. Ordinary cardiovascular disease. Physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of	Objective evidence of moderately physical activity. They are comfortable at rest. Less than severe cardiovascular disease. ordinary activity causes fatigue, palpitation, dyspnea, or angina pain.
IV	Patients with cardiac disease resulting in inability to carry on	Objective evidence of severe any physical activity without discomfort. Symptoms of heart cardiovascular disease. Failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

- Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Ninth Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[51]

Appendix 4: List of Relevant Cytochrome P450 Inhibitors and Inducers

Strong CYP2C19 Inhibitors		
fluconazole	fluvoxamine	ticlopidine
Moderate CYP3A4 Inhibitors		
amprenavir	darunavir/ritonavir	fosamprenavir
aprepitant	diltiazem	grapefruit juice (a)
atazanavir	erythromycin	imatinib
ciprofloxacin	fluconazole	verapamil
Strong CYP3A4 Inhibitors		
boceprevir	ketoconazole	ritonavir
clarithromycin	lopinavir/ritonavir	saquinavir
conivaptan	mibefradil (b)	telaprevir
grapefruit juice (a)	nefazodone	telithromycin
indinavir	nelfinavir	voriconazole
itraconazole	posaconazole	
Clinically Significant Enzyme Inducers		
carbamazepine	rifabutin	St. Johns Wort
phenobarbital	rifampin	
phenytoin	rifapentine	

Source: fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

Note that these lists are not exhaustive.

(a) The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation- dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (e.g., high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (e.g., low dose, single strength).

(b) Withdrawn from the United States market because of safety reasons.

Appendix 5: Guidelines for TAK-228/TAK-117 and Paclitaxel Dose Modification and Delay

Table Guidelines for TAK-228/TAK-117 and Paclitaxel Dose Modification and Delay (after cycle 1 only)

Please refer to MLN0128 dose changes in the following tables to include both TAK-228 and TAK-117.

Adverse Event	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
Absolute Neutrophil Count (ANC)		
Grade 2 (< 1500 - 1000/mm^3)	No change: Continue MLN0128 at same dose and schedule.	Continue paclitaxel at same dose and schedule as per label instructions. For ANC ≤ 1500/mm^3 consider the use of prophylactic myeloid growth factors (ie, GCSF); however, paclitaxel should be reduced or delayed first, as per label instructions: • Start 1 or 2 days after paclitaxel infusion and use for 2–6 days according to patient's need, at physician discretion, and to avoid dose reduction. • Growth factor should not be given on the same day as paclitaxel infusion. • GCSF is preferred over peg-filgrastim due to the weekly dosing of paclitaxel in this study.
Grade 3 (< 1000 – 500/mm^3)	No change: Continue MLN0128 at same dose and schedule. Consider use of prophylactic myeloid growth factor support per guidelines above.	Hold paclitaxel until ANC > 1000/mm^3 Resume paclitaxel based on timing of recovery and number of previous episodes: • ≤ 2 weeks of interrupting planned therapy o First episode: no change to paclitaxel dose. o ≥ Second episode: reduce paclitaxel dose by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • > 2 weeks of interrupting planned therapy: stop paclitaxel and discontinue subject from study.
Grade 4 (< 500/mm^3)	Hold MLN0128 until ANC > 1000/mm^3 Resume MLN0128 based on timing of recovery: • ≤ 1 week: no change to MLN0128 dose. • > 1 but ≤ 2 weeks: reduce MLN0128 to the next lower dose level for all subsequent cycles. • > 2 weeks: stop MLN0128 and discontinue subject from study. Consider use of prophylactic myeloid growth factor support per guidelines above.	Hold paclitaxel until ANC > 1000/mm^3 Resume paclitaxel based on timing of recovery and number of previous episodes: • ≤ 2 weeks of interrupting planned therapy. o First episode: no change to paclitaxel dose. o ≥ Second episode: reduce paclitaxel dose by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • > 2 weeks of interrupting planned therapy: stop paclitaxel and discontinue subject from study. Consider use of prophylactic myeloid growth factor support per guidelines above.

Table Guidelines for TAK-228/TAK-117 and Paclitaxel Dose Modification and Delay

Adverse Event	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
Thrombocytopenia		
Grade 1 ($\geq$ 75,000/mm^3)	No change: Continue MLN0128 at same dose and schedule.	No change: Continue paclitaxel at same dose and schedule.
Grade 2 (50,000–74,999/mm^3)	No change: Continue MLN0128 at same dose and schedule.	Hold paclitaxel until platelets > 75,000/mm^3 Resume paclitaxel based on timing of recovery within 2 weeks of interrupting planned therapy: • $\leq$ 1 week: no change to paclitaxel. • > 1 but $\leq$ 2 weeks of interrupting planned therapy: reduce paclitaxel by 25% from starting dose (60 mg/m^2) for all subsequent cycles • > 2 weeks of interrupting planned therapy: stop paclitaxel and discontinue subject from study.
Grade 3 (25,000–44,999/mm^3)	Hold MLN0128 until platelets > 75,000/mm^3 Resume MLN0128 based on timing of recovery within 2 weeks: • $\leq$ 1 week: no change to MLN0128 dose. • > 1 but $\leq$ 2 weeks: reduce MLN0128 dose to the next lower dose level for all subsequent cycles. • > 2 weeks: stop MLN0128 and discontinue subject from study. Platelet transfusions in the absence of bleeding should not be administered.	Hold paclitaxel until platelets > 75,000/mm^3. Resume paclitaxel based on timing of recovery within 2 weeks of interrupting planned therapy: • $\leq$ 1 week: no change to paclitaxel. • > 1 but $\leq$ 2 weeks of interrupting planned therapy: reduce paclitaxel dose by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • > 2 weeks of interrupting planned therapy: stop paclitaxel and discontinue subject from study. Platelet transfusions in the absence of bleeding should not be administered.
Grade 4 (< 25,000/mm^3)	Hold MLN0128 until platelets $\geq$ 75,000/mm^3 Resume MLN0128 according to the number of episodes that are resolved to Grade $\leq$ 1 or baseline values within 2 weeks: • First episode: resume MLN0128 at same dose and schedule. • Second episode: reduce MLN0128 dose to the next lower dose level for all subsequent cycles. • Third episode: reduce MLN0128 dose to the next lower dose level from the first reduced dose for all subsequent cycles. • Fourth episode: stop MLN0128 and discontinue subject from study. Platelet transfusions should be administered prophylactically if platelets $\leq$ 10,000/mm^3 or as clinically indicated if there is bleeding.	Hold paclitaxel until platelets $\geq$ 75,000/mm^3 Resume paclitaxel according to the number of episodes that are resolved to Grade < 1 or baseline values within 2 weeks: • First episode: reduce paclitaxel by 25% from starting dose (60 mg/m^2) for all subsequent cycles. • Second episode: resume paclitaxel at the reduced dose (60 mg/m^2) for all subsequent cycles. • Third episode: reduce paclitaxel by 50% from starting dose (40 mg/m^2) for all subsequent cycles. • Fourth episode: stop paclitaxel and discontinue subject from study. Platelet transfusions should be administered prophylactically if platelets $\leq$ 10,000/mm^3 or as clinically indicated if there is bleeding.

Table Guidelines for TAK-228/TAK-117 and Paclitaxel Dose Modification and Delay (> cycle 1)

Adverse Event	MLN0128 Dose Reduction and/or Delay	Paclitaxel Dose Reduction and/or Delay
	• Second episode: reduce MLN0128 dose to the next lower dose level for all subsequent cycles. • Third episode: reduce MLN0128 dose to the next lower dose level from the reduced dose for all subsequent cycles. • Fourth episode: stop MLN0128 and discontinue subject from study.	subsequent cycles. • Second episode: resume paclitaxel at the reduced dose (60 mg/m^2) for all subsequent cycles. • Third episode: reduce paclitaxel dose by 50% (40 mg/m^2) from starting dose for all subsequent cycles. • Fourth episode: stop paclitaxel and discontinue subject from study.
Renal (Creatinine)		
Grade 1 (> ULN-1.5 × ULN or > 1-1.5 × baseline)	No change: Continue MLN0128 at same dose and schedule. Rule out prerenal azotemia and consider IV hydration. Collect the following tests to help identify cause of renal dysfunction: • Chemistry. • Urinalysis. • 12-hour urine collection. • Spot urine for electrolytes, protein, creatinine.	No change: Continue paclitaxel at same dose and schedule. Rule out prerenal azotemia and consider IV hydration. Collect the following tests to help identify cause of renal dysfunction: • Chemistry. • Urinalysis. • 12-hour urine collection. • Spot urine for electrolytes, protein, creatinine.
Grade 2 (> 1.5-3 × ULN or > 1.5-3.0 × baseline)	Hold MLN0128 until creatinine improves to ≤ Grade 1 or baseline values in ≤ 2 weeks. Collect the following tests to help identify cause of renal dysfunction: • Chemistry. • Urinalysis. • 12-hour urine collection. • Spot urine for electrolytes, protein, and creatinine. Consider IV hydration. Resume MLN0128 based on timing of recovery: • ≤ 1 week: no change to MLN0128 dose. • > 1 but ≤ 2 weeks: reduce MLN0128 to the next lower dose for all subsequent cycles. • > 2 weeks: stop MLN0128 and discontinue patient from study.	Hold paclitaxel until creatinine improves to ≤ Grade 1 or baseline values in ≤ 2 weeks of interrupting planned therapy. Collect the following tests to help identify cause of renal dysfunction: • Chemistry. • Urinalysis. • 12-hour urine collection. • Spot urine for electrolytes, protein, and creatinine. Consider IV hydration. • Resume paclitaxel at the same dose and schedule.
≥ Grade 3 (> 3-6 × ULN/ >3 baseline or >6 x ULN)	Hold MLN0128 until creatinine improves to ≤ Grade 1 or baseline values in ≤ 2 weeks.	Hold paclitaxel until creatinine improves to ≤ Grade 1 or baseline values ≤ 2 weeks of interrupting planned therapy.

Please refer to recommended labs, listed under Grade 2. This is per investigator's discretion.

APPENDIX 6: HEALTH RELATED QUALITY OF LIFE

HEALTH-RELATED QUALITY OF LIFE (HRQOL), LINEAR ANALOGUE SELF ASSESSMENT (LASA)

Patient Name: _____ Date: _____
Patient Number: _____

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today**.

How would you describe:

1. your overall Quality of Life?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

2. your overall mental (intellectual) well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

3. your overall physical well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

4. your overall emotional well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

5. your level of social activity?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

6. your overall spiritual well being?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

APPENDIX 7: THERAPY RELATED SYMPTOMS CHECKLIST

THERAPY-RELATED SYMPTOMS CHECKLIST (TRSC)

Name: _____ Hospital #_____ Date:_____

PLEASE **CHECK** THE PROBLEMS YOU HAVE HAD IMMEDIATELY AFTER AND SINCE YOUR LAST TREATMENT. PLEASE CIRCLE HOW SEVERE THE PROBLEM WAS ACCORDING TO THE FOLLOWING SCALE:

0 = NONE 1 = MILD 2 = MODERATE 3 = SEVERE 4 = VERY SEVERE

CHECK	EXAMPLE	Degree of Severity **(CIRCLE)**				
☒☒	Pain	0	1	2	③③	4
☐☐	Taste Change	0	1	2	3	4
☐☐	Loss of appetite	0	1	2	3	4
☐☐	Nausea	0	1	2	3	4
☐☐	Vomiting	0	1	2	3	4
☐☐	Weight loss	0	1	2	3	4
☐☐	Sore mouth	0	1	2	3	4
☐☐	Cough	0	1	2	3	4
☐☐	Sore throat	0	1	2	3	4
☐☐	Difficulty swallowing	0	1	2	3	4
☐☐	Jaw pain	0	1	2	3	4
☐☐	Shortness of breath	0	1	2	3	4
☐☐	Numbness in fingers and/or toes	0	1	2	3	4
☐☐	Feeling sluggish	0	1	2	3	4
☐☐	Depression	0	1	2	3	4
☐☐	Difficulty concentrating	0	1	2	3	4
☐☐	Fever	0	1	2	3	4
☐☐	Bruising	0	1	2	3	4
☐☐	Bleeding	0	1	2	3	4
☐☐	Hair loss	0	1	2	3	4
☐☐	Skin changes	0	1	2	3	4
☐☐	Soreness in vein where chemotherapy was given	0	1	2	3	4
☐☐	Difficulty sleeping	0	1	2	3	4
☐☐	Pain	0	1	2	3	4
☐☐	Decreased interest in sexual activity	0	1	2	3	4
☐☐	Constipation	0	1	2	3	4
	Other problems (please list below)					
☐☐		0	1	2	3	4
☐☐		0	1	2	3	4
☐☐		0	1	2	3	4
☐☐		0	1	2	3	4

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