CLINICAL STUDY PROTOCOL

Takeda X31026/Baylor 017-113

Phase II Clinical Trial of Treatment with the oral combination of TAK-228 and TAK-117 to inhibit homologous recombination (HR) followed by cisplatin and nab paclitaxel in patients with chemotherapy-pretreated metastatic triple negative breast cancer

Indication:	Metastatic breast cancer
Phase:	2

Protocol History

Original	07 April 2017
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Amendment 3	20 July 2018

Investigator and Study Center:
Joyce O'Shaughnessy, MD
Baylor Scott and White Research Institute
3410 Worth Street, Suite 400
Dallas, TX 75246

Phone: 214-370-1795

This is an investigator-initiated study. The principal investigator, Joyce O'Shaughnessy, MD, (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: Phase II clinical trial of treatment with the oral combination of TAK-228 and TAK-117 to inhibit homologous recombination (HR) followed by cisplatin and nab paclitaxel in patients with chemotherapy-pretreated metastatic triple negative breast cancer

Phase: 2

Number of Patients: 10-20

Study Objectives

Primary

- To assess the objective response rate associated with sequential treatment with the oral combination of TAK-228 and TAK-117 followed by cisplatin plus nab paclitaxel in metastatic triple negative breast cancer (metTNBC) patients.

Secondary

- To assess the safety of TAK-228 and TAK-117 followed by cisplatin plus nab paclitaxel in metTNBC pts.
- To assess the duration of response to sequential treatment with the oral combination of TAK-228 and TAK-117 followed by cisplatin plus nab paclitaxel in metTNBC pts.
- To assess the metastatic TNBC tissues for homologous recombination deficiency (HRD) by evaluating inactivating mutations in HR genes on Next Generation Sequencing (NGS) as well as by evaluating the overall and pattern-specific mutational load in the cancers on NGS.
- To collect frozen and/or formalin-fixed paraffin embedded (FFPE) tissue for biomarker development.

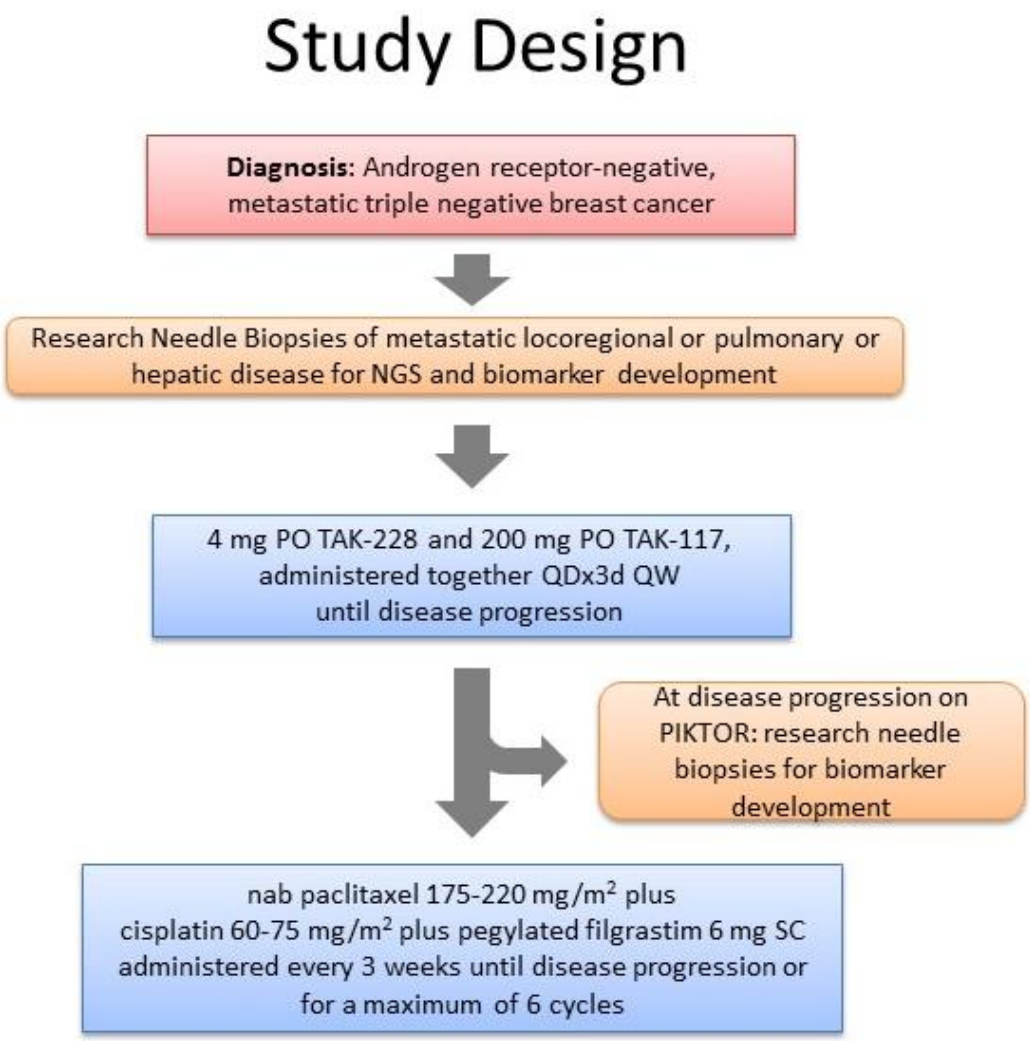
Overview of Study Design:

Seventy to 80% of breast cancers have a basal gene expression profile which is characterized by homologous recombination deficiency (HRD) and high proliferation. HRD leads to upregulation of the activity of the non-homologous end joining (NHEJ) error-prone pathway that repairs DNA double strand breaks, a process required for TNBC survival. The hypothesis of this Phase II trial is that administration of the oral combination of TAK-228 and TAK-117 (PIKTOR) will inhibit NHEJ in metastatic triple-negative breast cancer (TNBC), leading at the time of disease progression to metastases that are HR-deficient and sensitive to cisplatin plus nab paclitaxel therapy. A patient with an exceptional complete and durable response of her primary-refractory metastatic TNBC with PI3K pathway inhibition followed at disease progression by nab paclitaxel/cisplatin provides the rationale for a prospective trial of PIKTOR followed by the cisplatin/nab paclitaxel regimen in pretreated metastatic TNBC patients.

Patients will receive PIKTOR until PD, followed by nab paclitaxel plus cisplatin for 6 cycles. Patients will undergo core needle biopsies of metastatic locoregional or pulmonary or hepatic disease prior to the start of PIKTOR treatment, and at the time of disease progression on PIKTOR (prior to beginning nab paclitaxel plus cisplatin) for NGS and biomarker development.

Patients who have residual locally recurrent or metastatic disease upon completion of nab paclitaxel/cisplatin may be treated with standard of care breast cancer therapies **off study**, at the recommendation of the treating physician.
Study Population: Androgen receptor-negative, metastatic triple negative breast cancer patients who have not received more than 3 prior chemotherapy regimens for metastatic disease.
Duration of Study: The duration of patient participation in the study will be a maximum of 18 months.

STUDY OVERVIEW DIAGRAM



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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

Abbreviation	Term
AE	adverse event
AKT	Protein kinase B
ALP/ SGPT	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
ASCO	American Society of Clinical Oncologists
AST/ SGOT	aspartate aminotransferase
BC	Breast cancer
BCRP	breast cancer resistance protein
BID	bis in die; twice a day
BSWRI	Baylor Scott & White Research Institute
CBC	complete blood count
CL	clearance, IV dosing
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CRF	Case report form
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
EGFR	Epidermal Growth Factor Receptor
EOS	End of Study (visit)
EOT	End of Treatment (visit)

Abbreviation	Term
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
Hb	Hemoglobin
HbA1c	Glycosylated hemoglobin
Hct	Hematocrit
HDPE	high-density polyethylene
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HR	Homologous recombination
HRD	Homologous recombination deficiency
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
IEC	independent ethics committee
IGFR	Insulin-like growth factor receptor
IHC	Immunohistochemistry
IM	Internal mammary
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
LN	Lymph node
LVEF	Left ventricular ejection fraction
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
metTNBC	Metastatic triple negative breast cancer

Abbreviation	Term
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
NGS	Next generation sequencing
NHEJ	Non-homologous end-joining
NHL	non-Hodgkin lymphoma
nM	Nanomolar
NPO	nothing by mouth
NYHA	New York Heart Association
OTC	Over the counter
PD	progressive disease (disease progression)
PGx	Pharmacogenomic(s)
PIKTOR	TAK-228 + TAK-117 combination
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PPI	Proton 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	*quarter in die;* 4 times a day
QOD	*quaque altera die*; every other day
QOL	quality of life
QTc	rate-corrected QT interval (millisec) of electrocardiograph
QW	Once per week
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Term
RP2D	Recommended phase 2 dose
RPPA	Reverse phase protein array
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
TEAE	Treatment emergent adverse event
TGI	tumor growth inhibition
TIA	Transient ischemic attack
T_{max}	single-dose time to reach maximum (peak) concentration
TNBC	Triple negative breast cancer
TPN	Total parental nutrition
TTP	Time to progression
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 Background on Triple Negative Breast Cancer

Breast cancer is the most common malignancy in women worldwide, with incidence rates as high as 89.7 per 100,000 women.(1) Although there have been a number of important treatment advances in recent years, and overall mortality is declining due to earlier detection and more effective treatment of early stage disease, metastatic breast cancer (MBC) remains incurable and is the second leading cause of cancer deaths among women.(2)

Triple-negative breast cancer (TNBC) is defined by the absence of ER, PgR, and HER2 receptor expression. By hierarchical clustering of gene expression patterns, these cancers most often segregate with the "basal-like" intrinsic subtype.(3) Compared with other breast cancer subtypes, TNBC is associated with a worse prognosis, including a shorter time to recurrence in early-stage disease, and a shorter time between recurrence and death in the metastatic setting.(4) Because currently available targeted therapies such as endocrine or HER2-targeted agents are ineffective against this breast cancer subtype, treatment options for TNBC are limited to chemotherapy at this time. To date, no clear molecular target has been identified and proven to have therapeutic value.

1.2 Homologous Recombination Deficiency in Breast Cancer

Seventy to 80% of breast cancers have a basal gene expression profile which is characterized by homologous recombination deficiency (HRD) and high proliferation.(5) HRD leads to upregulation of the activity of the non-homologous end joining (NHEJ) error-prone pathway that repairs DNA double strand breaks, a process required for TNBC survival.(6) A key nuclear enzyme that orchestrates NHEJ is DNA-Dependent Protein Kinase catalytic subunit (DNA-PKcs), a member of the PI3K super-family.(7)

Nuclear Epidermal Growth Factor Receptor (EGFR) is activated by phospho-AKT and both nuclear EGFR and nuclear AKT phosphorylate and activate DNA-PK to promote NHEJ-mediated repair of DNA double-strand breaks.(8) Loss of HR proficiency, which occurs in most TNBCs (the basal-like TNBCs), leads to increased EGFR expression in mammary epithelial cells.(9) However, it is not known whether activated, nuclear EGFR T564 and nuclear AKT that phosphorylate DNA-PK are increased in the setting of HRD in chemotherapy-resistant TNBC.

BEZ-235 is a potent inhibitor of DNA-PKcs, as well as PI3K and TORC1/2, which inhibits NHEJ-mediated DNA double strand break repair, sensitizing cancers to DNA damaging agents.(10) A phase I trials of the sachet formulation of BEZ-235 demonstrated that BEZ-235 was safe with manageable toxicities(including mild to moderate fatigue, nausea, diarrhea, hyperglycemia, stomatitis and anemia) and had demonstrated antitumor activity against breast cancer.(11) However, although the mechanisms behind its activity were compelling, clinical development of this agent was stopped because of highly unpredictable intrapatient bioavailability that could not be overcome with various formulations (Novartis Oncology, personal communication, October, 2015).

Another mechanism which inhibits DNA repair response is the dual inhibition of mTORC1/2. In preclinical studies, the dual inhibition of mTORC1 and mTORC2 decreased

DNA repair response as well as decreased the activity of AKT. This dual inhibition allowed for the partial re-sensitization of platinum-resistant ovarian cancer cells both in vitro and in vivo to platinum chemotherapy, as compared to single inhibition of mTORC1.(12) Blockade of the mTOR complexes may be a novel strategy to sensitize cancers to DNA damaging agents.

1.3 PIKTOR (TAK-228 + TAK-117)

1.3.1 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 2 distinct mTOR complexes, mTORC1 and mTORC2.

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

1.3.2 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 Together, the combination is referred to as PIKTOR.

1.4 Nab-Paclitaxel in MBC

In a phase I study, the MTD of nab-paclitaxel was determined to be 300 mg/m^2 by 30 minute infusion Q3W, without premedication or G-CSF support.(13) No severe hypersensitivity reactions occurred with nab-paclitaxel despite the absence of premedication. Dose-limiting toxicities included sensory neuropathy, stomatitis, and superficial keratopathy, which occurred at a dose of 375 mg/m^2.

Two multicenter phase II studies have evaluated 2 dose levels of nab-paclitaxel (300 mg/m^2, n=63, and 175 mg/m^2, n=43) in patients with metastatic breast cancer.(14,15) The ORRs in these 2 phase II trials were 40% (95% CI 25-54%) for the 175 mg/m^2 dose, and 48% (95% CI 35-60%) for the 300 mg/m^2 dose. Of 39 patients receiving 300 mg/m^2 as first-line therapy for metastatic breast cancer, 64% (95% CI 49-79%) responded. This was contrasted

with a 45% response rate in similar patients at the lower dose level. Grade 4 neutropenia was noted in 24% of patients at the higher dose level, occurred primarily during the first cycle and resolved rapidly.

A Phase III trial in patients with metastatic breast cancer compared nab-paclitaxel 260 mg/m^2 (n=229) to solvent-based paclitaxel 175 mg/m^2 (n=225) given Q3W.(16) Efficacy analyses were based on the intent-to-treat (ITT) population. The ORR was significantly greater for nab-paclitaxel than for paclitaxel for all patients (33% v 19%, respectively; P = 0.001), patients who received first-line therapy (42% v 27%, respectively; P = 0.029), patients who received second-line or greater therapy (27% v 13%, respectively; P = 0.006), and patients who had received prior anthracycline therapy in either the adjuvant/metastatic setting (34% v 18%, respectively; P = 0.002) or the metastatic setting only (27% v 14%, respectively; P = 0.010). Tumor response rate was also significantly higher for nab-paclitaxel than for paclitaxel in patients with visceral dominant lesions (34% v 19%, respectively; P = 0.002) and in patients aged younger than 65 years (34% v 19%, respectively; P < 0.001). ORR also was greater for nab-paclitaxel compared with standard paclitaxel in patients with nonvisceral dominant lesions (34% v 19%, respectively) and in patients ≥ 65 years old (27% v 19%, respectively), but the results did not reach statistical significance because of the small number of patients in these subsets.

Median time to progression (TTP) was significantly longer with nab-paclitaxel than with paclitaxel for all patients (23.0 v 16.9 weeks, respectively; hazard ratio [HR] = 0.75; P = 0.006). There was a trend for greater median survival for all patients treated with nab-paclitaxel than with paclitaxel (65.0 v 55.7 weeks, respectively; P = 0.374). Although no difference in survival was observed in first-line patients, the difference was statistically significant in patients who received nab- paclitaxel, compared with paclitaxel, as second-line or greater therapy (56.4 v 46.7 weeks, respectively; HR = 0.73; P = .024).(16)

As expected with a higher dose of paclitaxel, treatment-related grade 3 sensory neuropathy occurred more frequently in the nab-paclitaxel arm than in the solvent-based paclitaxel arm (10% v 2%, respectively; P < 0.001); however, these episodes improved with interruption of treatment to grade 2 or 1 in a median 22 days and were easily managed with treatment interruption and dose reduction. By day 28 after its first occurrence, the number of patients with persistent grade 3 sensory neuropathy was the same (n = 4) in both study arms. No episodes of motor neuropathy or grade 4 sensory neuropathy were reported in either group.

1.5 Nab-Paclitaxel plus Cisplatin in MBC

The combination of nab-paclitaxel plus cisplatin was evaluated in a phase II study in 73 patients with MBC.(17) nab-Paclitaxel was administered at a dosage of 125 mg/m^2 IV on days 1, 8 and 15, together with cisplatin 75 mg/m^2 IV on day 1, of an every-28-day cycle, for a maximum of 6 cycles. The ORR was 67% in all evaluable patients and 81% for patients receiving first-line treatment. Median PFS was 9.8 months, and median OS was 26.9 months, demonstrating that the efficacy of nab-paclitaxel can be improved by the addition of cisplatin. Grade 4 neutropenia was reported in 63% of patients, with a 12% incidence of febrile neutropenia. Grade 3 peripheral neuropathy occurred in 26% of patients, and was cumulative and dose-limiting.

1.6 Nab paclitaxel plus Carboplatin in Metastatic TNBC

The combination of nab paclitaxel (nab pac) and carboplatin (carbo) was evaluated in a phase II study in 191 patients with metastatic TNBC. Nab pac plus carbo reduced the risk of progression or death by 40% as compared to 2 other chemotherapy regimens (nab pac/gemcitabine (gem) and gem/carbo), according to results from the tnAcity study presented at the 2016 San Antonio Breast Cancer Symposium.(18) The median progression-free survival (PFS) was 7.4 months with nab pac/carbo as compared to 5.4 months for nab pac/gem and 6 months for gem/carbo. The overall response rate (ORR) of nab pac/carbo was 72%, while the ORR for nab pac/gem was 39% and 44% with gem/carbo.

Based on these data, de novo metastatic TNBC patients are eligible for this study (PIKTOR followed by nab paclitaxel plus cisplatin) due to the high degree of effectiveness of this combination chemotherapy regimen as first-line therapy.

1.7 Exceptional Responder Clinical History and Tumor Molecular Alterations

The following description of the clinical and molecular tumor characteristics of a metastatic TNBC exceptional responder patient (19) provides the clinical rationale for conducting the proposed prospective pilot clinical trial of the oral combination of TAK-228 and TAK-117, followed by cisplatin and nab paclitaxel:

At age 58 in 2006, the patient had a T1c 1+ node TNBC (denoted below: “Jul 2006 pre-BEZ-235 Primary BC”) that was treated with adjuvant 5-fluorouracil, epirubicin, cyclophosphamide plus docetaxel (FEC/T) in addition to lumpectomy and breast radiotherapy. The patient has no family history of BC.

Between 2008 and 2011 she had 4 locoregional recurrences in her axilla, supraclavicular (SC) fossa and internal mammary (IM) LNs treated unsuccessfully with surgery, radiation, and multiple cytotoxic agents including carboplatin.

In February 2011, following an SC LN biopsy (denoted below: “Feb 2011 pre-BEZ-235 SC LN”), she was treated on a clinical trial with single agent BEZ-235, a PI3K/mTOR, ATM, ATR, and DNA-PKcs inhibitor, and had a partial response of 3 months duration, which was her first response to systemic therapy. The tempo of her disease changed following BEZ-235 in that the SC LN that had been biopsied in Feb 2011 grew very rapidly at disease progression; this disease was resected in October 2011 (denoted below: “Oct 2011 post-BEZ-235 SC LN”). She subsequently developed very rapidly enlarging IM LNs in November 2012, which pushed her sternum anteriorly (denoted below: “Nov 2012 post-BEZ-235 IM LN”).

In January 2013, she began treatment with 6 cycles of nab paclitaxel and cisplatin and developed a durable complete response (CR) that has been ongoing for 3.5 years.

The pre-BEZ-235 SC LN tissue from February, 2011 that was highly chemotherapy- and radiation-refractory showed very strong EGFR signaling on RPPA (Figure 1). The nuclear phospho-EGFR T564 moiety was overexpressed in the patient’s pre-BEZ-235 chemotherapy-refractory February 2011 SC LN (Figure 2). Following treatment with BEZ-235, when the IM lymph node disease was very rapidly progressing in November 2012,

RPPA analysis on this tissue showed that EGFR and p-EGFR expression were not detectable (Figure 1).

FIGURE 1

Tissues Analyzed	Her2	pHer2 Y1248	Her1	pHer1 Y1068	Her3	pHer3 Y1289	pAkt S473	pmTOR S2448	Ribo. Prot. S235-236	p4E. BP1 S65	pMek 1/2 S217-221	pErk 1/2 T202 Y204	pJak 2 Y1007-1008	pStat3 Y705	AR	pAR
Population mean	*0.100*	*0.265*	*0.096*	*0.370*	*0.259*	*0.232*	*0.299*	*0.233*	*0.319*	*0.223*	*0.151*	*0.258*	*0.301*	*0.316*	*0.201*	*0.138*
Plus 1 SD	*0.228*	*0.404*	*0.194*	*0.519*	*0.367*	*0.375*	*0.503*	*0.375*	*0.497*	*0.377*	*0.281*	*0.470*	*0.441*	*0.446*	*0.383*	*0.292*
Plus 2 SD	*0.356*	*0.543*	*0.292*	*0.701*	*0.475*	*0.526*	*0.683*	*0.517*	*0.678*	*0.538*	*0.411*	*0.649*	*0.581*	*0.577*	*0.566*	*0.445*
Jul 2006 pre-BEZ-235 Primary BC	0.015	0.119	0.083	0.269	0.270	0.014	0.030	0.297	0.465	0.180	0.102	0.084	0.290	0.311	0.016	0.095
Feb 2011 pre-BEZ-235 SC LN	0.030	0.243	0.196	0.485	0.391	0.446	0.149	0.159	0.418	0.385	0.224	0.271	0.268	0.388	0.092	0.103
Oct 2011 post-BEZ-235 SC LN	0.116	0.184	0.116	0.525	0.381	0.187	0.069	0.188	0.145	0.301	0.190	0.117	0.482	0.490	0.054	0.098
Nov 2012 post-BEZ-235 IM LN	0.043	0.179	0.075	0.274	0.335	0.335	0.072	0.215	0.173	0.106	0.296	0.098	0.071	0.202	0.045	0.087

Green = at the mean; yellow = between mean and 1 standard deviation (SD) from the mean; orange = increased between 1 SD and 2 SD from the mean; red = increased over 2 SD from the mean.

FIGURE 2

Tissues Analyzed	Histone H2AX S139	P90 RSK S380	CREB S133	EGFR T564 (nuclear)
Population mean	*0.410*	*1.605*	*2.279*	*9.858*
Plus 1 SD	*0.611*	*2.669*	*3.259*	*16.146*
Plus 2 SD	*0.812*	*3.733*	*4.239*	*22.434*
Jul 2006 pre-BEZ-235 Primary BC	ND	**1.216**	**2.145**	ND
Feb 2011 pre-BEZ-235 SC LN	ND	ND	ND	**17.527**
Oct 2011 post-BEZ-235 SC LN	ND	**1.430**	**2.307**	ND
Nov 2012 post-BEZ-235 IM LN	**0.535**	ND	ND	ND

Note: population is not established, therefore these are considered preliminary results (denoted with shaded colors).
Green = at the mean; yellow = between mean and 1 standard deviation (SD) from the mean; orange = increased between 1 SD and 2 SD from the mean; red = increased over 2 SD from the mean; gray=not done.

All of the patient's longitudinal tissues that underwent NGS revealed a deletion of the *SMARCA4* (*BRG1*) gene which is essential for normal HR proficiency.(20, 21) However, the Myriad HRD score on her primary breast cancer from 2006 was low, demonstrating non-deficient HR, suggesting that the alternative DNA double strand repair mechanism, NHEJ, was functional in her primary breast cancer. The patient's TNBC HRD score changed from HR non-deficient in her primary BC to HR-deficient following BEZ-235 treatment possibly due to inhibition of the PI3K/AKT pathway that drives NHEJ by BEZ-235, which amplified her cancer's intrinsic HRD that was due to the *SMARCA4* deletion. The November 2012 rapidly progressive metastatic TNBC that had a high HRD score responded completely to cisplatin/nab paclitaxel chemotherapy.

In this metastatic TNBC patient, the high EGFR expression and PI3K pathway activation observed on RPPA in her cancer pre-BEZ-235 switched to loss of EGFR and PI3K

activation and increased MAPK pathway activation in the November 2012 tissue post-BEZ-235 (Figure 1). Of note, this switch from PI3K to MAPK pathway activation, with a concomitant substantial increase in HRD (as measured by H2AX overexpression) is precisely what was observed in the seminal work by Juvekar, Baselga and Cantley when the active PI3K pathway was inhibited by buparlisib in preclinical TNBC models.(22)

The above patient's exceptional complete and durable response of her primary-refractory metastatic TNBC with PI3K pathway inhibition followed at disease progression by nab paclitaxel/cisplatin provides the rationale for a prospective trial of PIKTOR followed by the cisplatin/nab paclitaxel regimen in pretreated metastatic triple negative breast cancer patients.

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.(23, 24) The mTOR kinase binds with other proteins to form 2 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).(25) 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.(26, 27)

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.(24) Thus, rapamycin and the rapalogs are only partial inhibitors of TORC1.(24)

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.(28-30)

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.(31, 32) 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.(23, 27, 33, 34)

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.(35) 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. (31, 35, 36) Dual TORC1/2 inhibition mitigates the feedback activation of AKT, which is known to facilitate resistance to TORC1-only inhibitors such as rapamycin.(37) 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).(38)

2.2 Nonclinical Experience with TAK117

Activating somatic missense mutations (eg, 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.(39-41) 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.(42)

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 IC50 of 21.4 nM and shown similar potency against PIK3CA 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), 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 either single agent alone. Antitumor activity of PIKTOR was assessed in 3 xenograft models in mice: 2 breast cancer cell line models, HCC70 (triple negative breast cancer, PTEN null) and MDA-MB-361 (HER2 amplified breast cancer with mutated PIK3CA), and 1 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.(43)

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 (44), study INK128-002 in patients with multiple myeloma, non-Hodgkin lymphoma and Waldenström macroglobulinemia (45) 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×3days per week (once daily for 3 consecutive days followed by a 4-day dosing holiday every week), and QD×5days per week (once daily for 5 consecutive days followed by a 2-day dosing holiday every week).

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 (Table 1) 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.(38)

Table 1. Summary of TAK-228 Clinical Studies

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

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

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

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

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 1 FIH, dose-finding study in patients with advanced nonhematologic 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 (Table 2).

TAK-117 is also being investigated in combination with TAK-228 in study C32001 as described in Table 3.

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Table 2. 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-armcombination, 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 nonhematologic 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 suggest 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.(38, 46)

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 predose 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 postdose 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.(38, 46)

As of the clinical data cutoff for the most recent IB (10 March 2015), the 2 agents had been co-administered in a single open-label, phase 1b study (Study C32001) in patients with advanced nonhematologic 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 TEAE (3 with related AEs). The most frequently reported TEAEs, regardless of causality, were nausea, fatigue, diarrhea, vomiting, decreased appetite, aspartate aminotransferase increased, stomatitis, ALT, constipation, and rash maculo-papular.

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, rash)
- Gastrointestinal disorders (diarrhea, mucosal inflammation, nausea, stomatitis, vomiting)
- Generalized disorders (anorexia, asthenia, decreased appetite, fatigue)
- Hematologic disorders (lymphoid, bone marrow depletion)
- Metabolic disorders (decreased blood chloride, hypercholesterolemia, 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 (eg, metformin), and subjects with ≥ Grade 2 hyperglycemia (FSG > 160 mg/dL) are treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated. Daily home monitoring and early treatment have resulted in good control of glucose levels for the majority of TAK-228-treated subjects who developed hyperglycemia. 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 09 December 2015, there has been 1 report of ventricular fibrillation and cardiac arrest post dose that had a fatal outcome and was assessed as related to TAK-228 (see IB for further details).(38) Routine cardiac monitoring with baseline electrocardiogram (ECG) or multigated acquisition (MUGA) scan and on-study ECGs and physical examination constitute the core cardiac safety monitoring in all TAK-228 studies.

Preliminary results from a dedicated study of the effects of TAK-228 on the QTc interval (study C31002) show lack of clinically relevant effects on QTc interval, PR and QRS intervals, minimal effects on heart rate, and absence of treatment-emergent ECG morphology findings and therefore the treatment with TAK-228 is not associated with clinically meaningful effects on the overall electrocardiographic safety profile (for further details refer to current IB version). (38)

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 to 3. For the most part, rash and pruritus improve with antihistamines, topical steroid creams, and/or dose interruption. Some subjects have required pulse systemic steroids, dose reduction, and/or study treatment discontinuation.

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 with other Medicines and other Forms of 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 × 3d QW). The MTD for TAK-228 in combination with TAK-117 both given QD × 3d QW was 6 mg TAK-228 + 200 mg TAK-117.

Table 3. Study C32001 Treatment Schema PIKTOR Dose Limiting Toxicity

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

Abbreviations: DLT = dose-limiting toxicity; QD × 3d 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 × 3d QW was chosen as the RP2D for milled TAK228 + TAK-117 for further development.

6. STUDY RATIONALE

The hypothesis of this pilot trial is that administration of the oral combination of TAK-228 and TAK-117 will inhibit NHEJ in metastatic TNBC leading at the time of disease progression to metastases that are HR-deficient and sensitive to cisplatin plus nab paclitaxel therapy. The exceptional responder patient's treatment history described in the Introduction provides the clinical rationale for the present trial which will utilize PIKTOR to inhibit HR proficiency prior to administration of cisplatin plus nab paclitaxel. The trial will include in depth analysis of the patients' TNBC genome and phosphoproteome to evaluate HR-proficiency and deficiency, and nuclear proteins that drive NHEJ, before and upon progression with PIKTOR therapy.

7. STUDY OBJECTIVES

7.1 Primary Objectives

The primary objective of this study is to assess the objective response rate associated with sequential treatment with the oral combination of TAK-228 and TAK-117 (PIKTOR) followed, upon progression on PIKTOR, by cisplatin plus nab-paclitaxel in metastatic triple negative breast cancer (metTNBC) patients.

7.2 Secondary Objectives

To assess the safety and duration of response to sequential treatment with the oral combination of TAK-228 and TAK-117 (PIKTOR) followed by cisplatin plus nab-paclitaxel in metastatic TNBC patients.

To assess the metastatic TNBC tissues for homologous recombination proficiency and deficiency by evaluating inactivating mutations in HR genes on Next Generation Sequencing (NGS), the overall and pattern-specific mutational load in the cancers on NGS, as well as collect frozen and/or formalin-fixed paraffin embedded (FFPE) tissue for biomarker development.

8. STUDY ENDPOINTS

8.1 Primary Endpoints

The primary endpoints of this study are to assess the objective response rate associated with sequential treatment with the oral combination PIKTOR followed by nab-paclitaxel plus cisplatin in metastatic TNBC.

8.2 Secondary Endpoints

The secondary endpoints of this study are safety and duration of response associated with sequential treatment with the oral combination PIKTOR followed by nab-paclitaxel plus cisplatin, as well as homologous recombination deficiency, next-generation sequencing, and collection of frozen and/or formalin-fixed paraffin embedded (FFPE) tissue for biomarker development.

9. STUDY DESIGN

9.1 Overview of Study Design

This exploratory open label pilot trial will evaluate the sequential administration of PIKTOR followed by nab-paclitaxel plus cisplatin in patients with metastatic TNBC.

Patients will receive 4 mg PO TAK-228 and 200 mg PO TAK-117, administered together QDx3d QW, continuously (eg, Monday-Tuesday-Wednesday each week) until disease progression.

Patients will then receive treatment with standard nab paclitaxel 175 – 220 mg/m^2 plus cisplatin 60 – 75 mg/m^2 with standard pegylated filgrastim 6 mg SC administered every 3 weeks until disease progression or for a maximum of 6 cycles. Dosing of chemotherapy will be determined per cycle, per physician's discretion. **NOTE:** Patients have the option to switch to carboplatin (AUC of 5 – 6) given every 3 weeks instead of cisplatin due to cisplatin toxicity, and remain on study. The dose and choice of cisplatin or carboplatin will be determined per cycle, per physician's discretion, based on patient's cumulative toxicity from cisplatin.

Patients will undergo core needle biopsies of metastatic locoregional or pulmonary or hepatic disease prior to the start of PIKTOR treatment, and at the time of disease progression on PIKTOR (prior to beginning nab paclitaxel plus cisplatin) for NGS and biomarker development. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted.

Patients who have residual locally recurrent or metastatic disease upon completion of nab paclitaxel/cisplatin may be treated with standard of care breast cancer therapies **off study**, at the recommendation of the treating physician.

9.2 Number of Patients

Twenty patients with metastatic TNBC will be enrolled over 12-18 months. The enrollment process begins when the Coordinator has obtained a signed informed consent form. See Section 11.5.2 for registration procedures.

9.3 Duration of Study

The duration of patient participation in the study will be a maximum of 18 months.

10. STUDY POPULATION

10.1 Inclusion Criteria

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

1. Female patients 18 years or older.
2. Have a diagnosis of metastatic TNBC, including de novo metastatic TNBC.(18)
3. Have not received more than 3 prior chemotherapy regimens for metastatic disease. Prior platinum and/or taxane therapy in the adjuvant or metastatic setting is permitted.
4. Androgen receptor-negative (less than 10% positive nuclei) on standard IHC performed at the local pathology laboratory.
5. Have locoregional (eg, breast, chest wall, regional lymphatic) or pulmonary or hepatic metastatic disease that is amenable to core needle biopsy. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (See Appendix I)
7. 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, agree to practice 1 effective methods 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 [eg, 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 [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
8. Screening clinical laboratory values as specified below:

a. Bone marrow reserve consistent with: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L; platelet count ≥ 100 x 10^9/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 ≥60 mL/min based either on Cockroft-Gault estimate (See Appendix II) 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

9. Ability to swallow oral medications.
10. Must be able to fast for glucose monitoring throughout PIKTOR treatment.
11. 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 ≥2 months before the first dose of study drug.

    c. No hemorrhage after treatment

    d. Off-treatment with dexamethasone for 3 weeks before administration of the first dose of PIKTOR

    e. No ongoing requirement for dexamethasone or anti-epileptic drugs

12. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

10.2 Exclusion Criteria

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

1. Leptomeningeal disease that is symptomatic or cytology-proven.
2. Other clinically significant co-morbidities, 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 or TORC1 inhibitors.
10. Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of PIKTOR. In addition, patients with enteric 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 III)
    f. Pulmonary embolism
12. Significant active cardiovascular or pulmonary disease including:
    a. Uncontrolled hypertension (ie, systolic blood pressure >180 mm Hg, diastolic blood pressure > 100 mm Hg). Use of anti-hypertensive agents to control hypertension before Cycle1 Day 1 is allowed.
    b. Pulmonary hypertension
    c. Need for supplemental oxygen
    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) (eg, 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 (See Appendix IV).
15. Patients receiving systemic corticosteroids (either IV or oral steroids, 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 TREATMENT ADMINISTRATION

1. Once patients sign informed consent, they will be evaluated with a complete history, physical examination as well as initial studies as described in Section 11.5.
2. Metastatic TNBC Patients will receive 4 mg PO TAK-228 and 200 mg PO TAK-117, administered together once per day, 3 days per week (QD x 3d QW), continuously (eg, Monday-Tuesday-Wednesday each week) until disease progression.
3. Upon disease progression on PIKTOR, patients will be treated with standard nab paclitaxel 175 – 220 mg/m^2 plus cisplatin 60 – 75 mg/m^2 with standard pegylated filgrastim 6 mg SC administered every 3 weeks until disease progression or for a maximum of 6 cycles. Dosing of chemotherapy will be determined per cycle, per physician's discretion. **NOTE:** Patients have the option to switch to carboplatin (AUC of 5 – 6) given every 3 weeks instead of cisplatin due to cisplatin toxicity, and remain on study. The dose and choice of cisplatin or carboplatin will be determined per cycle, per physician's discretion, based on patient's cumulative toxicity from cisplatin.
4. Patients will undergo core needle biopsies of metastatic locoregional or pulmonary or hepatic disease prior to the start of treatment, and upon disease progression on PIKTOR (prior to starting nab paclitaxel plus cisplatin) for NGS and biomarker development. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted.
5. Patients who have residual locally recurrent or metastatic disease upon completion of nab paclitaxel/cisplatin may be treated with standard of care breast cancer therapies **off study**, at the recommendation of the treating physician.

The treatment schema is shown in Table 4.

Table 4. Treatment schema			
Agent	**Dose**	**Frequency of administration**	**Route of administration**
TAK-228	4 mg	[a]QD x 3 days, QW	PO
TAK-117	200 mg	[a]QD x 3 days, QW	PO
Nab-Paclitaxel[b]	175 – 220 mg/m^2	Cycle 1-6, Day 1, q21 days	IV
Cisplatin[b,c]	60 – 75 mg/m^2	Cycle 1-6, Day 1, q21 days	IV
Pegfilgrastim	6 mg	Cycle 1-6, Day 1 or Day 2	SC

[a]The 3 days of treatment with TAK-228 and TAK-117 should be continuous, eg, Monday-Tuesday-Wednesday each week.
[b]Nab-paclitaxel plus cisplatin treatment will begin upon disease progression on PIKTOR. Dosing of chemotherapy will be determined per cycle, per physician's discretion.
[c]Patients have the option to switch to carboplatin (AUC of 5 – 6) given every 3 weeks instead of cisplatin due to cisplatin toxicity, and remain on study. The dose and choice of cisplatin or carboplatin will be determined per cycle, per physician's discretion, based on patient's cumulative toxicity from cisplatin.

11.1 PIKTOR Administration

All protocol-specific criteria for administration of TAK-228 + TAK-117 (PIKTOR) 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 (**NOTE:** on clinic visit days, when fasting serum glucose must be taken 2 hrs after study drug administration, it is acceptable for patients to take their doses at a different time than is typical).

TAK-228 and TAK-117 must always be taken together, 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 (± 12 hours of the 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

readministered, 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).

11.2 Chemotherapy Administration

In this protocol, the following chemotherapy products are FDA-approved for MBC:

- Nab-paclitaxel and cisplatin
- Supportive therapy (ie, pegfilgrastim)

Preparation and administration will be followed per the site's guidelines and standard FDA labeling. The doses to be used for nab-paclitaxel and cisplatin are below, and in Table 4 (dosing of chemotherapy will be determined per cycle, per physician's discretion):

- **Nab paclitaxel:** 175 – 220 mg/m^2 administered IV every 3 weeks (Day 1 every 21 days)
- **Cisplatin:** 60 – 75 mg/m^2 administered IV every 3 weeks (Day 1 every 21 days)
- **Pegfilgrastim:** 6 mg SC, Cycles 1-6, Day 1 or Day 2

NOTE: Patients have the option to switch to carboplatin (AUC of 5 – 6) given every 3 weeks instead of cisplatin due to cisplatin toxicity, and remain on study. The dose and choice of cisplatin or carboplatin will be determined per cycle, per physician's discretion, based on patient's cumulative toxicity from cisplatin.

11.3 TAK-228 Dose-Modification Guidelines

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, in the event of a needed dosing interruption for toxicity (see Table 5 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. 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. Please refer to the guidelines for dose interruption and for dose reduction in Section 11.3.1.

11.3.1 Criteria for Dose Interruption during a PIKTOR 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 nonhematologic 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 5. Dose Reduction Schedule for TAK-228 and TAK-117

Dose Level	TAK-228 Dose	TAK-117 Dose	TAK-228 Capsules and Strength
0	4 mg QD x 3d QW	200 mg QD x 3d QW	One 3 mg capsule and 1-mg capsule
-1	3 mg QD x 3d QW	200 mg QD x 3d QW	One 3 mg capsule
-2	2 mg QD x 3d QW	200 mg QD x 3d QW	Two 1 mg capsules
-3	1 mg QD x 3d QW	200 mg QD x 3d QW	One 1 mg capsule

11.3.2 Criteria for Discontinuation of PIKTOR

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, TAK-228 + TAK-117 therapy will be stopped and the patient will be discontinued from the study, and the EOT visit will be completed within 30 to 40 days of the last administration of TAK-228 + TAK-117.

11.3.3 Dose Modifications for Chemotherapy Treatment Associated Toxicity

Standard of care dose modifications are to be made according to the system showing the greatest degree of toxicity and per physician's discretion. Toxicities will be graded according to the NCI CTCAE Version 4.03 as linked in Appendix V. Each chemotherapy treatment cycle will begin only when:

- ANC ≥1000
- Platelets ≥100,000
- Resolution of non-hematologic toxicities to ≤Grade 1 or baseline

For hematologic toxicity, treatment decisions on standard of care drug should be made based on ANC and platelet counts on the day of treatment administration. Dose modifications must be recorded on the CRF.

- Patients must have ANC of ≥1000/mm^3 on Day 1 of each cycle (if pegfilgrastim is being used) or of ≥1200/mm^3 on Day 1 (if no pegfilgrastim is being used) to

receive scheduled treatment. Treatment may be delayed to allow sufficient time for recovery.

- Patients must have a platelet count of ≥100,000/mm^2 on Day 1 of each cycle to receive scheduled chemotherapy treatment. Nab-paclitaxel and cisplatin should be delayed until platelet counts recover to ≥100,000/mm^2 and then treated with either full dose or reduced dose chemotherapy at the physician's discretion. Treatment may be delayed to allow sufficient time for recovery.

NOTE: Patients have the option to switch to carboplatin (AUC of 5 – 6) given every 3 weeks instead of cisplatin due to cisplatin toxicity, and remain on study. The dose and choice of cisplatin or carboplatin will be determined per cycle, per physician's discretion, based on patient's cumulative toxicity from cisplatin.

Use of hematopoietic growth factors to ameliorate hematologic toxicity is at the discretion of the physician investigator and should be in accordance with the American Society of Clinical Oncologists (ASCO) guidelines.

11.4 Chemotherapy Treatment Delay or Discontinuation

If a treatment day variation is needed for reasons other than toxicity, an attempt should be made to keep the variation within the following parameters: **±4 calendar days.** Any delay within this window is NOT a deviation. **Note**: This delay window **does not** apply to Cycle 1.

1. Treatment may be delayed no more than 3 weeks for any reason (Note: Delays do not count scheduled weeks of rest).
2. Patients who are off study treatment for more than 3 weeks for any reason will be considered off treatment.

11.5 Schedule of Assessments

The schedule of assessments for the trial is shown in Appendix VI. If a required observation or procedure is missed, documentation is required in the source records, on the Protocol Deviation Form, and on the CRF, to explain the reason for this protocol deviation.

11.5.1 Prestudy Assessments

Note: Assessments that are part of the standard of care and obtained within 3- 4 weeks of prestudy assessment visit, are acceptable as part of the screening tests. Results of such tests will be acceptable even if obtained prior to the execution of the Inform Consent.

Prior to entry into the study, the following assessments will be performed to determine if patient is eligible to continue in the study as per Sections 10.1 and 10.2 describing the inclusion and exclusion criteria for the study.

1. A signed Patient Informed Consent Form must be obtained.
2. A signed Patient Authorization Form (HIPAA) must be obtained.
3. It has been confirmed that the patient meets **all** inclusion criteria and **none** of the exclusion criteria.
4. A complete medical history must be obtained **within 3 weeks prior to registration**.

5. A complete physical examination (including vital signs, height, and body weight) must be obtained **within 3 weeks prior to registration**.
6. Assessment of PS on the ECOG scale (Appendix I) must be obtained **within 3 weeks prior to registration.**
7. Assessment of concomitant medications must be obtained **within 4 weeks prior to registration.**
8. A complete blood count (CBC) with differential and platelet count **within 4 weeks prior to registration.**
9. Complete metabolic profile (CMP) including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total carbon dioxide [CO_2], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT]) and electrolytes (total calcium, chloride, potassium, sodium), must be performed **within 4 weeks prior to registration**.
10. Coagulation (PT/INR, aPTT) must be performed **within 3 weeks prior to registration.**
11. Fasting lipid profile must be performed **within 3 weeks prior to registration.**
12. HbA1c must be performed **within 3 weeks prior to registration.**
13. Fasting serum glucose must be performed **within 3 weeks prior to registration.**
14. Females of childbearing potential must have a serum or urine pregnancy test performed **within 7 calendar days prior to registration**.
15. Urinalysis must be performed **within 4 weeks prior to registration**.
16. EKG must be performed **within 4 weeks prior to registration**.
17. Pulmonary function tests, only if clinically indicated, must be performed **within 4 weeks prior to registration.**
18. A clinical assessment of the patient's disease (ie, by physical examination) must be performed **within 3 weeks prior to registration**.
19. Radiological assessment of tumors (ie, chest and abdomen CT scan, radionuclide bone scan) must be performed **within 4-6 weeks of registration**. The methods used for prestudy assessments should be used throughout the study. If possible, the same equipment should be used each time.
20. Assessments of other lesions must be performed **within 4 weeks prior to registration**.
21. If safely accessible, research biopsies of the patient's metastatic locoregional or pulmonary or hepatic disease must be obtained prior to the first day of treatment. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted.
22. Whole blood collection (40 mL) for germline exome sequencing studies.
23. Distribution of patient diaries: 1) PIKTOR dosing, and 2) in-home glucometer readings (see Appendices).

11.5.2 Registration Procedures

Written documentation of full, noncontingent IRB approval must be on file before a patient can be registered. The registration process begins when the Coordinator has obtained a signed informed consent.

Study ID, consent date, status of patient (eg, active or screen failure), relevant comments,

and date of patient discontinuation are to be recorded on the Patient/Enrollment Log by the Coordinator. The Patient/Enrollment Log will be maintained for review for any reason (ie, monitoring/audit). Once a study ID is assigned, this will constitute the registration confirmation. **Treatment must begin within 10 working days (not counting the day of dosing) after the patient's registration on the study.**

The PI may be allowed the opportunity to review and grant exceptions for minor deviations in eligibility, in order to maximize patient accrual without jeopardizing patient safety or scientific integrity of these studies. Examples might include minor deviations of baseline labs, timing of prior treatment or tests, etc. It is recognized that these questions arise frequently. The procedure to be followed is for the Investigator or his/her representative (ie, research nurse) to e-mail the request to the PI for an exception. The PI would then make a determination, which is binding. In no instance should this exception constitute a safety issue for the patient or a significant deviation from the scientific purpose of the study.

11.5.3 Assessments During Treatment

11.5.3.1 Assessments During PIKTOR

The following assessments will be performed during therapy prior to the start of each cycle, unless otherwise specified. **A PIKTOR Cycle is defined as 28 days**. Patients will continue PIKTOR until disease progression.

There is a window (**up to 4 calendar days prior to the scheduled time point**) for assessments during the study. Any delay within this window is NOT a deviation. Assessments that are to be done on days when study drug is administered must be done **prior to dosing** as these assessments (CBC, CMP, assessment of response, etc) may determine whether or not drug is administered, or if a dose reduction is necessary, unless otherwise noted.

1. A brief medical history, to capture events that have occurred since the last cycle. Events that were not captured in the baseline complete medical history should be recorded on the AE page of the CRF.
2. A brief physical examination, including vital signs and body weight.
3. ECOG performance status (PS)
4. Assessment of concomitant medications
5. A CBC with differential and platelet count every 14 days for the first Cycle, Day 1 of cycles thereafter.
6. A CMP every 14 days for the first Cycle, Day 1 of cycles thereafter.
7. Coagulation (PT/INR, aPTT)
8. Fasting lipid profile
9. HbA1c must be obtained Cycle 1 Day 1, Cycle 3 Day 1 and every 3 cycles thereafter.
10. Fasting serum glucose (in-clinic): patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hrs). The blood sample should be taken approximately 2 hrs after study drug administration with the patient continuing to fast until the blood sample is taken. See Section 11.9.1. **NOTE:** on clinic visit days, when fasting serum glucose must be taken 2 hrs after study drug

administration, it is acceptable for patients to take their doses at a different time than is typical.

11. Fasting serum glucose (in-home): patients will be given a glucometer to monitor their daily fasting blood glucose performed daily from Cycle 1 Day 2 through last dose of PIKTOR, and may be decreased to once weekly after the first 2 months, per Section 11.9.1.
12. Urinalysis must be obtained prior to Day 1 and Day 15 for Cycle 1, and on Day 1 every subsequent cycle.
13. Serum or urine pregnancy test
14. EKG, as clinically indicated.
15. Tumor response by clinical assessment of the patient's disease (ie, by physical examination)
16. Radiological assessment of tumors (ie, chest and abdomen CT scan, radionuclide bone scan) as clinically indicated. The methods used for prestudy assessments should be used throughout the study. If possible, the same equipment should be used each time.
17. If safely accessible, research biopsies of the patient's metastatic locoregional or pulmonary or hepatic disease must be obtained at the time of disease progression on PIKTOR, prior to treatment with nab paclitaxel and cisplatin. If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted.
18. Assessments of other sites of disease must be performed **only to confirm a CR**.
19. A toxicity assessment must be performed.
20. Whole blood collection (40 mL) for germline exome sequencing studies at the time of disease progression (or off treatment) on PIKTOR.
21. Patient diary assessment of PIKTOR dosing
22. Patient diary assessment of in-home glucometer readings. **NOTE:** In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic. See Section 11.9.1.

11.5.3.2 Assessments During Chemotherapy, Cycles 1 – 2

The following assessments will be performed during chemotherapy prior to the start of each cycle, unless otherwise specified. **A chemotherapy (nab paclitaxel plus cisplatin) Cycle is defined as 21 days.**

Note: Assessments will only be completed for the first 2 cycles of nab paclitaxel/cisplatin. For Cycles 3 – 6 data will be collected by chart review.

There is a window (**up to 4 calendar days prior to the scheduled time point**) for assessments during the study. Any delay within this window is NOT a deviation. Assessments that are to be done on days when study drug is administered must be done **prior to dosing** as these assessments (CBC, CMP, assessment of response, etc) may determine whether or not drug is administered, or if a dose reduction is necessary, unless otherwise noted.

1. A brief medical history, to capture events that have occurred since the last cycle. Events that were not captured in the baseline complete medical history should be recorded on the AE page of the CRF.
2. A brief physical examination, including vital signs and body weight.
3. ECOG PS
4. Assessment of concomitant medications
5. A CBC with differential and platelet count
6. A CMP
7. EKG if clinically indicated.
8. Tumor response by clinical assessment of the patient's disease (ie, by physical examination)
9. Radiological assessment of tumors (ie, chest and abdomen CT scan, radionuclide bone scan) as clinically indicated. The methods used for prestudy assessments should be used throughout the study. If possible, the same equipment should be used each time.
10. Assessments of other sites of disease must be performed **only to confirm a CR**.
11. A toxicity assessment must be performed.

11.5.3.3 Assessments During Chemotherapy, Cycles 3 – 6

The following research data will be collected for research purposes. Clinic visits will continue per standard of care.

1. Vital signs, body weight, and ECOG PS
2. Assessment of concomitant medications
3. CBC
4. CMP
5. Tumor response by clinical assessment of the patient's disease
6. Radiological assessment of tumors
7. Toxicity assessment

11.5.4 Off Treatment/End of Treatment Assessments

This is a single assessment that will be performed within 30 days ± 2 days when patient finishes treatment or goes off treatment because of PD from nab paclitaxel plus cisplatin, or toxicity that places patients off treatment, or in cases of physician decision or where patient withdraws consent. Patients who withdraw consent may not want any further assessment; however, they should be encouraged to have these final assessments done.

NOTE: End of treatment, or off treatment, is NOT considered off study or withdrawn from the study. Patients withdrawn under the criteria under Section 11.15 will not be followed.

The following evaluation will be performed at this visit:

1. A brief medical history should be done to capture events that have occurred since the last cycle. Events that were not captured in the baseline complete medical history should be recorded on the AE page of the CRF.

2. A brief physical examination, including vital signs and body weight.
3. A CBC with differential and platelet count.
4. A CMP
5. Coagulation
6. Fasting lipid profile
7. Fasting serum glucose
8. Urinalysis
9. EKG
10. A tumor clinical assessment of the patient's disease (ie, by physical examination).
11. A toxicity assessment.

11.5.5 Follow Up Assessments

The duration of patient participation in the study will be a maximum of 18 months, which is counted **from the start of treatment**, provided progressive disease on or post-nab paclitaxel plus cisplatin has not occurred. Follow-ups will be performed **every 3 months for 1 year from the date of last treatment dose for patients who have not had progression of disease from chemotherapy**.

Note: Patients who die or withdraw consent are considered **off study** and no further information will be collected.

1. Additional therapy
2. Date and site of relapse or progression, including new primary malignancies (new primary malignancies must be reported to Takeda, see Section 14.2).
3. Survival status
4. Toxicities will be recorded for the first 30 days following the last study treatment.
5. Clinical and radiological tumor assessment as per standard of care.

11.5.6 Unscheduled Visits

In special cases as judged by the Investigator, an additional visit to those scheduled can be performed. This visit will be recorded in the patient's records and on the "Unscheduled visit" CRF pages.

If the patient is discontinued prematurely, refer to Section 11.5.4 for required assessments. The resulting data should be documented on the appropriate CRF pages. If, at an unscheduled visit, the investigator determines the patient may remain on study drug, the visit assessments should be documented on the Unscheduled Visit CRF pages.

NOTE: Assessments for an Unscheduled Visit are identical to Section 11.5.3.

11.5.7 Blood Samples for Exome Sequencing

Whole blood collection (40 mL) for exome sequencing studies will be obtained at baseline and at the time of disease progression (or off treatment) from PIKTOR.

No information that identifies the patient will be given to any of the laboratories that will

analyze blood samples. Any material analyzed will be supplied with code number identifiers only, without the patient's name or other identifying information. Access to the database which contains patient identifiers is limited to study investigators and project managers only and is safeguarded by a password protection system. Passwords are not shared. If research findings are published from this study, the research patient will not be identified by name.

11.5.8 Biopsies

Research biopsies will be obtained at the following time points (See Appendix VII for tissue collection and handling):

- A minimum of four*14-gauge needle biopsy cores (or the largest core biopsy deemed safe) will be collected at baseline, prior to the initiation of PIKTOR.
- A minimum of four* 14-gauge needle biopsy cores (or the largest core biopsy deemed safe) will be collected at the time of disease progression on PIKTOR, prior to treatment with nab paclitaxel and cisplatin.

Tissue biopsies of a patient's metastatic locoregional or pulmonary or hepatic disease will be analyzed by next generation sequencing (NGS) for mutations in DNA repair and PI3K pathways, as well as others. Remaining tissue will be frozen and/or formalin-fixed paraffin embedded (FFPE) for biomarker development.

If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted.

11.6 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 (eg, methotrexate, imatinib, topotecan, lapatinib, rosuvastatin, etc.) and organic cation transporter protein 1 or 2 (OCT1 or OCT2) substrates (eg, 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, and targeted agents. Palliative radiation may be administered after discussion with the Principal Investigator.
- Systemic corticosteroids (either IV or oral steroids, excluding inhalers) during TAK-228 and TAK-117 administration, unless necessary for treatment of TAK-228 related AE, ie, rash.
- Enzyme-inducing anti-seizure drugs for patients with treated brain metastasis
- Concomitant administration of any PPI is not permitted during the study administration of TAK-228 and TAK-117. 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 administration of TAK-228 and TAK-117. 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 in Section 11.7 that apply to the use of CYP3A4, CYP2C19 and YP2C9 inhibitors and inducers, histamine H2 receptor antagonists, neutralizing antiacids, calcium and anti-gas preparations.
- Herbal therapies or alternative therapies
- Bisphosphonates or denosumab during the study administration of TAK-228 and TAK-117.

11.7 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.

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 (see Appendix IV). Alternative treatments, if available, should be considered.

All concomitant treatments, including blood and blood products, must be reported on the

source documentation and must be documented on the Concomitant Medications page of the CRF:

- Blood and blood products
- Prophylactic antibiotics
- Premedications (ranitidine, diphenhydramine)
- Antifungals
- Growth factors

All baseline concomitant medications should be collected in the CRF, as well as all OTC concomitant medications. All concomitant medications should be recorded on the source documentation.

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

11.8 Precautions and Restrictions

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 of TAK-228 and TAK-117. Patients will monitor their glucose levels at home daily while on TAK-228 and TAK-117 per Section 11.9.1.

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 [eg, 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 [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

11.9 Management of Clinical Events

11.9.1 Management of Hyperglycemia

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 and have been either Grade 1 or Grade 2, and have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since the institution of a standard regimen for early treatment of hyperglycemia.

All patients developing hyperglycemia during the study should have their glucose closely monitored by study staff. The investigator may choose to continue close monitoring of patients who develop Grade 1 hyperglycemia (fasting glucose >ULN ≤160 mg/dL) or, alternatively, consider initiating treatment with an oral hypoglycemic agent, such as metformin. All patients with ≥Grade 2 hyperglycemia (fasting glucose >160 mg/dL) must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated. The investigator should consult an endocrinologist, if needed, to aid in optimizing the patient's hyperglycemia treatment plan.

It is recommended that patients be initially treated with a fast acting insulin sensitizer such as metformin at 500 mg orally QD, and titrate up to a maximum of 1000 mg orally BID as needed. Concurrent addition to metformin of DPP-4 inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution, due to the higher risk of inducing hypoglycemia in 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.

If any fasting serum glucose reading performed at the site indicates hyperglycemia (>ULN or ≥110 mg/dL), the study staff should first confirm that the patient was fasting at the time of blood specimen collection (ie, nothing by mouth for at least 8 hours before collection).

In-Home Daily Fasting Glucose Monitoring

In addition to obtaining fasting glucose levels at the clinic visits as outlined in the Schedule of Events, all patients will be given a glucometer to monitor their daily fasting blood glucose (FBG) levels at home. The level should be collected daily, predose on study drug dosing days, and at approximately the same time each day.

On Cycle 1 Day 1, the patient will be provided an in-home glucometer. Patients will be trained on proper use of the glucometer and instructed to collect a daily FBG level every morning (predose on dosing days), starting on Cycle 1 Day 2. Patients will be instructed to bring the glucometer and glucometer diary with them to each study visit so that the data

collected can be reviewed and recorded in the source documents. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia.

The patient will be instructed to contact the site immediately if the value is abnormal (ie, ≥150 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic.

If no irregularities in the fasting blood glucose level are observed during a minimum of 2 consecutive months, then the frequency of in-home fasting blood glucose testing can be reduced to a minimum frequency of once weekly, depending on the investigator's judgment and approval. Patients will continue to notify the investigator of fasting blood glucose levels that exceed 150 mg/dL and, if blood glucose levels are not well controlled, or if the patient requires 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.

Guidance on study drug dose modification for patients with hyperglycemia is provided in the tables below.

Table 6. Management of Hyperglycemia

Grade	Description	Treatment	Dose Modification
1	Fasting blood glucose: FGG >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 and TAK-117 by 1 dose level • >2 weeks: discontinue patient from the study.

Table 6. Management of Hyperglycemia

Grade	Description	Treatment	Dose Modification
Prevention/Prophylaxis:			
• Follow fasting glucose levels during clinic visits. • Monitor home glucometer test results. • Check HbA1c levels every 3 months 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.

11.9.2 Management of Hyperlipidemia

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

Table 7. Management of Hyperlipidemia

Grade	Description	Treatment	Dose Modification
1	Cholesterol >ULN to 300 mg/dL Triglycerides >150 to 300 mg/dL	None	None
2	Cholesterol >300 to 400 mg/dL Triglycerides >300 to 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 to 500 mg/dL Triglycerides >500 to 1000 mg/dL	Same as for Grade 2.	Hold TAK-228 and TAK-117 until recovery to ≤Grade 1, then reinitiate TAK-228 and TAK-117 at a dose reduced by 1 level
4	Cholesterol >500 mg/dL 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 of normal

11.9.3 Management of Oral Mucositis

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

Table 8. Management of Oral Mucositis

Grade	Description	Treatment	Dose Modification
1	Asymptomatic or mild symptoms.	• Nonalcoholic mouth wash, or 0.9% salt water rinse. • Consider topical corticosteroids at earliest signs of mucositis.	None
2	Moderate pain, not interfering with oral intake. Modified diet indicated.	• Topical analgesic mouth treatments. • Topical corticosteroids. • Initiate antiviral or antifungal therapy, if indicated.	• Maintain 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 TAK-228 and TAK-117 until recovery to ≤Grade 1, then restart TAK-228 and TAK-117 at a dose reduced by 1 level
4	Life-threatening consequences.	• Same as for Grade 2 • Consider intra-lesional corticosteroids	• Stop TAK-228 and TAK-117 and discontinue patient from the study

Prevention/Prophylaxis:

- Initiation of a nonalcoholic mouth wash, or 0.9% salt water rinses 4 to 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.

11.9.4 Management of Rash

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

Table 9. 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 and TAK-117 by 1 dose level • >3 weeks: stop TAK-228 and TAK-117 and discontinue patient from the study
4	Rash acneifom/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.

11.9.5 Management of Nausea/Vomiting

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

Table 10. Management of Nausea/Vomiting

Grade	Description	Treatment	Dose Modification
≤2	Loss of appetite with or without decreased oral intake; 1 to 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 and TAK-117 reduced by 1 level.
Prevention/Prophylaxis: Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications are encouraged and may be used before each TAK-228 dosing as needed throughout the study.	

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

11.9.6 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 11. 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.

11.9.7 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 12. Management of QTc Prolongation

Grade	Description	Treatment	Dose Modification
2	480 msec <QTc <501 msec	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication, etc).	None; continue TAK-228 and TAK-117 at the same dose and schedule.

Table 12. Management of QTc Prolongation

Grade	Description	Treatment	Dose Modification
≥3	QTc ≥501 msec	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication).(a) 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 TAK-228 and TAK-117 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/

11.9.8 Management of Asthenia, Weakness and Fatigue

Guidance on dose adjustment for patients with other nonhematologic toxicities is provided below.

Table 13. 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 TAK-228 and TAK-117 until recovery to ≤ Grade 1. Reinitiate TAK-228 and TAK-117 at dose reduced by 1 level. Patients who develop Grade 4 nonhematological toxicities (with the exception of isolated non-clinically significant laboratory

Table 13. Management of Asthenia, Weakness, and Fatigue

Grade	Description	Treatment	Dose Modification
			values) should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤ Grade 1 severity.

11.9.9 Management of Aspartate Aminotransferase/Alanine Aminotransferase Elevations

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

Table 14. 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	• Closely monitor LFTs at least weekly or more frequently as indicated. • Assess patient for other causes of transaminitis (eg, past medical history, concomitant medications).	None
3	>5 to 20×ULN; >5×ULN for >2 weeks	Same as for Grade 2.	Hold TAK-228 and TAK-117 until ≤Grade 1; Restart TAK-228 and TAK-117 at the same dose. Permanently discontinue study treatment if in combination with Grade 2 total bilirubin elevation when alternative causes cannot be identified (ie, Hy's Law);
4	>20×ULN	Same as for Grade 2.	Stop 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 (ie, Hy's Law).
Prevention/Prophylaxis: Ensure proper screening of patients for study participation.			

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

11.9.10 Management of Non-infectious Pneumonitis

Guidance for the management of pneumonitis is provided below.

Table 15. 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 and TAK-117 at a dose reduced by 1 level. 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 TAK-228 and TAK-117 until symptoms resolve to ≤Grade 1. • Consider reinitiating TAK-228 and TAK-117 at a dose reduced by 1 level • 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 TAK-228 and TAK-117.

11.10 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 + MLN1117 (TAK-228 + TAK-117) IB for full details.(43)

11.11 Preparation, Reconstitution, and Dispensing

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.

11.12 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 30-ct, 60-cc high density polyethylene (HDPE) bottles with polypropylene, child-resistant caps and induction seal.

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

11.13 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.

11.14 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.

11.15 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, and will be considered "off study". After EOT assessments are completed at withdrawal, no further follow up will be completed. Patients will be withdrawn from the study if any of the following occur:

1. Withdrawal of consent (patient will not be contacted and no further information will be collected). If the patient withdraws consent, then no additional data will be collected without his/her explicit consent; all data collected prior to withdrawal of consent may be used in the data analysis.
2. Termination of study by Baylor IRB or Principal Investigators
3. Disease progression from nab paclitaxel plus cisplatin treatment
4. Intolerable toxicity
5. An intercurrent illness, which would in the judgment of the Investigator, affect assessments of clinical status to a significant degree or require discontinuation of study treatment.
6. Non-protocol therapy (chemotherapy, radiotherapy, hormonal therapy, immunotherapy, or surgery) that is administered during study
7. Noncompliance with protocol or treatment
8. Pregnancy
9. Lost to follow-up (3 attempts should be documented in the patient's source document before the site considers the patient as LFU.)

The date of and reason for discontinuation must be noted on the Case Report Form (CRF). Every effort should be made to complete the appropriate assessments.

If the patient is withdrawn for any reason, the end of study assessments must be completed. Patients who withdraw from the study treatment due to intolerable toxicity will still be followed for outcome and toxicity, per protocol.

Patients must still be followed for adverse events (AEs) for 30 calendar days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, or after 30 days (whichever comes first), unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patients' medical records and as a comment on the CRF.

All patients who have CTCAE grade 3 or 4 laboratory abnormalities at the time of withdrawal must be followed until the laboratory values have returned to grade 1 or 2, or until 30 days after the date of withdrawal (whichever comes first), unless it is, in the opinion of the investigator, not likely that these values are to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the CRF.

12. EFFICACY ASSESSMENTS (SOLID TUMOR)

12.1 Response Criteria

All efficacy assessments will be investigator assessments of response, time to response, and duration of response. Investigator will determine complete response (CR), partial response (PR), stable disease (SD), or progression of disease (PD).

13. STATISTICAL AND QUANTITATIVE ANALYSES

13.1 Statistical Methods

Ten patients with metTNBC will be enrolled in this proof of concept Phase II study and will be treated with TAK-228/TAK-117 followed by cisplatin plus nab paclitaxel at disease progression on PIKTOR. If zero of 10 patients have an objective response with TAK-228/TAK-117, enrollment will be stopped. If at least 1 of 10 patients has an objective response with this combination, an additional 10 patients will be enrolled on study. With a sample size of 20 patients, there is an 80% chance of observing 4 or more responses if the true response rate is at least 20%. The complete response rate and duration of response will also be assessed to determine if TAK-228/TAK-117 followed by cisplatin/nab paclitaxel will produce any exceptional responses of at least 12 months duration following cessation of chemotherapy.

13.1.1 Determination of Sample Size

Twenty patients will be enrolled over 12-18 months.

Twenty patients provides 80% power to reject the null hypothesis that more than 20% of patients will develop toxicity with the combination that leads to treatment cessation, or delay in treatment of more than 4 weeks.

13.1.2 Populations for Analysis

Intent-To-Treat (ITT) Population: Includes all patients registered on the study (eligible and ineligible). This population will be included in overall patient listings, in summary tables of patient demographics and baseline disease characteristics, and also in the list of treatment discontinuations after enrollment.

Evaluable Population: Includes all eligible patients who meet the protocol-specified efficacy analyses requirements and who have received at least 1 dosing of PIKTOR therapy. This population will comprise those patients who will be assessed for pathologic response. Early discontinuation of treatment (in Cycles 1-2), secondary to toxicity, will be considered a treatment failure. If death occurs before the completion of 1 cycle, the patient will be reported as evaluable, early death, but deemed not evaluable for response.

Safety Population: Includes all patients (eligible and ineligible) who receive at least 1 dosing of PIKTOR therapy. This safety population will also be used for the summaries and analysis of all safety parameters (drug exposure, tables of adverse events information, including serious adverse events, etc.). Adverse events that are unrelated to treatment and

that occur >30 days after the administration of treatment will not be reported or analyzed.

13.1.3 Patient Characteristics and Disposition

Patient characteristics including demographics and pretreatment characteristics, breast mass and axillary lymph node size, staging evaluation at baseline, medical history, and family history will be summarized. Descriptive statistics including sample size, mean, standard deviation, median, and minimum and maximum values will be presented for continuous variables. Frequency distributions will be presented for categorical variables.

Patient disposition including the number of patients enrolled, completed, and discontinued from the study will be summarized overall and by study site. The reasons for discontinuation will also be summarized, and patients who discontinued will be listed.

13.1.4 Hypothesis and Endpoints

The hypothesis of this proof of concept Phase II trial is that administration of the oral combination of TAK-228 and TAK-117 will inhibit NHEJ in metastatic TNBC leading at the time of disease progression to metastases that are HR-deficient and sensitive to cisplatin plus nab paclitaxel therapy.

This is an exploratory and descriptive clinical trial in which the primary objective is to assess the objective response rate associated with sequential treatment with the oral combination of TAK-228 and TAK-117 (PIKTOR) followed, upon progression on PIKTOR, by cisplatin plus nab paclitaxel in metastatic triple negative breast cancer (metTNBC) patients.

The secondary objectives of this trial are to assess the safety, duration of response; assess the metastatic TNBC tissues for homologous recombination proficiency and deficiency; and collect frozen and/or formalin-fixed paraffin embedded (FFPE) tissue for biomarker development.

13.1.5 Biopsies

Tissue biopsies of a patient's metastatic locoregional or pulmonary or hepatic disease will be analyzed by next generation sequencing (NGS) for mutations in DNA repair and PI3K pathways, as well as others. Remaining tissue will be frozen and/or formalin-fixed paraffin embedded (FFPE) for biomarker development.

If a research biopsy from a patient's metastatic disease cannot be safely obtained, a skin biopsy is permitted.

14. ADVERSE EVENTS

14.1 Definitions

14.1.1 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.

14.1.2 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.

14.1.3 Serious Adverse Event Definition

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

- Results in **death** (NOTE: Any death from any cause while a patient is receiving treatment on this protocol, or ≤ 30 days following the last dose of protocol treatment must be reported.)
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting

Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

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/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

14.2 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 PIKTOR. Any SAE that occurs at any time after completion of PIKTOR 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 periods must be reported, regardless of causality to study regimen, for a minimum of 3 years after the last dose of the investigational product, starting from the first dose of study drug. 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 (ie, 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 Joyce O'Shaughnessy, MD, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs must also be reported in English to Takeda Pharmacovigilance or designee:

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

See below for contact information for the reporting of SAEs to Takeda Pharmacovigilance.

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

14.3 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 14.2). The pregnancy must be followed for the final pregnancy outcome (eg, 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 14.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

15. ADMINISTRATIVE REQUIREMENTS

15.1 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 14.2).

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17. APPENDICES

Appendix I: 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.

Appendix II: 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:

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

OR

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

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

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Appendix III: New York Heart Association Classification of Cardiac Disease

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

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.

Appendix IV: 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 (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).

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

Appendix V: NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0

Publish Date: May 28, 2009

COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)
Version 4.0

As of May 28, 2009 (v4.03: June 14, 2010), NCI has edited version 4.0 of the Common Terminology Criteria for Adverse Events. These may be obtained at the following web link http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

DO NOT USE CTC VERSION 3.0 TO GRADE TOXICITIES IN THIS STUDY!

Appendix VI: Schedule of Assessments

Assessment	**Prestudy** As per 11.5.1	**During Treatment** ***prior to each cycle, unless otherwise specified*** As per 11.5.3			**End of Treatment** *up to 30±2 days following* As per 11.5.4	**Follow-up** ***every 3 months for 1 year from the date of last treatment*** As per 11.5.5
		PIKTOR	**Chemo, Cycles 1-2**	**Chemo, Cycles 3-6 (*research data only*)**		
Informed consent	✔					
Signed patient authorization (HIPAA)	✔					
Inclusion/exclusion criteria	✔					
Complete medical history	Within 3 weeks prior to registration (PTR)					
Complete physical examination (including vital signs, height, and body weight)	Within 3 weeks PTR					
Brief medical history		✔	✔		✔	
Brief physical exam (vitals, weight)		✔	✔	✔	✔	
Assessment of ECOG PS	Within 3 weeks PTR	✔	✔	✔		
Assessment of conmeds	Within 4 weeks PTR	✔	✔			
CBC with differential and platelet count	Within 4 weeks PTR	✔ [1]	✔	✔	✔	
Complete metabolic profile (CMP)	Within 4 weeks PTR	✔ [2]	✔	✔	✔	
Coagulation (PT/INR, aPTT)	Within 3 weeks PTR	✔			✔	
Fasting lipid profile (total cholesterol, HDL-C,LDL-C, triglycerides)	Within 3 weeks PTR	✔			✔	
HbA1c	Within 3 weeks PTR	✔ [3]				
In-clinic fasting serum glucose	Within 3 weeks PTR	✔ [4]			✔	
In-home daily fasting glucose monitoring		✔ [5]				
Serum or urine pregnancy test	Within 7 days PTR	✔				
Urinalysis	Within 4 weeks PTR	✔ [6]			✔	
EKG	Within 4 weeks PTR	As clinically indicated	As clinically indicated		✔	
Pulmonary function test (if clinically indicated)	Within 4 weeks PTR					
Clinical assessment of disease	Within 3 weeks PTR	✔	✔	✔	✔	✔

Assessment	**Prestudy** As per 11.5.1	**During Treatment** ***prior to each cycle, unless otherwise specified*** As per 11.5.3			**End of Treatment** *up to 30±2 days following* As per 11.5.4	**Follow-up** ***every 3 months for 1 year from the date of last treatment*** As per 11.5.5
		PIKTOR	**Chemo, Cycles 1-2**	**Chemo, Cycles 3-6 (*research data only*)**		
Radiological assessment of disease	Within 4-6 weeks PTR	As clinically indicated	As clinically indicated	✔		As clinically indicated
Assessment of other lesions	Within 4 weeks PTR	To confirm CR	✔			
Research biopsies	Prior to the first day of treatment	At the time of PD on PIKTOR, prior to nab pac/cis				
Whole blood (40 mL)	✔	✔ [7]				
Patient diary: glucometer		✔				
Patient diary: PIKTOR dosing		✔				
Toxicity/AE		✔	✔	✔	✔	For 30 days following last dose
Survival, relapse or PD, additional therapy						✔

[1] A CBC with differential and platelet count every 14 days for the first Cycle of PIKTOR, Day 1 of PIKTOR cycles thereafter.
[2] A CMP every 14 days for the first Cycle of PIKTOR, Day 1 of PIKTOR cycles thereafter.
[3] HbA1c must be obtained Cycle 1 Day 1, Cycle 3 Day 1 and every 3 PIKTOR cycles thereafter.
[4] Fasting serum glucose will be measured in the clinic. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hrs). The sample should be taken approximately 2 hrs after study drug administration with the patient continuing to fast until the blood sample is taken. In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic. See Section 11.9.1.
[5] Patients will be given a glucometer to monitor fasting glucose levels at home collected daily predose on dosing days, at approximately the same time each day, and will be instructed to notify the PI anytime the fasting glucose is abnormal (≥150 mg/dL).
[6] Urinalysis must be obtained prior to Day 1 and Day 15 for Cycle 1, and on Day 1 every subsequent cycle.
[7] Whole blood collection (40 mL) for germline exome sequencing studies at the time of disease progression (or off treatment) on PIKTOR.

Appendix VII: Research Biopsies

Tissue Collection Guidelines for Snap Freezing Tissue for Storage

Tissue will be snap frozen according to the Baylor Biobank Project Management Core (BBPMC) protocol. Briefly, immediately after biopsy, tissue will be placed in a screw-capped cryovial, and submerged in liquid nitrogen for rapid freezing and preservation of tissue. Tissue will then be stored in -80^{o}C freezer until further use.

Tissue Collection Guidelines for TGen Sequencing Testing

The purpose of this Standard Operating Procedure (SOP) is to outline the process for snap freezing tissue for processing and storage at TGen. Tissue samples will be collected from participants who have been properly consented and who have agreed to participate in the research study. Tumor tissues are only suitable for molecular studies if frozen in a timely and appropriate manner. The purpose of this document is to outline standardized procedures for collection sites to follow for snap freezing tissue.

I. **SAFETY**

A. Wear personal protective equipment (PPE), such as lab coats and gloves when handling liquid nitrogen.

B. Liquid nitrogen is extremely cold and can cause 'burns'. Wear gloves that are specially made to withstand liquid nitrogen, as well as eye protection and a lab coat to protect skin from splashes and spills.

II. **MATERIALS & EQUIPMENT**

1. Container with dry ice (for transport of frozen tissue)
2. Clean forceps
3. Liquid nitrogen
4. Pre-labeled cryovials
5. Dry shipper
6. FedEx Airway Bill
7. Biohazardous bag for shipping
8. Dry Ice
9. Personal protective equipment (PPE) to include gloves, lab coat.
10. TGen Specimen Submission Form

III. **PROCEDURES**

This procedure is intended to ensure that tissue samples collected from consented participants will be frozen in a safe and efficient manner while eliminating the risks of contamination and loss of molecular integrity. To facilitate the use of molecular techniques, tissue that has been adequately frozen is vital to obtaining products with high integrity and quality.

For each biopsy, we will collect two to four, 1-2 centimeter 18-gauge core needle specimens from safely accessible tumor. Depending on availability, either two or three cores will be placed in externally-threaded cryovials and immediately flash frozen in liquid nitrogen and stored at -80^{o}C until shipping on dry ice to TGen. An additional tissue core will be formalin-fixed and paraffin-embedded.

A. Tissue Priority

In cases where there is insufficient accessible tumor for collection of four core needle biopsies, sample processing will be prioritized as follows:

1. Flash frozen core for DNA/RNA analysis
2. FFPE core for histopathology
3. Flash frozen cores for biobanking and additional analyses

B. Snap freezing of Tumor Tissue

1. Treat all tissue as potentially infectious.
2. Freezing is performed by research study staff as designated by the collection site principal investigator.
3. Have materials and equipment ready for tissue processing prior to surgery. Have pre-labeled cryovials ready.
4. Fresh tumor tissue should be frozen as soon as possible. Optimally, tissue should be frozen within 30 minutes from biopsy.
5. Do not freeze the tissue directly on ice.
6. Ensure that the biopsied tissue never desiccates or is contaminated by surrounding tissue or other samples. Use clean forceps between samples to avoid cross contamination. Do not place the sample in contact with formalin at any point in the process. Do not add serum to the sample.
7. With clean forceps, place the specimen to be frozen into an empty screw capped cryovial.
8. Close the cryovial.
9. Submerge the cryovial with the specimen into liquid nitrogen. The specimen should freeze within 30-60 seconds.
10. Once snap frozen, samples should be packaged with dry ice and immediately shipped to the TGen.
11. If samples cannot be immediately shipped, samples should be placed on dry ice to be carried to the freezer or liquid nitrogen storage facility for storage until shipping.
12. Complete the TGen Specimen Submission and Requisition Form. Place a patient barcode label on the submission form. The barcode on the Specimen Submission and Requisition Form should match the barcode on the informed consent document and the tissue collection cryovials.
    a) Send the original form with the specimen.
    b) Keep a copy of the requisition in the patient's study binder if applicable.

C. Fresh Frozen Tissue shipment to TGen

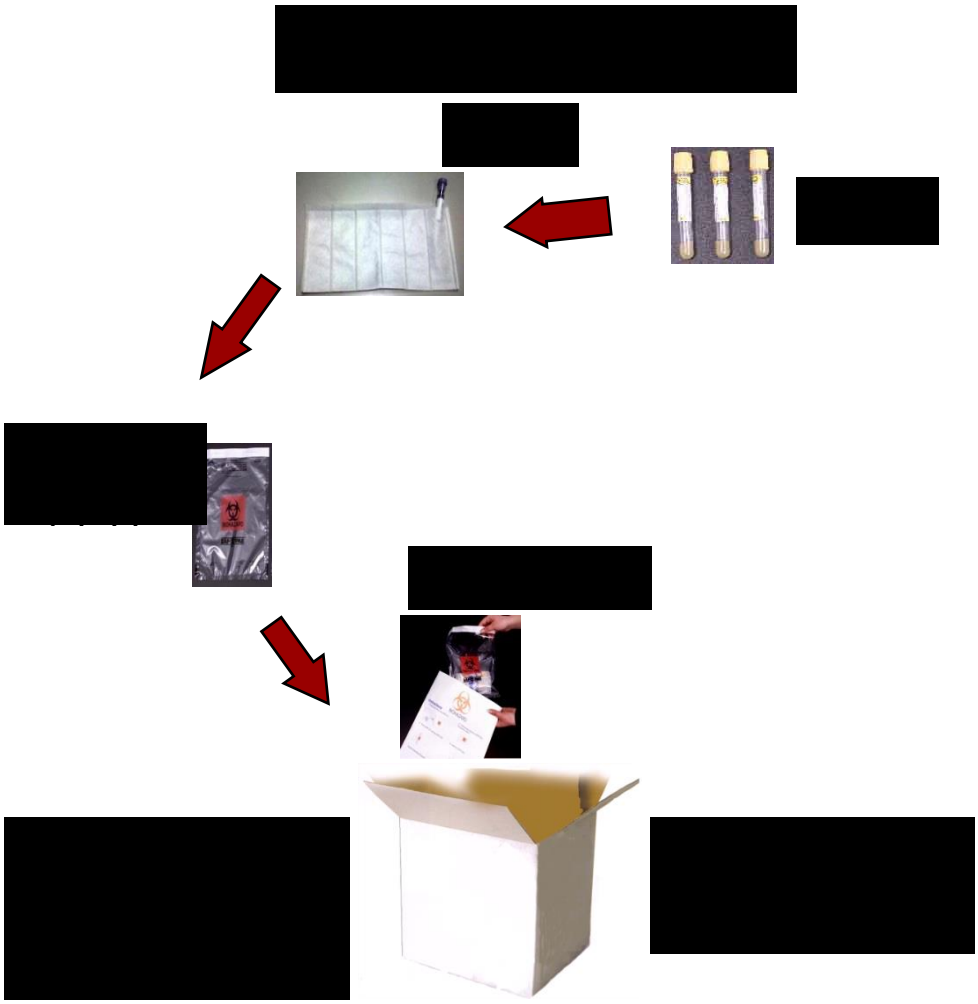
NOTE: Ship Monday through Thursday only unless prior notification is made is made with TGen. Do not ship the day before a U.S. Holiday.

1. Verify the barcode label matches the barcode number of the Specimen Submission and Requisition form.
2. Place cryovial containing frozen specimen in biohazard bag.
3. Place 2-3 inches of dry ice in the bottom of a Styrofoam cooler. Place biohazard bag in the center of the cooler on top of the dry ice, and then fill the cooler the rest of the way with dry ice (preferably pelleted). Place a single paper-towel or

piece of paper across top of ice, then put lid on the cooler and tape the lid tightly to the cooler, sealing all the way around the lid.

4. Place the cooler in the cardboard box, placing all paperwork associated with the case on top of the cooler, and tape shut.
5. The outermost container must be marked with the words Exempt Human Specimen (use labels or write by hand when necessary).
6. The U.S. DOT does not require these labels; however, IATA does require these labels. Therefore, include these labels on all packages in this category to streamline processes. Do not put the universal biohazard symbol on the outside of an exempt package as this may cause confusion regarding classification.
7. The outermost container must be labeled with a hazard class 9 label, UN1845, and net weight of dry ice in kilograms. The label should be affixed to a vertical side of the box (not the top or bottom) and orientated as shown in the picture in Appendix V. The maximum allowable net quantity of dry ice allowed per package is 200kg.
8. Verify the following on the FedEx air bill:
    a) Standard Overnight Shipping
    b) The Airbill must include the statement “Dry ice, 9, UN1845, number of packages X net weight in kilograms”. FedEx has a check box on their Airbill to satisfy their requirement.
9. Call Courier Service to pick up specimens
10. Ship frozen tissue to:

TGen
Collaborative Sequencing Center
c/o L Cuyugan
445 North 5th St.
Phoenix, AZ 85004
602-343-8776
602-343-8545 (fax)



Blood Collection Guidelines for TGen Sequencing Testing

I. Collections at Clinical Site

a. Blood: Collect 2 to 3 tubes of whole blood in 10 mL purple-top EDTA hematology tubes (processing as soon as possible, <1 hour, according to Appendix I).

II. Further Processing

a. Buffy Coat isolation per BPM Core standard protocol, and store at -80°C as usual.

III. Kit contents

1. Three barcoded labels for 10mL purple top EDTA hematology tubes
2. Four to 6 externally threaded cryovials with barcoded labels
3. Consent form

Blood Processing for Extraction of Constitutional Analytes at TGen

Blood samples will be drawn from patients who have been through the informed consent process for participation in the research study. Blood samples will be obtained by personnel qualified to draw blood from participants at the collection site. The purpose of this document is to outline standardized procedures for Collection Sites to follow for blood collection.

Collection kits containing all relevant clinical data collection forms, system-generated barcodes to pre-label tissue and blood collection tubes, shipping manifests, return labels and materials, and appropriate transport documentation will be assembled by trained shipping technicians within the TGen repository. The system-generated barcodes will represent global specimen identifiers that will be tracked by a biobanking software solution hosted by TGen. The system allows the assignment of multiple, unique identifiers to a single biospecimen, and the system can generate and assign a new, unique barcode label for a biospecimen received from a clinical site that may arrive with barcode labels specific to their institution. The system records the new barcode identifier along with the clinical site-specific barcode identifier and the global specimen identifier.

Clinical sites will be provided with SOPs detailing the proper packaging and shipping vessels to be employed for each sample type to protect them from loss, damage, and temperature variations during shipment. These protocols include the use of insulated packing material, refrigerated gel packs, frozen gel packs, dry ice pellets, and liquid nitrogen as appropriate.

I. SAFETY

Always use universal precautions when dealing with any blood samples. Dispose of all blood collection equipment in the appropriate receptacles at the collection site.

II. MATERIALS & EQUIPMENT

1. Tourniquet
2. Alcohol Swab
3. Phlebotomy needle
4. Gauze
5. Pre-labeled purple top EDTA blood collection tubes
6. Adhesive bandage

III. PROCEDURES

This procedure is intended to ensure that blood samples will be obtained from consented participants in a safe and efficient manner while eliminating the risks of contamination. Patient identifiers will remain under HIPAA compliance, and clinical information will be kept in accordance with each site's standard practice. Sample collection kits containing barcoded tubes for shipping samples to the appropriate laboratory will be provided to the collection sites.

A. Timing for Blood Collection

1. Identify the person responsible for processing the blood.
2. Contact this person before or soon after blood collection to arrange timely processing of the sample.

B. Blood Collection Procedure – Preparation

1. Blood collection must be performed by personnel qualified to draw blood.
2. Prior to blood collection, identify the participant, verify identification, and check that informed consent has been obtained.
3. Ensure that the barcoded labels on the blood collection tube match the barcode on the informed consent document.
4. Assemble proper equipment to draw blood.

C. Blood Collection Procedure - Venipuncture

1. Apply tourniquet to expose veins. Do not place too tightly. If superficial veins are not easily apparent, force blood into the vein by massaging the arm from wrist to elbow, tap the site with index and second finger, apply a warm, damp cloth to the site or lower extremity to allow veins to fill.
2. Select appropriate site for venipuncture. Avoid areas with excessive scars or hematomas. While hand and wrist veins are acceptable it is optimal to select an antecubital vein.
3. Prepare the participant's arm using an alcohol prep. Cleanse in a circular fashion, beginning at the site and working outward. Allow to air dry.
4. Anchor the vein and swiftly insert the needle (at a 15-30 degree angle with the surface of the arm) into the lumen of the vein. Avoid excessive probing and trauma to the site.
5. Draw blood 20-30 mL into an evacuated purple top EDTA blood collection tube.
6. When the last tube to be drawn is filling, remove the tourniquet.
7. Remove the needle from the participant and apply a gauze and adequate pressure to the site of venipuncture to avoid hematoma formation.
8. If needed, apply an adhesive bandage to the venipuncture site.
9. Dispose of needles and supplies in a safe manner.
10. Samples should be slowly inverted 8 to 10 times to ensure the mixing of the sample and the anti-coagulant liquid inside the tube.
11. Recheck that the barcode label on the blood collection tube matches the barcode on the informed consent document.
12. Complete the Specimen Submission Form. Place a patient barcode label on the submission form. The barcode on the Specimen Submission Form should match the barcode on the informed consent document and the blood collection tubes.
    a) Send the original form with the specimen.
    b) Keep a copy of the requisition in the patient's study binder if applicable.
13. Transfer the specimen and form as soon as possible to research laboratory for downstream processing (BPM Core).

Appendix VIII: Patient Diaries for PIKTOR administration

PIKTOR Diary

Patient: _____

Dates: _____ **to** _____

When you take your study medication, write the date and time taken in each of the corresponding boxes. Put an "X" in the appropriate boxes on a day that you did not take PIKTOR (missed day). **TAKE YOUR NEXT DOSE AT THE NEXT SCHEDULED TIME.**

PIKTOR (TAK-228 plus TAK-117) should be taken on an empty stomach, with 8 ounces (240 mL) of water. You should not eat for 2 hours before and 1 hour after each dose. You should take your study drug at about the same time each scheduled dosing day, and not take more than what is prescribed. The 2 drugs/capsules that make up PIKTOR must be taken together at the same time. You must swallow the study drug whole and not chew it or open it before swallowing. Keep out of reach of children and do not give to any other person.

On clinic visit days, when fasting serum glucose must be taken 2 hours after study drug, it is OK for you to take your dose at a different time than is typical. Please remember to bring the medication bottles and any remaining medication with you to your next study visit or as instructed by the study staff. Please also bring this diary.

Day of the Week:			
Date:	_____/_____/_____	_____/_____/_____	_____/_____/_____
Medications taken before PIKTOR Dose, if applicable	**Name:** **Time:**	**Name:** **Time:**	**Name:** **Time:**
Amount of PIKTOR taken:			
Dose Time:	☐ AM ☐ PM	☐ AM ☐ PM	☐ AM ☐ PM
TAK-228	**mg**	**mg**	**mg**
TAK-117	**mg**	**mg**	**mg**

Side Effects	Day	Start Time	Stop Time	Treatment	Time Taken	Result
Nausea						
Vomiting						
Diarrhea						
Fatigue						
Loss of Appetite						
Rash						
Mouth Sores						
Constipation						
Other (please describe): _____						

Side Effects	Day	Start Time	Stop Time	Treatment	Time Taken	Result

Appendix IX: Patient Diaries for glucometer readings

Glucometer Diary

Patient: _____

Dates: _____ **to** _____

When you take your fasting blood glucose (FBG), write the date and time taken in each of the corresponding boxes. Take your FBG **before** you take your study drug on the study drug dosing days. Please take your FBG at the same time each day. If any readings are equal to or above 150 mg/dL, please call the coordinator of your study! On days you visit the clinic, you do not have to take your FBG at home; this will be done for you in the clinic.

Date	Time	Glucose mg/dL