October 11, 2019

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
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Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #3 to EA2161, *A Phase II Study of MLN0128 (TAK-228) in Rapalog-Resistant Advanced Pancreatic Neuroendocrine Tumors (PNET)*.

This addendum is in response to a MLN128 (TAK-228) rapid request for amendment from Dr. Austin Doyle dated September 20, 2019.

No updates to the case report forms in Medidata Rave are planned as a result of this amendment.

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

Full IRB review of this addendum is **recommended**, however, ECOG-ACRIN will accept the method of review determined by the standard operating procedures for the IRB of record for this protocol. It is the decision of the local IRB whether or not subjects are to be re-consented.

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. If your local IRB has different SOPs, they must be available at future E-A audit.

The following revisions to EA2161 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date
2.	Section 5.3	Updated the MLN0128 (TAK-228) CAEPR list with Version 2.3, July 28, 2019.

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The following revisions to EA2161 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated Version Date
2.	"What possible risks can I expect from taking part in this study?"	Updated the MLN0128 (TAK-228) condensed risk list with Version 2.3, July 28, 2019.

If you have any questions regarding this addendum, please contact Kevin Pollard at kpollard@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to EA2161 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director, Protocol Development

Enclosure

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ECOG-ACRIN cancer research group
Reshaping the future of patient care

EA2161

A Phase II Study of MLN0128 (TAK-228) in Rapalog-Resistant Advanced Pancreatic Neuroendocrine Tumors (PNET)

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STUDY STATISTICIAN: Paul Catalano, ScD
GI COMMITTEE CHAIR: Peter O'Dwyer, MD

Version Date: October 11, 2019

STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology
SWOG / SWOG

NOTE: As of 11/17, all protocol changes will be noted by addendum number. Please reference the activation memo for the addendum activation date.

ACTIVATION DATE

February 1, 2017

Amendment #1 – 9/17
Amendment #2
Amendment #3

Agents	IND#	NSC#	Supply
MLN0128 (TAK-228) (MLN0128)		768435	DCTD, NCI

Table of Contents

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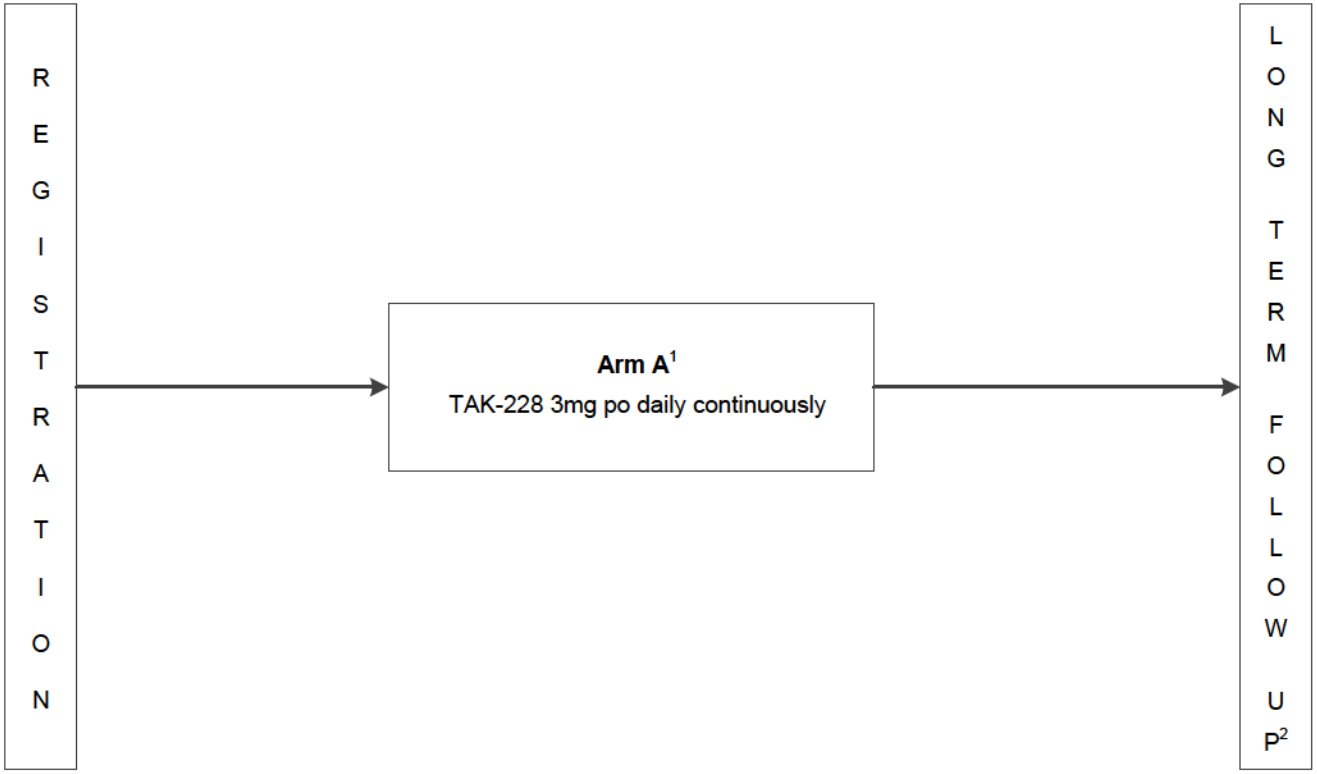
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Schema



Accrual: 40 patients
Cycle: 28 days

1.Treatment will continue until progression or unacceptable toxicity.
2. Patients will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration.

1. Introduction

1.1 Pancreatic Neuroendocrine Tumors (PNETs)

Pancreatic Neuroendocrine Tumors (PNETs) comprise 1.3% to 2.8% of new pancreatic malignancies each year. Despite the relatively low incidence of PNET diagnoses, the prevalence of PNETs has been estimated to be 9.9% of pancreatic malignancies [1]. PNET tumors are classified as functional (10-30% of the tumors) or nonfunctional (50-80%). PNETs are frequently diagnosed at a late stage, with approximately 65% of patients presenting with unresectable or metastatic disease; as a result, the patients have a poor prognosis. The medial survival time for patients with distant metastatic disease is 24 months [2].

Surgery is the mainstay of treatment for patients with localized pancreatic neuroendocrine tumors (NETs). Unfortunately the vast majority of patients with pancreatic NETs present with advanced disease that is not amenable to resection [3]. A variety of systemic therapeutic options can be considered in this setting. Historically, somatostatin analogs, cytotoxic chemotherapy, and, to a lesser extent, interferion, have been the main choices. However, in the past few years, targeted biologic therapies, including the mammalian target of rapamycin (mTOR) inhibitor everolimus and the tyrosine kinase inhibitor sunitinib, have been approved for the treatment of advanced pancreatic NETs.

1.2 mTOR Pathway and PNET

The mammalian target of rapamycin (mTOR) complexes are effectors of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) network that regulated critical and essential cellular functions, including mRNA translation and protein synthesis [4-9]. The engagement and activation of PI3K/AKT signaling results in tumor formation, by promoting celluar proliferation and by inducing antiapoptotic signals that promote survival of the cells [10-14]. The network includes oncogenes and tumor suppressor genes [15].

mTOR is inhibited, in part, by two tumor-suppressor proteins, TSC2 and PTEN. In a large study performed using archival tissue, low expression of TSC2 or PTEN was both observed and associated with shorter survival times in patients with pancreatic NETs [16]. Autocrine activation of the mTOR signaling pathway, mediated through insulin-like growth factor 1, has been implicated in the proliferation of pancreatic neuroendocrine tumor cells [17]. Consistent with this observation is the finding that inhibition of mTOR has a significant antiproliferative effect on pancreatic neuroendocrine tumor cell lines [18, 19]. Constitutive activation of the PI3K/AKT/mTOR pathway has been seen in pancreatic neuroendocrine tumors (PNETs) [16, 20].

Everolimus inhibits mammalian target of rapamycin (mTOR), a serine–threonine kinase that stimulates cell growth, proliferation, and angiogenesis [21].

The RADIANT-1 trial evaluated the effectiveness of everolimus in patients with advanced pancreatic neuroendocrine tumors (PNETs) who had progressed on cytotoxic chemotherapy [22]. Patients were randomized to everolimus monotherapy or a combination of everolimus with octreotide long-acting release (LAR). The PFS was higher in patients treated with the combination therapy (16.7 vs. 9.7 months), thus suggesting a role for this combination in these patients. The phase III RADIANT-3 was a large randomized study of everolimus

compared to placebo, both in combination with best supportive care [23]. This trial enrolled patients with PNET who had progressed in the year preceding enrollment. The median PFS was significantly improved in the treatment group (11 vs. 4.6 months). The commonest toxicities (ranging from 3% to 7%) observed with everolimus were hematologic events, diarrhea, stomatitis, and hyperglycemia. Although the results of this study are robust with regard to the progression-free survival endpoint, no differences in overall survival were observed between the two arms. Although such a trend could have been obscured because of the inclusion of a crossover arm in the study design, improvements in PFS in studies with other malignancies nevertheless have often translated into trends favoring OS.

Altogether, these studies have not only provided evidence that everolimus is well tolerated, but also it has clinical activity in advanced PNETs earning FDA approval.

1.3 mTORC1 and mTORC2

mTOR exists in two multi-protein complexes, mTORC1 and mTORC2, which differ in their binding partners and their sensitivity to rapamycin [24]. mTORC1 forms a complex with raptor (regulatory-associated protein of mTOR), GβL (mLST8), the proline-rich AKT substrate 40 kDa (PRAS40), disheveled, egl-10, and pleckstrin (DEP)-domain containing mTOR-interacting protein (deptor) [25-29]. Raptor appears to be critical for mTORC1 function as it acts as a scaffold to recruit mTORC1 targets [25, 26].

The mTORC1 complexes are the primary regulators for the initiation of signals that control mRNA translation for multiple mRNAs with established 5' terminal oligopyrimidine (TOP) motifs or TOP-like motifs [30]. On the other hand, mTORC2 complexes primarily mediate signals that promote a pro-survival cellular state [31-33]. mTORC2 phosphorylates and activates AKT, a key regulator of cell growth, metabolism and survival.

mTORC1 activity is inhibited by rapamycin (sirolimus) and associated analogs (temsirolimus/CCI-779, everolimus/RAD001, and ridaforolimus/AP23573), which are collectively termed rapalogs. The limited effectiveness of rapalogs as cancer therapy can be explained by its biochemical mechanism as well as its complex and variable signaling responses in cancer cells. These agents suppress mTORC1 activity through their association with FK506 binding protein 12 (FKBP-12) [34]. This drug mechanism does not block all mTORC1 outputs and does not directly target mTORC2-dependent AKT function. mTORC2 is considered to be largely insensitive to rapalogs, although prolonged treatment may be able to reduce mTORC2 activity in some cell types [35-37]. Further contributing to rapamycin resistance is the mTORC1 negative feedback regulation of PI3K pathway. In preclinical and clinical settings, treatment of certain tumor types with rapamycin elevates PI3K-AKT activity and counteracts the therapeutic potential of mTORC1 inhibition.

Rev. Add2

1.4 MLN0128 (TAK-228)

MLN0128 (TAK-228) is an investigational, potent, and highly selective inhibitor of mTORC1/2, which are integral to cell proliferation, angiogenesis, and cellular metabolism. Millennium has developed MLN0128 (TAK-228), which is a novel, highly selective, orally bioavailable adenosine 5' triphosphate (ATP)-competitive

inhibitor of the serine/threonine kinase referred to as the mechanistic target of rapamycin (mTOR). MLN0128 (TAK-228) (formerly INK128) targets 2 distinct mTOR complexes, mTORC1 and mTORC2. MLN0128 (TAK-228) selectively and potently inhibits mTOR kinase (IC50 = 1.1 nM), inhibits mTORC1/2 signaling, and prevents cellular proliferation [40].

Like rapamycin, several newly approved rapalogs (temsirolimus and everolimus) are specific and allosteric inhibitors of mTORC1, and only partially inhibit mTORC1 signaling pathways. They do not directly inhibit mTORC2, which has shown to be an emerging target in cancer research. MLN0128 (TAK-228) was developed to address the incomplete inhibition of the mTOR pathway by rapalogs by targeting both mTORC1 and mTORC2.

1.5 NONCLINICAL SUMMARY

1.5.1 Pharmacology

MLN0128 (TAK-228) selectively and potently inhibits mTOR kinase (the concentration inhibiting 50% of enzyme activity [IC50] is 1.1 nM), inhibits mTORC1/2 signaling, and prevents cellular proliferation.

MLN0128 (TAK-228) inhibited phosphorylation of downstream modulators of mTORC1and mTORC2 in human U87 glioblastoma tumor xenograft models in mice and showed strong tumor growth inhibition (TGI) at tolerable oral (PO) doses in all 8 xenograft models tested (see IB Ed8 for details).

1.5.2 Safety Pharmacology

MLN0128 (TAK-228) has a low potential to affect the human ether-à-go-go related gene (hERG) potassium ion channel and did not affect cardiovascular (CV) parameters in vivo intelemeterized monkeys.

Rev. Add2

1.5.3 Drug Metabolism and Pharmacokinetics

MLN0128 (TAK-228) was rapidly absorbed after PO administration to mice, rats, dogs, and monkeys, with high oral bioavailability. [14C]MLN0128 (TAK-228) was rapidly and widely distributed throughout the body in Long-Evans rats; radioactivity was eliminated from most tissues at 48 hours postdose. MLN0128 (TAK-228) displayed dose-proportional plasma exposures, a moderate ropensity to cross the blood-brain barrier, and was modestly bound (70.5%) to human plasma proteins. MLN0128 (TAK-228) distributed mainly to the plasma of human blood. There was no obvious concentration-dependent red blood cell (RBC) distribution of MLN0128 (TAK-228) in human blood.

MLN0128 (TAK-228) did not inhibit P-glycoprotein, but did inhibit breast cancer-resistance protein (BCRP), organic cation transporter (OCT) 1 and OCT2. M1, the single metabolite (monohydroxylation product) observed in human microsomal incubations, was also observed in rats and monkeys. The main isozymes responsible for phase 1 metabolism appear to be cytochrome P450 (CYP) 2C9, 2C19, and 3A4. MLN0128 (TAK-228) did not induce CYP1A2, 2B6, and 3A4 activity and expression at concentrations up to 10 M. MLN0128 (TAK-228) displayed low potential for inhibition and is not a

time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5.

Oral administration of MLN0128 (TAK-228) in humans has a low potential for metabolic and transporter-based drug-drug interactions (DDIs), especially given clinical exposures observed to date after administration of the highest anticipated therapeutic dose to be used in the clinic in oncology indications (total maximum plasma concentration [Cmax] of 0.48 µM [free Cmax of 0.14 µM] at 30 mg once weekly [QW]).

1.5.4 Toxicology

The toxicologic profiles obtained in the Good Laboratory Practice (GLP)-compliant and non-GLP-compliant studies in rats and monkeys were generally consistent with pharmacologic inhibition of mTORC1/2 activity. Observed toxicities were mostly consistent between sexes. MLN0128 (TAK-228) repeat-dose GLP studies include completed 28-day and preliminary 3-month toxicology studies in rat and monkeys, and embryo-fetal studies in rats and rabbits.

The primary dose-limiting toxicities (DLTs) of MLN0128 (TAK-228) in rats and monkeys were secondary to an exaggerated pharmacologic response and consisted of body weight loss and associated clinical observations that included hunched posture, dehydration, gastrointestinal (GI) distress and decreased activity, appetite, and body temperature. In addition to the previously mentioned effects, a single monkey in the 3-month toxicology study demonstrated a DLT of skin toxicity characterized as progressive acanthosis. The highest exposures tolerated in the preliminary 3-month rat and monkey toxicology studies were 1233 and 194 ng·hr/mL, respectively.

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

The adverse effects in monkeys included hunched posture, dehydration, GI distress, and decreased activity, appetite, and body

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

The findings in rat and monkey repeat-dose toxicology studies with MLN0128 (TAK-228), including bone marrow and lymphoid depletion; GI, liver, pancreas, and skin effects; and effects on glucose and insulin levels, can be monitored in clinical trials. The toxicities seen in the repeat-dose toxicology studies, such as GI effects and glucose and insulin increases, are consistent with the treatment-emergent adverse events (TEAEs), including mucositis and hyperglycemia, observed to date in patients receiving MLN0128 (TAK-228).

Rat and rabbit range-finding embryo-fetal studies demonstrated teratogenic, fetotoxic, and abortive effects with MLN0128 (TAK-228). Embryo-fetal lethality and/or teratogenic effects have been reported with the mTORC1 inhibitors rapamycin and the rapalogs.

MLN0128 (TAK-228) was negative for genotoxicity in an in vitro bacterial mutagenesis (Ames) assay, an in vivo rat micronucleus assay, and an in vivo rat comet assay. An in vitro chromosomal aberration assay with MLN0128 (TAK-228) in human peripheral blood lymphocytes (PBLs) was positive for chromosomal aberrations in the presence and absence of metabolic activation. However, the weight of evidence from the combined results of a negative mutagenicity assay and negative genotoxicity assessments in 2 in vivo assays in 3 tissues (bone marrow, liver, and duodenum) demonstrate that MLN0128 (TAK-228) does not present a genotoxic risk.

MLN0128 (TAK-228) was negative for phototoxicity in the 3T3 fibroblast assay.

1.5.5 Preclinical Data with MLN0128 (TAK-228) in PNET

Promising preliminary data is available from experiments conducted in our lab at the Albert Einstein College of Medicine, Bronx, N.Y. Using a transgenic mouse model of PNETs (insulin producing) that we developed [38], we evaluated the in vivo activity of MLN0128 (TAK-228). The novel transgenic mouse models, Pdx-Cre Men1 floxed/floxed have been shown to develop iinsulinoma with increased cell proliferation, vascularity, and abnormal vascular structures, recapitulating the phenotypes seen in human patients. We tested the effect of MLN0128 (TAK-228) on inhibiting insulin secretion and tumor growth using our developed mouse model. 15 Pdx1-Cre: Men1floxed/floxed mice were assigned to three groups treated with MLN0128 (TAK-228) (N=5), Rapamycin (N=5), and control PBS

(N=5), respectively. A single-dose for MLN0128 (TAK-228) (oral administration) and Rapamycin (i.p) was 1.0mg/kg and 0.5mg/kg, respectively. The mice from treated and control groups received therapy for one month.

The ability of MLN0128 (TAK-228) group to decrease insulin levels, compared to Rapamycin and PBS groups was more significant. By day 7 after administration of MLN0128 (TAK-228), Rapamycin, or PBS control, there was a significant difference in serum insulin levels in the MLN0128 (TAK-228), Rapamycin, or PBS groups: 2.513±0.631 µg/L (MLN0128 (TAK-228) vs PBS: P=0.046), 3.052±0.321 µg/L (Rapamycin vs PBS: P=0.176), and 3.314±0.180 µg/L, respectively by an insulin ELISA assay. Furthermore, with one month treatment, the ability of MLN0128 (TAK-228) group to decrease insulin levels, compared to Rapamycin and PBS groups remained significant: 0.533±0.231µg/L (MLN0128 (TAK-228) vs PBS: P<0.0001), 2.036±0.551 µg/L (Rapamycin vs PBS: P=0.02), 3.478±0.497 µg/L.

The size of insulinoma from each mouse was also analyzed by hisological staining. The PBS and Rapamycin treated group had a significantly larger average tumor size of 0.982±0.176 mm2, and 0.378±0.109 mm2 (Rapamycin vs PBS: P<0.05) compared to the MLN0128 (TAK-228) treatment group with an average tumor size of 0.112±0.034 (MLN0128 (TAK-228) vs PBS: P<0.001). Administration of MLN0128 (TAK-228) reduced insulinoma tumor size in Pdx1-Cre: Men1floxed/floxed mice were more significant compared to Rapamycin, or PBS treated mice.

The size of insulinoma from each mouse was also analyzed by hisological staining. The PBS and Rapamycin treated group had a significantly larger average tumor size of 0.982±0.176 mm2, and 0.378±0.109 mm2 (Rapamycin vs PBS: P<0.05) compared to the MLN0128 (TAK-228) treatment group with an average tumor size of 0.112±0.034 (MLN0128 (TAK-228) vs PBS: P<0.001). Administration of MLN0128 (TAK-228) reduced insulinoma tumor size in Pdx1-Cre: Men1floxed/floxed mice were more significant compared to Rapamycin, or PBS treated mice.

Our results show that the effect of MLN0128 (TAK-228) on inhibiting insulin secretion and tumor cell proliferation is more significant compared to Rapamycin or PBS in our transgenic mouse model with PNETs.

1.6 SUMMARY OF EFFECTS IN HUMANS

MLN0128 (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, study INK128-002 in patients with multiple myeloma [MM], non-Hodgkin lymphoma [NHL] and Waldenström macroglobulinemia [WM]) and study C31002 to measure the effect of MLN0128 (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) [40].

MLN0128 (TAK-228) dosing regimens tested thus far include QD, QW, QD×3days per week (once daily for 3 consecutive days followed by a 4-day dosing holiday every week), and QD×5days per week (once daily for 5 consecutive days followed by a 2-day dosing holiday every week) [40].

Please note that the data described in this section was obtained with the original unmilled MLN0128 (TAK-228) active pharmaceutical ingredient (API); current manufacturing process produces milled MLN0128 (TAK-228) API

1.6.1 Pharmacokinetics

Overall, pharmacokinetic (PK) data from Studies INK128-001, INK128-002, and INK128 003 indicate that MLN0128 (TAK-228) exhibits fast oral absorption (time to reach Cmax [tmax], generally between 1 4 hours after dosing); has dose-linear PK, with a mean plasma half-life of approximately 8 hours; and does not accumulate meaningfully in plasma when dosed as frequently as once daily (QD) and under any of 4 tested dosing regimens. The PK of MLN0128 (TAK-228) was generally consistent, with no appreciable differences across the clinical studies that measured PK. Neither paclitaxel nor MLN0128 (TAK-228) appeared to alter the PK of the other agent when co administered.

1.6.2 Safety

As of the clinical data cutoff (09 December 2014), a total of 335 patients had received ≥ 1 dose of study drug across studies. A total of 18 deaths that occurred within 30 days of the last study drug dose had been reported to the clinical database as of the data cutoff; of these events, 1 (cardiac arrest; Study INK128-001) was considered related to MLN0128 (TAK-228) (see Section 5.3 of the IB Ed 8).

At least 1 treatment-emergent SAE, regardless of causality, had been reported in 125/335 patients (37%). Across the studies and regardless of causality or dosing regimen, the most common TEAEs included nausea, fatigue, hyperglycemia, vomiting, diarrhea, stomatitis, and decreased appetite.

1.6.3 Study INK128-001

Study INK128-001 is a phase 1, first-in-human, dose-escalation study of single-agent MLN0128 (TAK-228) administered to patients diagnosed with advanced solid malignancies, including, but not limited to, colorectal, renal, endometrial, and urothelial tumors. Four dosing schedules are being evaluated (QD, QW, QD×3days per week, and QD×5days per week). Each schedule is administered in 28-day cycles.

As of 09 December 2014, a total of 194 patients had been enrolled. Median age at baseline was 60 years (range, 24-89 years), most (95%) patients are white, and 54% are women. As of data cutoff, 42% had received ≥ 1 dose of MLN0128 (TAK-228) in 2 treatment cycles, while 8% had entered 3 cycles, and 10% had entered 4 cycles. The

highest number of cycles that had been initiated as of data cutoff was 46.

The maximum tolerated doses (MTDs) for the 4 schedules investigated in INK128-001 were determined to be 6 mg for QD dosing, 16 mg for QD×3days per week dosing, 10 mg for QD×5days per week dosing, and 40 mg for QW dosing.

Deaths

As of 09 December 2014, a total of 7 patients in this study had died within 30 days of their last dose of study drug as reported to the clinical database. One death was due to ventricular fibrillation and cardiac arrest, 1 was due to pleural effusion, 1 was due to sepsis, 1 was due to respiratory failure, and the remainder was due to disease progression. The event of ventricular fibrillation and cardiac arrest was the only case considered study drug-related; details are provided in Section 5.3. of the IB Ed8.

Serious Adverse Events

As of the clinical database cutoff date, treatment-emergent SAEs had been reported for 82 patients (42%) in this study. The most commonly reported (≥ 4 patients, overall) preferred terms were stomatitis in 7 patients (4%), pneumonia in 6 patients (3%), abdominal pain or anemia in 5, each (3%), and vomiting, asthenia, or renal failure acute in 4, each (2%).

Treatment-Emergent Adverse Events

Overall, ≥ 1 TEAE was reported for 194 (100%) of the patients. Across the dosing groups, the most commonly reported TEAEs were nausea or hyperglycemia, which were each reported in 125 patients (64%). The second most common TEAE was vomiting (54% of patients), followed by fatigue (51%).

Across all dosing groups, ≥ 1 TEAE of severity ≥ Grade 3 had been reported for 68% of treated patients as of the clinical data cutoff date. Severity ≥ Grade 3 TEAEs, regardless of causality, that were reported in ≥ 5% of patients as of the data cutoff were hyperglycemia (14% of patients), fatigue or hypophosphatemia (8% each), asthenia (7%), anemia or stomatitis (6% each), and lymphopenia or nausea (5% of patients each).

Events leading to study discontinuation

Of the 194 patients treated in Study INK128-001 as of the clinical data cutoff, 110 (57%) discontinued because of disease progression, 20 (10%) withdrew consent, and 15 (8%) were lost to follow-up or discontinued for other reasons.

A total of 68 AEs led to study discontinuation among 35 patients (18%). Of these events, 32 (47%), including 16 nonserious AEs, were reported as severity Grade 3, and 6 SAEs were Grade 5. No Grade 4 events were reported as resulting in study discontinuation. Most (71%) events were considered study drug-related and had resolved as of the data cutoff date.

A total of 12 preferred terms were reported as leading to discontinuation for > 1 patient, including rash (9 patients, including the terms maculopapular [5 patients], rash [2], and rash erythematous or rash pruritic [1 each]), nausea or stomatitis (7 patients each), pruritus or pruritus generalized (4 patients total), and asthenia, fatigue, renal failure/renal failure acute (3 patients, each). Events reported in 2 patients included hyperglycemia, pain or pain in extremity, performance status decreased, and vomiting.

1.6.4 Study INK128-002

Study INK-002 is a completed phase 1, open-label, dose-escalation study of oral MLN0128 (TAK-228) administered as a single agent in patients with relapsed or refractory hematologic malignancies (MM or non-Hodgkin lymphoma, including WM). A total of 39 patients received MLN0128 (TAK-228) in 1 of 2 regimens: 26 patients received QD doses (range, 2-7 mg) and 13 patients were dosed on a QD×3days per week schedule (range, 9-12 mg). The MTD for the QD schedule was 4 mg. The MTD for the QD×3days per week schedule was 9 mg.

A total of 21 of the patients (54%) in this study were male and 87% were white. The median age at baseline was 61 years (range, 46-85 years).

Deaths

Two patients died during Study INK128-002. One death was due to a subdural hemorrhage, and the other was due to disease progression. Both events were considered by the investigator to be unrelated to MLN0128 (TAK-228).

Serious Adverse Events

Treatment-emergent SAEs were reported in Study INK128-002 for 11 patients (28%). No SAE occurred in more than 1 patient. Overall, most SAEs were considered severity Grade 2 or 3. Grade 4 SAEs were reported in 2 patients: hyperviscosity syndrome and hyponatremia were reported in 1 patient in the 2-mg QD dose group (both events resolved); and acute renal failure was reported in 1 patient in the 12-mg QD×3days per week dose group (resolved with sequelae).

No SAEs were considered to be related to MLN0128 (TAK-228) treatment, with the exception of 3 events that were reported in 1 patient. This patient experienced Grade 2 pneumonia on Day 58 that resolved without sequelae on Day 60. On Day 121, the same patient experienced SAEs of pneumonia (Grade 2) and hypoxia (Grade 3). The 3 events improved by Day 125 and were resolved as of Day 142. All 3 events were considered by the investigator to be related to MLN0128 (TAK-228).

Treatment-Emergent Adverse Events

All patients in Study INK128-002 experienced at least 1 TEAE. Overall, nausea was the most frequently reported preferred term (in

56% of patients), followed by fatigue (49%), hyperglycemia (38%), thrombocytopenia (36%), and diarrhea (28%).

TEAEs of severity ≥ Grade 3 were reported in 24 patients (62%); of these, 18 patients (46%) experienced ≥ Grade 3 events that were considered related to study drug. The most common study drug-related ≥ Grade 3 TEAEs were thrombocytopenia (in 15% of patients) and fatigue (10%).

Events Leading to Study Discontinuation

Overall, a total of 20 patients (51%) in Study INK128-002 discontinued due to progressive disease, 11 patients (28%) withdrew consent, and 6 (15%) discontinued due to investigator decision or other reasons.

Most events leading to study discontinuation were considered non-serious. Fatigue was reported as resulting in study discontinuation in 2 patients; all other events were reported as leading to study discontinuation in 1 patient only.

1.6.5 Study INK128-003

Study INK128-003 is a phase 1, open-label, dose-escalation study of oral MLN0128 (TAK-228) administered in 4-week cycles in combination with paclitaxel in patients with advanced solid malignancies (lung, ovarian, endometrial, breast, pancreatic, prostate, etc).As of the clinical data cutoff date, the treatment period for the primary endpoint had completed and long-term treatment for 1 patient remained ongoing.

In this study, 67 patients received ≥ 1 study drug dose under 1 of 3 dosing schedules: QW; QD×3days per week; and QD×5days per week. With each regimen, paclitaxel 80 mg/m^2 was dosed on Days 1, 8, and 15 of each cycle. Patients who tested positive for HER2+ received the combination and also received trastuzumab QW.

At total of 57% of the patients are women and 93% are white. At baseline, the median age was 60 years (range, 21-81 years).

On the basis of dose escalation data, 8 mg of MLN0128 (TAK-228) on the QD×3days per week schedule was selected for the dose expansion phase in patients with breast cancer. The QD×5days per week and QW schedules were abandoned before MTDs were declared, as they were viewed as being less convenient relative to the QD×3days per week schedule from the perspective of administering the paclitaxel and trastuzumab combination.

Overall in the dose expansion phase, patients entered a median of 3.0 treatment cycles (range, 1-19 cycles) and a mean (SD) of 5.6 (6.07) cycles. The overall median duration of exposure was 7.5 weeks, with a duration over 2-fold greater (11.1 weeks) in the MLN0128 (TAK-228) 8 mg QD×3days per week HER2- treatment group relative to the MLN0128 (TAK-228) 8 mg QD×3days per week HER2+ plus trastuzumab group (5.2 weeks). The median cumulative dose was 189.0 mg. Across treatment groups, patients received approximately 75% of their planned dose of MLN0128 (TAK-228).

Deaths

As of the clinical data cutoff date, 9 patients in this study had died within 30 days of administration of their last dose of study drug. Of these patients, 6 died due to disease progression, 1 died due to failure to thrive, 1 died due to enlarging tumor mass causing tracheal compression, and 1 died due to pneumonia. None of the events were considered related to MLN0128 (TAK-228).

Serious Adverse Events

As of the clinical data cutoff date, 55 SAEs had been reported among 29 patients (43%) in this study. Overall, 23 patients (49%) reported ≥ 1 SAE during the Dose Escalation phase and 6 patients (30%) reported ≥1 SAEs during the Expansion phase. The most frequently reported SAEs overall were pneumonia (6 patients), vomiting (2 patients, plus hematemesis in 1 patient), small intestinal obstruction (3 patients), and stomatitis, esophageal carcinoma, sepsis, and failure to thrive in 2 patients each. SAEs reported in most patients (85%) were considered not study drug-related, including all of the fatal events. No SAE event terms were reported in > 1 patient in the dose escalation phase.

Treatment-Emergent Adverse Events

All patients treated in Study INK128-003 reported at least 1 TEAE. The most common (≥ 10% of patients) TEAEs, regardless of causality, that were reported as of the clinical database cutoff include fatigue, nausea, and diarrhea, which were reported in 67%, 60%, and 52% of patients, respectively.

Regardless of causality, TEAEs reported in 54 patients (81%) overall were assessed as severity ≥ Grade 3. The most commonly reported ≥ Grade 3 TEAEs included neutropenia (21% of patients), hypophosphatemia (15%), diarrhea or hyperglycemia (12% of patients each), and fatigue, hypokalemia, and vomiting (10% of patients each).

Events Leading to Study Discontinuation

All but 1 patient had discontinued from MLN0128 (TAK-228) treatment in Study INK128 003 as of the clinical data cutoff. Reasons for discontinuation for the other 66 patients included disease progression (54%), patient decision (24%), or ≥ 1 TEAE (21%). Events reported as leading to study discontinuation for more than 1 patient included fatigue (4 patients) and pneumonia, rash (erythematous or macular), failure to thrive, or vomiting (2 patients, each). A majority (52%) of the events were considered not related to MLN0128 (TAK-228). A total of 9 events (43%) were considered serious and 12 were assessed as severity ≥ Grade 3, including 3 fatal events. Ten events remained ongoing as of the last contact with the patients.

1.6.6 Study C31001

Study C31001 is a phase 1b/2 study of the safety and efficacy of MLN0128 (TAK-228) in combination with exemestane or fulvestrant in women with ER+/HER2– advanced or metastatic breast cancer that has progressed on prior treatment with everolimus in combination with

exemestane or fulvestrant. Patients in this study continue receiving their same prior therapy (either exemestane or fulvestrant) at the same dose, in combination with MLN0128 (TAK-228). As of the clinical data cutoff date, 16 patients had received ≥1 MLN0128 (TAK-228) dose along with either exemestane (7 patients) or fulvestrant (9 patients). A total of 88% of the women treated as of the data cut were white. At baseline, their median age was 56.5 years (range 42-74 years). Of the original 16 patients, 12 remained ongoing as of data cutoff.

Deaths

As of the clinical data cutoff date, no patient had died within 30 days of administration of their last dose of study drug.

Serious Adverse Events

As of the clinical data cutoff date, 3 treatment-emergent SAEs (ataxia, pneumonitis, and upper respiratory tract infection) had been reported in 3 patients (19%). The SAE of ataxia resulted in a dose delay, and no action was taken in response to the other events. All 3 events were reported as being severity Grade 3 and all had resolved as of the data cut. Only the event of pneumonitis was considered related to study drug.

Treatment-Emergent Adverse Events

The most common (≥ 12% of patients) TEAEs, regardless of causality, include nausea, fatigue, and diarrhea or stomatitis, which were reported in 69%, 50%, and 44% of patients, respectively. Regardless of causality, the most common TEAEs considered severity ≥ Grade 3 were alanine aminotransferase increased, diarrhea, fatigue, and nausea, each of which were reported in 2 patients.

Events Leading to Study Discontinuation

Four patients had discontinued from MLN0128 (TAK-228) treatment as of the clinical data cutoff. Reasons for discontinuation were disease progression (2 patients), patient decision (1), and ≥1 TEAEs (1). The TEAE leading to discontinuation was Grade 3 nausea in a patient in the MLN0218 + fulvestrant arm. The event was not considered related to study drug and had resolved as of data cutoff.

1.6.7 Study C31002

Study C31002 is a phase 1 open label, single-arm, multicenter study to evaluate the effect of a single dose of 40 mg MLN0128 (TAK-228) on the QT/QTc (QT interval corrected for heart rate) in patients with advanced solid tumors. After completing the per-protocol PK/ECG assessments on Cycle 1, Day 3, patients may continue to receive MLN0128 (TAK-228) if, in the opinion of the investigator, the patient is deriving clinical benefit, until they experience disease progression. Patients continuing treatment receive MLN0128 (TAK-228) 30 mg QW in 28-day cycles. As of the clinical data cutoff date, 19 patients had received ≥ 1 MLN0128 (TAK-228) dose in this study and 3 had entered Cycle 2. A total of 53% are women and 74% are white. At

baseline, their median age was 63.5 years (range, 46-76 years). Of the original 19 patients, 16 remained ongoing as of data cutoff.

Deaths

As of data cutoff, no reports of events having fatal outcomes had been reported to the clinical database as of data cutoff.

Serious Adverse Events

Serious adverse event information had not been reported to the clinical database as of the data cutoff date.

Treatment-Emergent Adverse Events

The most common (≥ 10% of patients) TEAEs, regardless of causality, include nausea, fatigue, decreased appetite, and vomiting, which were reported in 53%, 42%, 32%, and 21% of patients, respectively. Information regarding severity of TEAEs had not been reported to the clinical database as of data cutoff.

Events Leading to Study Discontinuation

As of data cutoff, 2 patients had discontinued due to ≥ 1 AE. The preferred term for 1 event was pelvic pain. The other event had not been coded as of data cutoff; both events were reported as being Grade 4 in severity, had not yet resolved as of data cutoff, and were not considered study drug-related.

1.7 UPDATED MANUFACTURING PROCESS

In order to allow more predictable absorption of MLN0128 (TAK-228) after oral administration and to allow scale-up manufacturing of MLN0128 (TAK-228) capsules, Millennium/Takeda developed a new milled formulation of the agent. The physical milling step during the granulation process controls particle size distribution of MLN0128 (TAK-228). In order to observe whether this milling step altered the safety and PK profile of MLN0128 (TAK-228), the company performed in vivo studies with PK analysis of milled MLN0128 (TAK-228). These studies indicated that the milled formulation may result in faster absorption with possibly a higher Cmax, which could result in a different safety profile, compared to the previous unmilled API capsules.

Takeda developed new MLN0128 (TAK-228) capsules containing milled API for clinical studies in 1 mg, 3 mg, and 5 mg strengths. Patients receiving the milled formulation were added onto ongoing studies C31001 and C31002, as well as a new study MLN0128-1004, with various treatment cohorts including daily and weekly administration of milled MLN0128 (TAK-228).

The RP2D of milled MLN0128 (TAK-228) was evaluated in 17 patients of MLN0128-1004, with PK, safety, and tolerability assessed. Six patients were given a 4 mg QD dose of milled MLN0128 (TAK-228) and 3 of them had dose-limiting toxicities (DLTs) of rash, appetite loss and fatigue. A dose of 3 mg QD was given to 11 patients with only 1 DLT (decreased platelets) observed. The 3 mg QD dose of MLN0128 (TAK-228) was declared the RP2D, and was generally well tolerated and demonstrated objective responses in patients.

The significant difference in tolerability observed in the comparison of the MTDs between unmilled and milled MLN0128 (TAK-228) when administered QD may

be possibly explained by the effect of food on the safety/tolerability of unmilled MLN0128 (TAK-228) in study IND128-001. The GastroPlusTM simulation performed under fasting conditions on the trial demonstrated that unmilled and milled MLN0128 (TAK-228) administration resulted in comparable exposures to MLN0128 (TAK-228); whereas in the fed state, milled MLN0128 (TAK-228) resulted in a higher Cmax (1.5- to 2-fold higher) and earlier time to Cmax (tmax) than unmilled MLN0128 (TAK-228). Consequently, a dose of 3 mg QD was chosen as the RP2D of milled MLN0128 (TAK-228) administered on empty stomach.

The RP2D for milled MLN0128 (TAK-228) on a QW schedule was determined to be 30 mg, which is the same weekly RP2D as that of the unmilled formulation. Six patients treated at 30 mg QW with the milled formulation did not demonstrate any DLT, but the agent was not escalated further. No DLT had been demonstrated for milled MLN0128 (TAK-228) at the 20 mg QW dose as well.

TAK-228-1004, a phase 1 open-label study, evaluated the safety, tolerability, and PK of milled MLN0128 (TAK-228) in combination with paclitaxel in adult patients with advanced non-hematological malignancies. The RP2D of milled MLN0128 (TAK-228) on this trial was 6 mg given for 3 consecutive days per week in combination with weekly paclitaxel at 80 mg/m2.

1.8 CLINICAL SUMMARY OF SAFETY

1.8.1 Special warnings and precautions for use

1.8.1.1 Insulin and Glucose Levels

On the basis of the clinical experience in MLN0128 (TAK-228) trials, most episodes of hyperglycemia occurred within the first 60 days after initiation of treatment with MLN0128 (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 with elevated fasting blood glucose (FBG) be initially treated with a fast acting insulin sensitizer such as metformin at 500 mg orally QD, which could be titrated up to a maximum of 1000 mg orally twice a day (BID) as needed. Concurrent addition to metformin

of DPP-4 inhibitors (e.g., sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (e.g., 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 (i.e., nothing taken 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 randomized to receive MLN0128 (TAK-228) will be given a glucometer to monitor their daily FBG levels at home. The level should be collected daily, predose on 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 should 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 with them to each study visit so that the data collected can be reviewed and recorded in the source documents. The 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 (i.e., ≥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 FBG level are observed during a minimum of 2 consecutive months, then the frequency of in-home FBG testing can be reduced to a minimum frequency of QW, depending on the investigator's judgment and approval.

Patients will continue to notify the investigator of FBG 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 QD.

Sites are responsible for ordering glucometers through standard institutional mechanisms prior to therapy. Reimbursements are available for non-standard of care

glucometers. Please refer to the funding sheet for additional information.

1.8.1.2 Cardiac Effects

Due to the cardiac death on study INK128-001, the subsequent phase 1 study C31002 evaluated the effect of a single dose of 40 mg MLN0128 (TAK-228) on the QT/QTc interval in patients with advanced solid tumors. After completing the per-protocol PK/ECG/cardiac contractility monitoring, the patients continued on MLN0128 (TAK-228) 30 mg QW with continued cardiac monitoring. The study results showed that treatment with MLN0128 (TAK-228) was not associated with clinically meaningful effects on the overall ECG safety profile or on cardiac contractility, and that ECHO/MUGA scans were not required to determine patient eligibility for MLN0128 (TAK-228) trials. Due to continued concern about the cardiac death of a patient on MLN0128 (TAK-228) treatment, CTEP has agreed to adopt the Takeda standards for ECGs (prior to treatment, end of treatment, and as medically indicated during treatment). CTEP has agreed to the Takeda protocol standard for cardiac eligibility requirements to enter CTEP trials with MLN0128 (TAK-228) regarding prior cardiopulmonary events and QTc eligibility.

1.8.1.3 Renal Function

Elevations in creatinine (regardless of causality) have been observed in subjects receiving MLN0128 (TAK-228), all of which have been reversible with drug interruption and/or supportive care with IV hydration. Further evaluation of the renal insufficiency with urine electrolytes suggested a pre-renal etiology with a low fractional excretion of sodium < 1%. However, the adverse event cases were confounded by multiple factors such as nausea, vomiting, hyperglycemia, concomitant medications with GI side effects such as metformin, and hydronephrosis, any of which may have also contributed to dehydration and elevated creatinine. Subjects should be encouraged to drink at least 20 ounces of fluids a day, especially on days requiring fasting (per protocol), with administration of IV fluids in the clinic as indicated to avoid dehydration.

Baseline macroscopic urinalysis and routine serum chemistries along with other safety laboratory assessments are performed in all MLN0128 (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.

1.8.1.4 Rash

Rash observed in clinical studies of MLN0128 (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.

1.8.1.5 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 MLN0128 (TAK-228) administration. Symptoms of pneumonitis will be closely monitored in all MLN0128 (TAK-228) study subjects.

1.8.2 Interactions with other medications and other forms of interaction

Clinical drug-drug interaction studies have not been conducted with MLN0128 (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 MLN0128 (TAK-228), suggest a low risk for MLN0128 (TAK-228) to precipitate a drug-drug interaction. Although potential drug-drug interactions with MLN0128 (TAK-228) cannot be ruled out based on the known metabolism characteristics of MLN0128 (TAK-228), the potential risk is considered low.

2. Objectives

2.1 Primary Endpoints

2.1.1 To evaluate overall response rate associated with MLN0128 (TAK-228) in patients with advanced pancreatic neuroendocrine tumors (PNETs)

2.2 Secondary Endpoints

2.2.1 To evaluate progression-free survival (PFS) associated with MLN0128 (TAK-228) in patients with advanced pancreatic neuroendocrine tumors (PNETs)

2.2.2 To measure the safety and tolerability of MLN0128 (TAK-228) in patients with advanced PNETs

2.2.3 To evaluate disease control rate associated with MLN0128 (TAK-228) in patients with advanced PNETs

2.2.4 To measure duration of response rate associated with MLN0128 (TAK-228) in patients with advanced PNETs

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician.

Rev. Add2

3.1 Eligibility Criteria

_____ 3.1.1 Patients must be at least ≥ 18 years of age.

_____ 3.1.2 Patients must have unresectable or metastatic, histologically confirmed low or intermediate grade (Klimstra Criteria) pancreatic neuroendocrine tumor (PNET) with radiological evidence of disease progression since last treatment.

_____ 3.1.3 Refractory disease to treatment with an mTOR inhibitor.

_____ 3.1.4 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements, are ineligible

_____ 3.1.5 Disease that is currently not amenable to surgery, radiation, or combined modality therapy with curative intent

_____ 3.1.6 Patients must not have poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoid and small cell carcinoma

_____ 3.1.7 Patients must have measurable disease as defined in Section 6.1.2

_____ 3.1.8 Documented radiological evidence for disease progression (measureable or nonmeasurable) ≤ 12 months prior to enrollment;

NOTE: if patient has had previous radiation to the marker lesion(s), there must be evidence of progression since the radiation; at least one measureable lesion as per Response Evaluation Criteria In Solid Tumors (RECIST)

_____ 3.1.9 Prior or concurrent therapy with SSA is permitted; a stable dose at least 2 months prior to study start and must continue on the stable dose while receiving study treatment; SSA is not considered as systemic treatment.

_____3.1.10 Recovered from adverse events to Grade 1 or less toxicity according to CTCAE 4.0 due to agents administered previously

NOTE: Chemotherapy-induced alopecia and grade 2 neuropathy are acceptable

_____3.1.11 Patients must have ECOG performance status of 0-1.

_____ 3.1.12 Patients must be able to swallow intact capsules.

_____ 3.1.13 Patients must have normal organ and marrow functions as defined below within less than or equal to 14 days prior to registration:

_____ 3.1.13.1 Leukocytes ≥ 3,000/mm^3

Leukocytes _____ Date: _____

_____ 3.1.13.2 Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

Neutrophil count: _____ Date: _____

_____ 3.1.13.3 Hemoglobin ≥ 10 g/dL

Hemoglobin: _____ Date: _____

_____ 3.1.13.4 Platelets ≥ 100 x 10^9/L

Platelets: _____ Date: _____

_____ 3.1.13.5 Total serum bilirubin ≤ institutional upper limit of normal (ULN)

ULN: _____ Bilirubin: _____ Date: _____

_____ 3.1.13.6 Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN

ULN: _____ AST _____ Date: _____

ULN: _____ ALT _____ Date: _____

_____ 3.1.13.7 Serum creatinine ≤ 1.5 X institutional ULN and creatinine clearance ≥ 60 ml/min

ULN: _____ Creatinine: _____ Date: _____

NOTE: Creatinine Clearance must be calculated using the Cockcroft-Gault equation.

_____ 3.1.13.8 Glycosylated hemoglobin (HbA1c) < 7.0%

Hb1A1c: _____ Date: _____

_____ 3.1.13.9 Fasting serum glucose ≤ 130mg/dL

Serum glucose: _____ Date: _____

_____ 3.1.13.10 Fasting triglycerides ≤ 300 mg/dL

Triglycerides: _____ Date: _____

_____ 3.1.14 Diabetics are allowed if:

- Fasting blood glucose (FBG) ≤ 130mg/dL (mmol/L),

OR

- HbA1c ≤ 7%

_____ 3.1.15 Women must not be pregnant or breast-feeding due to potential harm to the fetus from MLN0128 (TAK-228).

All females of childbearing potential must have a blood test or urine study within 7 days of registration to rule out pregnancy.

A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.16 Women of child-bearing potential and men must agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method of contraception, at the same time, from the time of signing the informed consent through 90 days (for female patients) and 120 day (for male patients) after the last dose of study drug, or agree to completely abstain from heterosexual intercourse. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men must agree not to donate sperm during the course of this study or within 120 days after receiving their last dose of study drug.

_____ 3.1.17 Patient is INELIGIBLE if patient discontinued prior mTOR inhibitor due to toxicity.

_____ 3.1.18 Patients must NOT have radiotherapy, or major surgery or active drug therapy for pNET (SSA permitted) within 4 weeks prior to study treatment start

_____ 3.1.19 Patient must NOT have had previous treatment with any PI3K or AKT inhibitor.

_____ 3.1.20 NO Hepatic artery embolization or cryoablation/ radiofrequency ablation of hepatic metastasis within 2 months of study treatment start.

_____ 3.1.21 Patients must NOT have previous or concurrent malignancy within 2 years. Exceptions are made for patients who meet any of the following conditions:

- Adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer

OR

- Adequately treated Stage I or II cancer currently in complete remission, or any other cancer that has been in complete remission for at least 2 years;

  Date of last evidence of disease: _____

_____ 3.1.22 No more than 3 prior systemic treatment regimens for advanced PNET

_____ 3.1.23 Patients with a history of the following within ≤ 6 months of study entry are NOT eligible:

Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures:

Yes: ____ Date: _____ No: ____

Ischemic cerebrovascular event, including transient ischemic attack (TIA) and artery revascularization procedures:

Yes: ____ Date: _____ No: ____

Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation or ventricular tachycardia):

Yes: ____ Date: _____ No: ____

New York Heart Association (NYHA) class III or IV heart failure

Yes: ____ Date: _____ No: ____

Pulmonary embolism

Yes: ____ Date: _____ No: ____

Placement of a pacemaker for control of rhythm

Yes: ____ Date: _____ No: ____

_____ 3.1.24 Patients with known significant active cardiovascular or pulmonary disease at the time of study entry are INELIGIBLE including:

Uncontrolled hypertension (i.e., systolic blood pressure >180 mm Hg, diastolic blood pressure > 95 mm Hg). Use of anti-hypertensive agents to control hypertension before Cycle1 Day 1 is allowed.

Yes: ____ Date: _____ No: ____

Pulmonary hypertension:

Yes: ____ Date: _____ No: ____

Uncontrolled asthma or O2 saturation < 90% by arterial blood gas analysis or pulse oximetry on room air:

Yes: ____ Date: _____ No: ____

QT syndrome, or torsades de pointes

Yes: ____ Date: _____ No: ____

Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention, or history of valve replacement:

Yes: ____ Date: _____ No: ____

Medically significant (symptomatic) bradycardia:

Yes: ____ Date: _____ No: ____

History of arrhythmia requiring an implantable cardiac defibrillator

Yes: ____ Date: _____ No: ____

Baseline prolongation of the rate-corrected QT interval (QTc) (e.g., repeated demonstration of QTc interval > 480 milliseconds, or history of congenital long:

Yes: ____ Date: _____ No: ____

_____ 3.1.25 Patients with known manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of MLN0128 (TAK-228) are INELIGIBLE

_____ 3.1.26 Patients who have a history of brain metastasis are eligible for the study provided that all the following criteria are met:

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

_____ 3.1.27 Human immunodeficiency virus (HIV)-positive patients on combination antiretroviral therapy are INELGIBLE because of the potential for pharmacokinetic interactions with MLN0128 (TAK-228)

_____ 3.1.28 NO treatment with strong inhibitors and/or inducers of cytochrome P450 (CYP) 3A4, or CYP2C19 within 1 week preceding the first dose of study drug.

_____ 3.1.29 NO 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.

_____ 3.1.30 Patients CANNOT have 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

_____ 3.1.31 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.

Physician Signature	Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Rev. Add2 **4. Registration Procedures**

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillabe PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering

credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. However, sites must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB (via IRBManager) to indicate their intention to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office for compliance in the RSS. The Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in a given study so that the study approval can be applied to those institutions. Other site registration requirements (e.g., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the EA2161 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the NCTN Group name link to expand, then select trial protocol #*EA2161*
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements For *EA2161* Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website.

NOTE: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Patient Enrollment

Patients must not start protocol treatment prior to registration.

Treatment should start within seven working days after registration.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Protocol Number

4.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.5 Additional Requirements

4.5.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.5.2 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the

appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.5.3 Digital RT Data Submission Using TRIAD

TRIAD is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit DICOM RT and other objects. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Site physics staff who will submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP Identity and Access Management (IAM) account. Please refer to CTEP Registration Procedures of the protocol for instructions on how to request a CTEP-IAM account.
- To submit images, the site physics user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role. RAs are able to submit standard of care imaging through the same method.

TRIAD Installations:

When a user applies for a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

This process can be done in parallel to obtaining your CTEP-IAM account username and password.

If you have any questions regarding this information, please send an e-mail to the TRIAD Support mailbox at TRIAD-Support@acr.org.

4.6 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA2161 Forms Completion Guidelines.

5. Treatment Plan

5.1 Administration Schedule

5.1.1 MLN0128 (TAK-228) – ARM A

Cycle = 28 days

MLN0128 (TAK-228) 3 mg po QD by mouth once daily every day until disease progression

MLN0128 (TAK-228) is formulated as 3 mg capsule, so patients will take one 3 mg capsule once daily.

Patients will repeat cycles until disease progression (as defined in Section 6.1.4) or unacceptable toxicity.

MLN0128 (TAK-228) will be administered on an empty stomach. 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 should be instructed to take their study medication at approximately the same time on each scheduled dosing day and not to take more than the prescribed dose at any time. Patients should 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 MLN0128 (TAK-228) dose within 12 hours of the scheduled time, then the dose should be skipped and considered a missed dose. Patients should record any missed doses in their diary and resume drug administration at the next scheduled time with the prescribed dosage. Under no circumstance should a patient repeat a dose or double-up doses.

NOTE: Please refer to the Patient Pill Calendar in Appendix II. Patients are required to return their completed Patient Pill Calendar and bring any remaining capsules at each clinic visit.

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

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.5.

5.2 Adverse Event Reporting Requirements

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded

from the CTEP web site
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.

- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). The CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)
- the NCI (301-897-7497)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 230-0159) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 Determination of Reporting Requirements

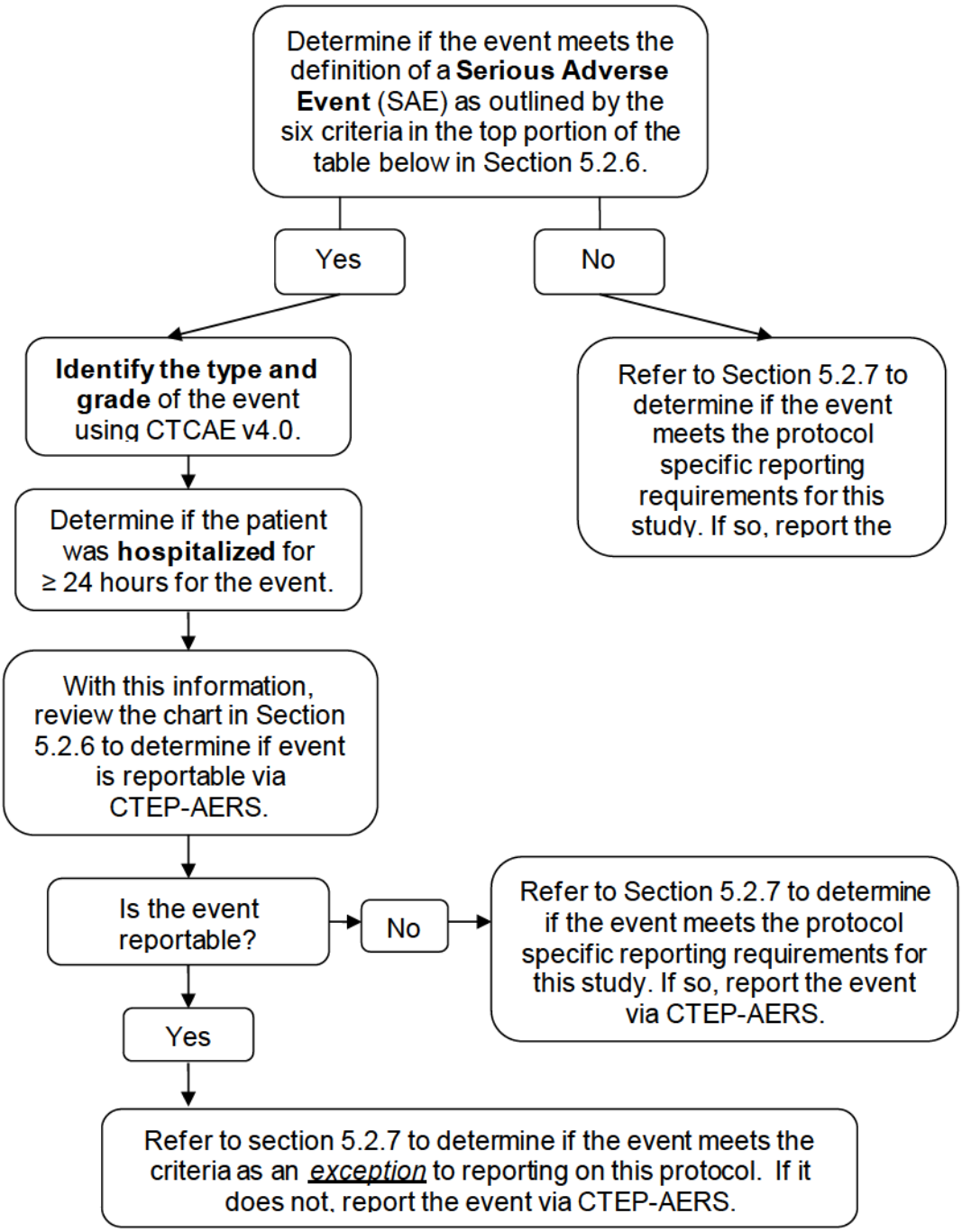
Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol EA2161 and outline the specific expedited adverse event reporting requirements for study EA2161.

5.2.5 Steps to determine if an adverse event is to be reported in an expedited manner – Arm A

5.2.5.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent.



5.2.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.2.6, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.2.6 Expedited Reporting Requirements for Arm A on protocol EA2161

Investigational Agents: MLN0128 (TAK-228)

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1]

Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events Effective Date: May 5, 2011

Rev. Add2

5.2.7 Additional instructions, requirements and exceptions for protocol EA2161

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

EA2161 specific expedited reporting requirements:

- Pregnancies: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the subject is on MLN0128 (TAK-228), or within 28 days of the subject's last dose of MLN0128 (TAK-228), are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix V for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EA2161 specific expedited reporting exceptions:

For study Arm A, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event

5.2.8 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.9 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.

- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for *MLN0128 (TAK-228) (INK128, NSC 768435)*

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 390 patients. Below is the CAEPR for MLN0128 (TAK228). *MLN0128 (TAK-228)*

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER.

Rev. Add3

Version 2.3, July 28, 2019[1]

Adverse Events with Possible Relationship to MLN0128 (TAK-228) (CTCAE 5.0 Term) [n= 390]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac arrest	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		
Mucositis oral			***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	General disorders and administration site conditions - Other (mucosal inflammation)		***General disorders and administration site conditions - Other (mucosal inflammation) (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Urinary tract infection		***Urinary tract infection (Gr 2)***
INVESTIGATIONS			
	Creatinine increased		***Creatinine increased (Gr 2)***

Adverse Events with Possible Relationship to MLN0128 (TAK-228) (CTCAE 5.0 Term) [n= 390]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Electrocardiogram QT corrected interval prolonged	
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 3)***
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
PSYCHIATRIC DISORDERS			
	Insomnia		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Oropharyngeal pain		
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Pruritus			***Pruritus (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on MLN0128 (TAK-228) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MLN0128 (TAK-228) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hyperviscosity syndrome); Blood and lymphatic system disorders - Other (Raynaud's phenomenon); Febrile neutropenia

CARDIAC DISORDERS - Heart failure; Pericardial effusion; Sinus tachycardia; Ventricular arrhythmia

EYE DISORDERS - Blurred vision; Eye pain; Photophobia; Vision decreased

GASTROINTESTINAL DISORDERS - Abdominal distension; Colitis; Dysphagia; Esophagitis; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Gastrointestinal disorders - Other (salivary hypersecretion); Hemorrhoids; Ileus; Oral pain; Pancreatitis; Small intestinal obstruction; Small intestinal perforation; Toothache

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (groin pain); Malaise; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Gallbladder obstruction

IMMUNE SYSTEM DISORDERS - Allergic reaction

INFECTIONS AND INFESTATIONS - Abdominal infection; Infections and infestations - Other (cystitis); Infections and infestations - Other (lower respiratory tract infection); Infections and infestations - Other (mucosal infection); Infections and infestations - Other (parotid gland); Kidney infection; Lung infection; Papulopustular rash; Sepsis; Skin infection; Upper respiratory infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Fracture; Injury, poisoning and procedural complications - Other (accidental overdose); Injury, poisoning and procedural complications - Other (postoperative fever); Injury, poisoning and procedural complications - Other (subdural hemorrhage); Tracheal obstruction

INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Blood lactate dehydrogenase increased; Cholesterol high; GGT increased; Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Metabolism and nutrition disorders - Other (severe chronic malnutrition); Metabolism and nutrition disorders - Other (vitamin D deficiency)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Flank pain; Generalized muscle weakness; Muscle cramp; Myalgia

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (non-hodgkin lymphoma); Treatment related secondary malignancy

NERVOUS SYSTEM DISORDERS - Ataxia; Intracranial hemorrhage; Lethargy; Nervous system disorders - Other (carotid artery occlusion); Nervous system disorders - Other (neuropathy peripheral); Paresthesia; Radiculitis; Stroke; Tremor

PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Psychiatric disorders - Other (mental status changes)

RENAL AND URINARY DISORDERS - Dysuria; Hematuria; Proteinuria; Renal and urinary disorders - Other (strangury)

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Hiccups; Hypoxia; Nasal congestion; Pleural effusion; Pleuritic pain; Pneumothorax; Postnasal drip; Productive cough

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Rash acneiform; Urticaria

VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Thromboembolic event

NOTE: MLN0128 (TAK-228) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Prohibited Concomitant Medication During Study

Subjects taking strong CYP3A4 and CYP2C19 inhibitors and/or inducers should be considered with caution. Alternative treatments that are less likely to affect MLN0128 metabolism, if available, should be considered. If a subject requires treatment with 1 or more of the strong CYP3A4 and CYP2C19 inhibitors and/or inducers, the study doctor should be consulted.

Otherwise, oral administration of MLN0128 in humans has a low potential for metabolic and transporter-based drug-drug interactions. Therefore, except for EIAED and herbal / non-traditional medication, the use of any concomitant medication/therapies deemed necessary for the care of the patient is allowed.

5.4.2 Management of Hyperglycemia

On the basis of the clinical experience in MLN0128 (TAK-228) trials, most episodes of hyperglycemia observed occurred within the first 60 days after initiation of treatment with MLN0128 (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 with elevated fasting blood glucose 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 randomized to receive MLN0128 (TAK-228) will be given a glucometer to monitor their daily FBG levels at home. The level should be collected daily, predose on 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 should 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 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.

Sites are responsible for ordering glucometers through standard institutional mechanisms prior to therapy. Reimbursements are available for non-standard of care glucometers. Please refer to the funding sheet for additional information.

5.4.3 Stomach Acid Neutralizing Agents

The solubility of MLN0128 is pH dependent. Acid neutralizing agents may impact the absorption of the weekly dose of MLN0128. Since the acid neutralizing effects of proton pump inhibitors (PPIs) is longer than that of H2 blockers or antacids, **PPIs (such as omeprazole, esomeprazole, lansoprazole, rabeprazole, pantoprazole, or dexlansoprazole) are <u>prohibited</u> in patients on weekly doses of MLN0128**. Patients on the weekly dose of MLN0128 may use an H2 blocker (such as famotidine, ranitidine, cimetidine, nizatidine) and/or an antacid, but these medications must be held for 24 hours before taking the weekly dose of MLN0128, as well as for 6 hours after taking the weekly dose of MLN0128.

5.4.4 Corticosteroids

Postoperatively, corticosteroids should be tapered to a stable dose as determined by the clinical status of the patient. The lowest required

steroid dose should be maintained throughout the duration of the study in order to eliminate steroid effects as a confounding variable in the interpretation of serial brain imaging studies. Corticosteroid doses can be tapered as clinically indicated if the patient appears to be responding to therapy as judged by serial scans. Corticosteroid dose may, of course, be increased in the event of clinical deterioration or at the discretion of the attending physician. In the event of suspected clinical deterioration, repeat brain imaging is recommended.

5.4.5 Antiemetics

The use of any antiemetic deemed necessary for the care of the patient is allowed.

5.4.6 Anticonvulsants

For this study, patients may not be on enzyme-inducing anti-epileptic drugs (EIAED); patients who require anti-epileptic drugs (AED) may be on non-enzyme inducing anti-epileptic drugs (NEIAED). If a patient on this study protocol needs to have an AED started or needs to have a second AED added, then only NEIAED should be used. There must be a ≥ 10 day period from discontinuation of an EIAED and initiation of therapy. In the event that an enzyme-inducing anti-epileptic drug must be used for a patient on study the patient will be removed from the protocol.

5.4.7 Herbal and Non-Traditional Medications

St. John's Wort is an inducer of CYP3A4 and should be avoided while on this protocol. No other data exist regarding the interaction of MLN0128 with commonly used herbal or non-traditional medications. Patients should be instructed not to use such medications while receiving MLN0128 therapy.

5.5 Dose Modifications

The side effects observed with MLN0128 (TAK-228) are consistent with those observed with other dual TORC inhibitors. Selected toxicities of interest for MLN0128 (TAK-228) include fatigue, gastrointestinal toxicities, pneumonitis, rash, stomatitis, and hyperglycemia and these are described in detail below.

MLN0128 (TAK-228) dose reduction instructions provided in **Table 1** are intended to serve as recommended guidelines to allow ongoing treatment for patients experiencing clinical benefit without signs or symptoms of progression while monitoring patient safety.

MLN0128 (TAK-228) administration should be withheld for MLN0128 (TAK-228)-related toxicities that are ≥ Grade 3 despite supportive treatment per standard clinical practice. If the event resolves to Grade 1 (or Grade 2 for hyperglycemia or rash) or baseline values within 3 weeks of interrupting treatment, the patient may resume study treatment at a dose reduced by 1 level. If dose modification is required for patients receiving 2 mg QD, then the dosing frequency should be decreased to 5 days per week instead of decreasing the daily dose administered. If MLN0128 (TAK-228) dosing is delayed for more than 21 consecutive days for MLN0128 (TAK-228)-related toxicity despite supportive treatment per standard clinical practice, or more than 2 dose reductions of MLN0128 (TAK-228) are

required in a patient, stop MLN0128 (TAK-228) therapy, discontinue the patient from the study.

The investigator may temporarily suspend MLN0128 (TAK-228) dosing for up to 21 days from the last scheduled dose not only due to a MLN0128 (TAK-228) related toxicity but also for an unanticipated medical event not associated with study treatment toxicity or with disease progression. Depending on the nature and the severity of the MLN0128 (TAK-228) -related toxicity, the investigator may resume MLN0128 (TAK-228) dosing in the patient at the same dose or at one dose level lower (as detailed in the tables below).

Table 1	Table of Dose Adjustments for dosing on a continuous (QD) schedule
Dose Level	Dose
1 RP2D	3 mg QD
-1	2 mg QD
-2	2 mg 5 days per week

If there is an indication for further dose reduction, the patient must permanently discontinue MLN0128 (TAK-228). Dose re-escalation is not allowed after a dose reduction.

5.5.1 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 with elevated fasting blood glucose 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 randomized to receive TAK-228 will be given a glucometer to monitor their daily FBG levels at home. The level should be collected daily, predose on 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 should 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 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.

Sites are responsible for ordering glucometers through standard institutional mechanisms prior to therapy. Reimbursements are available for non-standard of care glucometers. Please refer to the funding sheet for additional information.

Table 5.5.1 Management of Hyperglycemia

Grade	Description	Treatment	Dose Modification
1	Fasting blood sugar > ULN to 160 mg/dL	• Continue close monitoring of blood sugar. • Initiate oral hypoglycemic agent.	None
2	> 160 to 250 mg/dL	• Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	• None • If Grade 2 event reoccurs, continue at dose level -1
≥ 3	> 250 mg/dL	• Initiate oral hypoglycemic agent and/or insulin.	Hold MLN0128 (TAK-228) until ≤ Grade 2. Resume MLN0128 (TAK-228) based on timing of recovery after maximal treatment: • ≤ 1 week: resume MLN0128 (TAK-228) at same dose and schedule. • > 1 but ≤ 2 weeks: reduce MLN0128 (TAK-228) by 1 dose level • > 2 weeks: discontinue patient from the study.

Prevention/Prophylaxis:

- Follow fasting glucose levels during clinic visits.
- Monitor home glucometer test results.
- Check HbA1c levels every 3 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.

5.5.2 Management of Hyperlipidemia

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

Table 5.5.2 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 MLN0128 (TAK-228) until recovery to ≤ Grade 1. Re-initiate MLN0128 (TAK-228) at the same dose level • If Grade 2 event reoccurs, continue at dose level -1
3	Cholesterol > 400 to 500 mg/dL Triglycerides > 500 to 1000 mg/dL	Same as for Grade 2.	Hold MLN0128 (TAK-228) until recovery to ≤ Grade 1, then reinitiate MLN0128 (TAK-228) 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.			

5.5.3 Management of Oral Mucositis

Guidance on study drug dose modification for patients with oral mucositis

Table 5.5.3 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 MLN0128 (TAK-228) dose if tolerable • Hold only MLN0128 (TAK-228) if intolerable until recovery to ≤ Grade 1, then restart at same dose. • If Grade 2 event reoccurs, continue at dose level -1
3	Severe pain, interfering with oral intake.	• Same as for Grade 2. • Consider intralesional corticosteroids.	• Hold MLN0128 (TAK-228) until recovery to ≤ Grade 1, then restart MLN0128 (TAK-228) at a dose reduced by 1 level
4	Life-threatening consequences.	• Same as for Grade 2 • Consider intra-lesional corticosteroids	• Stop MLN0128 (TAK-228) 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.

Aggressive mouth care for oral mucositis and stomatitis with mouthwash formulations (e.g., combinations of local anesthetic, antihistamine, corticosteroid, antacid, antifungal and/or antibiotics) may also be helpful in managing symptoms, and it is recommended that these are implemented with early signs of dry mouth, Grade 1 mucositis, or Grade 1 stomatitis (see Table 5.5.3). Examples of mouth care include rinsing with nonalcoholic mouthwash, flossing after each meal, using a mild toothpaste and soft-bristled toothbrush, and avoiding agents containing hydrogen peroxide, iodine, and thyme derivatives. It may also be helpful to advise patients to avoid foods that are spicy, acidic, or salty.

5.5.4 Management of Rash

Treatment-related rash, including cases of Grade 3 rash, has occurred in patients who received MLN0128 (TAK-228) monotherapy or in combination with other anti-cancer drugs. This rash is commonly

manifested as maculopapular type with or without pruritus, with some having developed desquamation. Rash and other dermatological events should be closely monitored. Patients with severe rash should be monitored for associated signs and symptoms, such as fever and hypotension that may be suggestive of a systemic hypersensitivity reaction. For severe rash, hold all study treatment until Grade ≤ 1 (see Table 5.5.4 below), and patients should be treated with supportive therapy per standard of care. Use of topical antihistamine, as well as topical or systemic corticosteroids, may be considered.

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

Table 5.5.4 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 • If Grade 2 event reoccurs, continue at dose level -1
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 MLN0128 (TAK-228) until ≤ Grade 2 Resume MLN0128 (TAK-228) based on timing of recovery: • ≤ 3 weeks: reduce MLN0128 (TAK-228) by 1 dose level • > 3 weeks: stop MLN0128 (TAK-228) and discontinue patient from the study

Patients who develop Grade 4 rash should 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. Grade 4 rash is defined as 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 4.0, effective date 14 June 2010).

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.

Suggested topical steroids include, hydrocortisone 2.5% to face twice daily, triamcinolone 0.1% or fluocinonide 0.1% cream to body bid.

b Suggested oral steroids include methylprednisolone dose pack or prednisone 60 mg daily followed by a taper (e.g., 60 mg × 2 days, 40 mg × 2 days, 20 mg × 2 days, etc.).

5.5.5 Management of Nausea/ Vomiting

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

Table 5.5.5 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 • If Grade 2 event reoccurs, continue at dose level -1
≥ 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 MLN0128 (TAK-228) until ≤ Grade 1, then resume MLN0128 (TAK-228) without dose modification. If experienced for > 72 hours despite optimal therapy, hold MLN0128 (TAK-228) until ≤ Grade 1, then resume treatment with the dose of MLN0128 (TAK-228) reduced by 1 level.
Prevention/Prophylaxis: Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications are encouraged and may be used before each MLN0128 (TAK-228) dosing as needed throughout the study.			
IV=intravenous, IVF=intravenous fluids, TPN=total parental nutrition.			

5.5.6 Management of Cardiac Abnormalities

5.5.6.1 Management of Patients With Possible Cardiac Instability

For patients showing signs of cardiac instability after MLN0128 (TAK-228) administration, additional monitoring onsite before clinic discharge should be considered.

5.5.6.2 Management of Patients With Left Ventricular Dysfunction

Guidance for MLN0128 (TAK-228) dose adjustment for patients with left ventricular dysfunction is provided below.

Table 5.5.6.2 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 MLN0128 (TAK-228) 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.		

5.5.7 Management of Patients with QTc Prolongation

Guidance for MLN0128 (TAK-228) dose adjustment for patients exhibiting a prolonged QTc interval is provided below.

Table 5.5.7 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 MLN0128 (TAK-228) at the same dose and schedule. • If Grade 2 event reoccurs, continue at dose level -1
≥ 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 MLN0128 (TAK-228) 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/

5.5.8 Management of Other Nonhematologic Toxicities (Including Asthenia, Weakness and Fatigue)

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

Table 5.5.8 Management of Other Nonhematologic Toxicities (Including Asthenia, Weakness, and Fatigue)

Grade	Description	Treatment	Dose Modification
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Initiate appropriate medical therapy and monitor.	If tolerable, then no adjustment is required.
2	Moderate; minimal, local or noninvasive intervention indicated.	Initiate appropriate medical therapy and monitor.	• If tolerable, no adjustment required. • If toxicity becomes intolerable, hold MLN0128 (TAK-228) until recovery to ≤ Grade 1, then reinitiate at same dose. • If Grade 2 event reoccurs, continue at dose level -1
≥ 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated		Hold MLN0128 (TAK-228) until recovery to ≤ Grade 1. Reinitiate MLN0128 (TAK-228) at dose reduced by 1 level Patients who develop Grade 4 nonhematological toxicities (with the exception of isolated non-clinically significant laboratory values) should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤ Grade 1 severity.

5.5.9 Management of Aspartate Aminotransferase/ Alanine Aminotransferase Elevations

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

Table 5.5.9 Management of Aspartate Aminotransferase/Alanine Aminotransferase Elevations

Grade	Description	Treatment	Dose Modification
1	> ULN to 3×ULN	None	None
2	Asymptomatic with levels 3 to 5×ULN; > 3×ULN with the appearance of worsening fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia.	• Closely monitor LFTs at least weekly or more frequently as indicated. • Assess patient for other causes of transaminitis (eg, past medical history, concomitant medications).	• None • If Grade 2 event reoccurs, continue at dose level -1
3	> 5 to 20×ULN; > 5×ULN for > 2 weeks	Same as for Grade 2.	Hold MLN0128 (TAK-228) until ≤ Grade 1; Restart MLN0128 (TAK-228) 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 MLN0128 (TAK-228) 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.			

5.5.10 Management of Non-infectious Pneumonitis

Patients will be assessed for pulmonary signs and symptoms throughout the study (including physical examinations, pulse oximetry, and periodic CT scans). Oxygen saturation by pulse oximetry will be measured at every visit as part of the assessment of vital signs Use of

corticosteroids should be considered for symptomatic cases of noninfectious pneumonitis.

Guidance for the management of pneumonitis is provided below

Table 5.5.10 Management of Non-infectious Pneumonitis

Grade	Description	Treatment	MLN0128 (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.	Discontinue Treatment	• Discontinue Treatment

5.6 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

5.7 Excluded Concomitant Medications and Procedures and potential Drug-Drug interactions

The following medications and procedures are prohibited during the study:

- Other investigational agents including mTOR, PI3Kinase and AKT inhibitors
- Other anticancer therapies including chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation or surgery (subjects can have palliative radiation or surgery in the study for pre-existing lesions)
- Systemic corticosteroids (either IV or oral steroids, excluding inhalers), unless necessary for treatment of MLN0128 (TAK-228) related AE, ie, rash.
- Anti-epileptic drugs for subjects with treated brain metastasis
- Concomitant administration of any PPI is not permitted during the study. Patients receiving PPI therapy before enrollment must stop using the PPI for 7 days before their first dose of study drugs. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.
- Neutralizing antacid preparations (acid neutralizers) and calcium supplements are permitted except from 4 hours before until 2 hours after MLN0128 (TAK-228) 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."
- Consumption of grapefruit or grapefruit juice is not permitted during the study. Patients should not consume food or beverages containing the fruit or juice of grapefruits or Seville oranges within 7 days before the first dose of study drug and throughout the study.
- Strong CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2C9 should not be administered within 1 week preceding the first does of study drug(see Appendix VI):
    - CYP3A, 2C9, and 2C19 inducers: rifampin, rifapentine, rifabutin, phenytoin, carbamazepine, oxcarbazepine, phenobarbital, primidone, St. John's Wort, bosentan, nafcillin, modafinil.

- CYP3A, 2C9, and 2C19 inhibitors: ketoconazole, itraconazole, voriconazole, posaconazole, boceprevir, telaprevir, fluconazole, clarithromycin, telithromycin, troleandomycin, erythromycin, nefazodone, mibefradil, conivaptan, diltiazem, verapamil, dronedarone, aprepitant, casopitant, tofisopam, ciprofloxacin, amiodarone, fluvoxamine, and ticlopidine.

5.8 Permitted Concomitant Medications and Procedures

Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before the first dose and subsequent doses of study drug, as needed throughout the study, and as clinically indicated per standard practice. When selecting an anti-emetic agent, drugs that do not have an effect on the QT interval, such as palonosetron, are preferred.

Histamine H2 receptor antagonists may be allowed, if needed provided that the histamine H2 receptor antagonist is not taken within 12 hours before and within 6 hours after study drug administration. 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.

5.9 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA2161 Forms Packet.
- Patient develops disease progression per Section 6.1.4.1
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.

5.10 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

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

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and **never more than four weeks** before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response

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

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm

with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant Lymph Nodes

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

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

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

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

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any

objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

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

6.1.3 Methods for Evaluation of Disease

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

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

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI

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

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

PET-CT

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

Ultrasound

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

Endoscopy, Laparoscopy

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

Tumor Markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology

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

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

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

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered progression, See Section 6.1.4.2.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 8 weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis)

Non-CR/Non-PD

Persistence of one or more non-target lesion(s.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

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

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or

b) there is new pathological confirmation that it is disease (regardless of size).

6.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Rev. Add2

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥ 4 wks. Confirmation
CR	Non-CR***/Non-PD	No	PR	≥ 4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 8 wks. from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD***	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

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

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

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

For Patients with Only Non-Measurable Disease (i.e., Non-Target Disease)

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

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

6.1.4.5 Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 8 weeks.

7. Study Parameters

Rev. Add2

7.1 Therapeutic Parameters

NOTE: All assessments required prior to registration to treatment should be done ≤ 4 weeks prior to registration.

Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within 4 weeks prior to registration.

Prestudy CBC (with differential and platelet count) should be done ≤ 14 days before registration.

All required prestudy chemistries, as outlined in Section 3, should be done ≤ 14 days before registration – unless specifically required on Day 1 as per protocol.

Test/Assessment	Prior to Registration to Treatment	Treatment						End of Treatment	Follow Up[8]
		Every Cycle, prior to treatment	First 2 Cycles	C1D1, C1D14	C2D1, C2D14	Every 2 Cycles	Every 3 Cycles		
H&P, Height, Weight, Vital signs, pulse symetrices[1]	X	X[12]							X
Performance status	X	X[12]							X
CBC w/diff, plts[2]	X	X[12]		X					X
Serum chemistry[2]	X	X[12]		X					X
Urinalysis[3]		X[3]		X[3]	X[3]				
Radiologic evaluation[4]	X					X[5]			X[8]
β-HCG[6]	X								
Toxicity Assessment[7]		X						X	
Pill Count/Diary[9]		X						X	
EKG[10]	X[10]								
Fasting glucose[11]	X	X		X	X			X	
HbA1c	X						X		
Fasting lipid profile	X	X							
At Home Glucose Monitoring			X[13]						

1. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle). Height only needs to be measured at baseline.
2. Serum Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, and magnesium). For eligibility purposes, participants with creatinine levels above institutional normal. CBC w/diff,

platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease. Hyperglycemia management is described in Section 5.4.2.

3. Urinalysis is without microscopy every 2 weeks for C1 and C2, and starting Cycle 3 on D1 of each cycle.
4. CT of the chest, abdomen and pelvis. If only MRI of the abdomen and/or pelvis is available, this can be substituted for CT of the abdomen and/or pelvis but CT of the chest should still be obtained. Contrast agents should be administered unless otherwise contraindicated. PET-CTs can be used, so long as the CT portion is of the same diagnostic quality and included IV and oral contrast. The same screening technique used at baseline should be used for all subsequent follow-up scans. Radiographic imaging should be obtained every 8 weeks by calendar while on treatment.
5. Tumor measurements are repeated every 2 cycles for the first 26 cycles, and every 3 cycles thereafter until PD. Baseline evaluation must be performed within 4 weeks prior to registration, but as close as possible to the start of treatment. Documentation (radiologic) must be provided for patients removed from study for progressive disease.
6. Blood or urine pregnancy test (women of childbearing potential) required no more than 7 days prior to registration.
7. Site personnel should evaluate for toxicity and discuss treatment compliance with the patient in order to ensure the medication is taken correctly; this evaluation may be conducted by telephone or in person.
8. Every 3 months if patient is < 2 years from study entry, every 6 months for year 3, and yearly for years 4 and 5. Toxicity assessments and radiologic evaluations are not required to be done during Follow Up if progression has been previously reported; however if an adverse event occurs post treatment that meets the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred
9. The pill calendar will be collected at the end of every cycle.
10. Within 8 weeks of start of treatment and then as clinically indicated.
11. Fasting 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 hours before the assessment) for each of these measurements, beginning Cycle 1, Fasting glucose can be drawn day 14 ± 3 days and can be drawn at a local lab.
12. The following assessments do not need to be repeated in Cycle 1 if done within 7 days of Day 1: H&P, Weight, Vital Signs; Performance Status; CBC w/diff, plts; Serum chemistry; Concomitant Medications. The Toxicity Assessment and Pill Count/Diary are not required prior to Cycle 1, but required every subsequent cycle.
13. Patients will be responsible for testing Glucose at home daily for the first 2 cycles (8 weeks), then weekly thereafter.

8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

Drug Ordering: Millennium Pharmaceuticals, Inc. is supplying MLN0128 (TAK-228), through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol. Maintenance of NCI drug accountability records is required. MLN0128 (TAK-228) (NSC 768435) [(IND#)] may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information). NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password

NCI Supplied Agent(s) – General Information

NOTE: Under no circumstances can commercially supplied **MLN0128 (TAK-228)** be used or substituted for the NCI-supplied **MLN0128 (TAK-228)**.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-

276-6575. A separate NCI Investigational Agent Accountability Record must be maintained for each patient sequence number and for each agent on this protocol.

Drug Transfers: Vials **MAY NOT** be transferred from one patient to another patient, from one center to another center, or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating center to another participating center, the principal investigator at a participating center changes, etc.) must be approved **in advance** by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (FAX number 240-276-7893) a Transfer Investigational Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. The patient's sequence number and the patient's initials (minimum first three letters of last name) should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number.

8.1 MLN0128 (TAK-228)

8.1.1 Other Names

MLN0128, INK128

8.1.2 Classification

mTOR inhibitor, TORC1/2

8.1.3 Mode of Action

MLN0128 (TAK-228) is a non-rapamycin analog mTOR (mechanistic target of rapamycin) kinase inhibitor. The mTOR kinase regulates cell growth, translational control, angiogenesis, and cell survival by integrating nutrient and hormonal signals. The mTOR complex (TORC) is an intracellular point of convergence for a number of cellular signaling pathways. MLN0128 (TAK-228) is a potent and selective adenosine tri-phosphate (ATP)-competitive inhibitor of mTOR complex 1 and 2 (TORC1/2).

8.1.4 Storage and Stability

Capsules are to be stored in the original package between 15°C to 30°C, with allowed short-term excursions between 2°C and 40°C

8.1.5 Route of Administration

Orally, given 2 hours before or 1 hour after a meal. Do not chew, open or manipulate the capsule in any way prior to swallowing. Each dose should be taken with 8 ounces (240 mL) of water.

8.1.6 Availability

MLN0128 (TAK-228) is supplied by Millennium Pharmaceuticals, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as size 2 hard gelatin capsules in the following strengths: 1 mg (white opaque color) or 3 mg (orange opaque color). The composition of the drug product consists of a blend of MLN0128 drug substance, microcrystalline cellulose, and magnesium stearate. **Milled** formulations will have a white label with a large watermark of the strength on the label.

8.1.7 Side Effects

Please refer to Section 5.3 for a comprehensive list of side effects

8.1.8 Nursing/Patient Implications

Women of childbearing potential should use effective methods of contraception during and through 90 days after the last dose of MLN0128 (TAK-228).

Men should use effective methods of contraception and not donate sperm during and through 120 days after the last dose of MLN0128 (TAK-228).

8.1.9 References

Investigator's Brochure. MLN0128 (TAK-228), In: Takeda Pharmaceutical Co., ed.: 2016

9. Statistical Considerations

This trial will have a two-stage optimal design with a primary endpoint of evaluation of objective tumor response (CR + PR). Secondary endpoints are to estimate PFS, describe response duration, and to evaluate toxicity. The null hypothesis is a 5% true response rate versus the alternative hypothesis of a 20% true response. The first stage will recruit 13 patients in order to accrue 12 eligible and treated patients. If among the 12 eligible patients at least 1 patient has an objective response to therapy, the study will move to the second stage of accrual where 27 additional patients will be enrolled to achieve accrual of 25 eligible and treated patients. If necessary, accrual will halt during the first stage to allow assessment of response among the first cohort of patients. If accrual goes as projected, the minimum time interval for first stage analysis is roughly 10 months. If at the end of the second stage 4 or more patients attain objective response to therapy, the null hypothesis will be rejected and the agent will be recommended for further evaluation. This design has type I error of 0.094, 90.2% power and a probability of rejection at the first stage under the null hypothesis of at least 54%.

Adverse event evaluation is an important secondary endpoint. With full accrual of 37 eligible and treated patients, a 90% confidence interval for any given adverse event proportion will be no wider than 29%. In addition, in the first stage of 12 eligible patients, there is at least 80% probability of observing at least one toxicity if the true toxicity probability is as low as 13%. At full accrual of 37 eligible, and treated patients there is at least 80% probability of observing one or more adverse events if the true rate is as low as 5%. In order to allow for ineligibility, this trial will have an accrual goal of 40 patients. Based on previous studies in pancreatic neuroendocrine tumors, we expect to be able to accrual approximately 4 patients per month on this study.

Progression-free survival, disease control rate and duration of response are also secondary endpoints. Their analyses will be descriptive in nature.

Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

9.1 Gender and Ethnicity

Based on previous data from E2211 the anticipated accrual in subgroups defined by gender and race is:

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	2	0	0	5
White	13	19	1	1	34
More Than One Race	0	0	0	0	0
Total	16	22	1	1	40

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Electronic Data Capture

Please refer to the EA2161 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

10.1 Records Retention

FDA regulations (21 CFR 312.62) require clinical investigators to retain all trial-related documentation, including source documents, long enough to allow the sponsor to use the data to support marketing applications.

This study will be used in support of a US marketing application (New Drug Application), all records pertaining to the trial (including source documents) must be maintained for:

- two years after the FDA approves the marketing application, or
- two years after the FDA disapproves the application for the indication being studied, or
- two years after the FDA is notified by the sponsor of the discontinuation of trials and that an application will not be submitted.

Please contact the ECOG-ACRIN Operations Office – Boston prior to destroying any source documents.

11. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

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A Phase II Study of MLN0128 (TAK-228) in Rapalog-Resistant Advanced Pancreatic Neuroendocrine Tumors (PNET)

Appendix I

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

A Phase II Study of MLN0128 (TAK-228) in Rapalog-Resistant Advanced Pancreatic Neuroendocrine Tumors (PNET)

Appendix II

Patient Pill Calendar

Pill Calendar Directions

1. Take your scheduled dose of each pill.
2. Please bring the empty bottle or any leftover tablets and your pill calendar to your next clinic visit.
3. All doses should be taken at least 2 hours before a meal or 1 hour after a meal at approximately the same times each day, with water only.
4. MLN0128 (TAK-228) is to be once per day every day.
5. In the event that you vomit after MLN0128 (TAK-228) dosing, do not retake new tablet(s), but continue to take the next dose at the regular time on the following day.
6. Should you miss scheduled dose, you will be allowed to take the dose up to a maximum of 12 hours after the scheduled dose time. If greater than 12 hours after the scheduled dose time, the missed dose should not be taken and you should take their allotted dose at the next scheduled time.
7. If you need to take the dose earlier for whatever reason, you can take the dose up to 2 hours earlier than the scheduled dose time.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each pill. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed pill calendar to your doctor's visits.

MLN0128 (TAK-228) should be swallowed whole (not chewed) with one 8 ounce glass of water. You should take your dose of MLN0128 (TAK-228) at approximately the same time each day without food. If you miss a dose (if it is not taken within 12 hours after the scheduled dosing time) or vomit up the tablets of MLN0128 (TAK-228), you should skip that dose and start your dosing with the next scheduled dose. You will not be allowed to make up missed doses.

Patient ID#:_____

MLN0128 (TAK-228)

DAY	Date			Time capsules taken (Specify AM or PM)	Number of capsules taken (3 mg)	Number of capsules taken (1 mg)	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, if any dose was vomited, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year				
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							

DAY	Date Month	Day	Year	Time capsules taken (Specify AM or PM)	Number of capsules taken (3 mg)	Number of capsules taken (1 mg)	Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, if any dose was vomited, other medicine you have taken and anything else you think would be of interest.)
22							
23							
24							
25							
26							
27							
28							

Patient Signature: _____ Date: _____

A Phase II Study of MLN0128 (TAK-228) in Rapalog-Resistant Advanced Pancreatic Neuroendocrine Tumors (PNET)

Appendix III

CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

A Phase II Study of MLN0128 (TAK-228) in Rapalog-Resistant Advanced Pancreatic Neuroendocrine Tumors (PNET)

Appendix IV

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

A Phase II Study of MLN0128 (TAK-228) in Rapalog-Resistant Advanced Pancreatic Neuroendocrine Tumors (PNET)

Appendix V

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on MLN0128 (TAK-228), or within 28 days of the patient's last dose of MLN0128 (TAK-228) must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERs)

(http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERs report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERs report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERs report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERs.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.
- *It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERs report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* CTEP-AERs report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Fetal Death

A fetal death is defined in CTCAE as "*A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation.*"

It must be reported via CTEP-AERs as Grade 4 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions*".

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "*A disorder characterized by cessation of life occurring during the first 28 days of life*" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERs AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to MLN0128 (TAK-228) must also be reported via CTEP-AERs.

It must be reported via CTEP-AERs as Grade 4 "*General disorders and administration - Other (neonatal loss)*"under the System Organ Class (SOC) "General disorder and administration".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERs reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

A Phase II Study of MLN0128 (TAK-228) in Rapalog-Resistant Advanced Pancreatic Neuroendocrine Tumors (PNET)

Appendix VI

CYP3A4 Strong Inducers and Potent Inhibitors

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as Facts and Comparisons or Lexicomp; medical reference texts such as the Physicians' Desk Reference may also provide this information. The Principal Investigator should be alerted if the subject is taking any agent on these lists. Appropriate medical judgment is required.

CYP3A4 Inducing Agents:

Ketoconazole
Protease inhibitors (danoprevir, ritonavir, saquinavir, indanavir, tapranavir, telaprevir, elvitegravir, lopinavir, nelfinavir, bocepravir)
Cobicistat
Conivaptan
Nefazodone
Mebefradil
Itraconazole
Posaconazole
Voriconazole
Clarithromycin
Telithromycin
Troleandomycin

CYP3A4 Potent Inhibitors:

Phenobarbital
Carbamazepine
Phenytoin
Rifampicin
Rifabutin
Mitotane
Enzalutamide
St John's Wort

CYP2D6 Sensitive Substrates:

Amitryptyline
Atomoxetine
Cenlafaxine
Desipramine
Dextromethorphan
Doxepin
Metoprolol
Venlafaxine
Nebivolol
Nefazodone
Paroxetine
Perphenazine
Trimipramine
Tolterodine
Tropisetron

CYP2D6 Substrates with Narrow Therapeutic Range:

Thioridiazine

A Phase II Study of MLN0128 (TAK-228) in Rapalog-Resistant Advanced Pancreatic Neuroendocrine Tumors (PNET)

Appendix VII

Information On Possible Drug Interactions

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **MLN0128 (TAK-228)**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

MLN0128 (TAK-228) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- Some of the enzymes in question are UGT 1A9, 2B7 and CYP 3A4/5 and 2C9. MLN0128 (TAK-228) is broken down by these enzymes and is affected by other drugs that are potent inducers or inhibitors of UGT 1A9, 2B7 and CYP 3A4/5 and 2C9. Avoid use of other drugs that are strong inducers or inhibitors of these enzymes within 2 weeks (within 3 weeks for St John's Wort) of MLN0128 (TAK-228) administration.
- MLN0128 (TAK-228) may affect other drugs by inhibiting enzymes needed to clear them from the body. These enzymes are CYP 3A4/5, 2C9, 2D6, 2B6, 2C19. Avoid use of other drugs that are sensitive substrates of these enzymes within 2 weeks of MLN0128 (TAK-228) administration.
- The transport proteins in question are OATP1B1, OCT2 and BCRP. MLN0128 (TAK-228) may inhibit other drugs from being moved in and out of cells/organs by these transport proteins. In particular, metformin and certain statins may interact with MLN0128 (TAK-228) and need to be managed carefully in patients taking them concurrently.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

MLN0128 (TAK-228) may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

MLN0128 (TAK-228) must be used very carefully with other medicines that affect UGT 1A9, 2B7 and CYP 3A4/5, 2C9 enzymes needed to clear it from your body. MLN0128 (TAK-228) may affect enzymes CYP 3A4/5, 2C9, 2D6, 2B6, 2C19 that are needed to clear other drugs from your body. MLN0128 (TAK-228) inhibits OATP1B1, OCT2 and BCRP transport proteins that may be required to move other drugs in and out of cells/organs. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any

medicines and herbal supplements that are considered "strong inducers/inhibitors of UGT 1A9, 2B7 and CYP 3A4/5, 2C9 or substrates of CYP 3A4/5, 2C9, 2D6, 2B6, 2C19 or substrates of transport proteins OATP1B1, OCT2 and BCRP."

- Please be very careful! Over-the-counter drugs (including herbal supplements such as St John's Wort) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking MLN0128 (TAK-228)
- Drug interactions with medications that are strong inhibitors or potent inducers of CYP3A4 may occur
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is

  _____ and he or she can be contacted at

  _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **MLN0128 (TAK-228)**. This clinical trial is sponsored by the NCI. MLN0128 (TAK-228) may interact with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement
- MLN0128 (TAK-228) interacts with UGT 1A9, 2B7 and CYP 3A4/5, 2C9, 2D6, 2B6, 2C19 and transport proteins OATP1B1, OCT2 and BCRP and must be used very carefully with other medicines that interact with these enzymes and transport proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of UGT 1A9, 2B7 and CYP 3A4/5, 2C9 or substrates of CYP 3A4/5, 2C9, 2D6, 2B6, 2C19 or substrates of transport proteins OATP1B1, OCT2 and BCRP."
- Avoid ingesting grapefruit juice, grapefruit and Seville oranges while taking MLN0128 (TAK-228).
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.

Your study doctor's name is _____

and can be contacted at

_____.