FRONT SHEET:

MLN0128 FOR METASTATIC MERKEL CELL CARCINOMA

NCT02514824

IRB Approval Date: Amendment 4/March 18, 2016

DF/HCC Protocol #: 15-223

TITLE: MLN0128 in recurrent/metastatic merkel cell carcinoma

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IND #: 126536

Protocol Type / Version # / Version Date: Amendment 4/March 18, 2016

Agent: MLN0128

SCHEMA OF THE STUDY

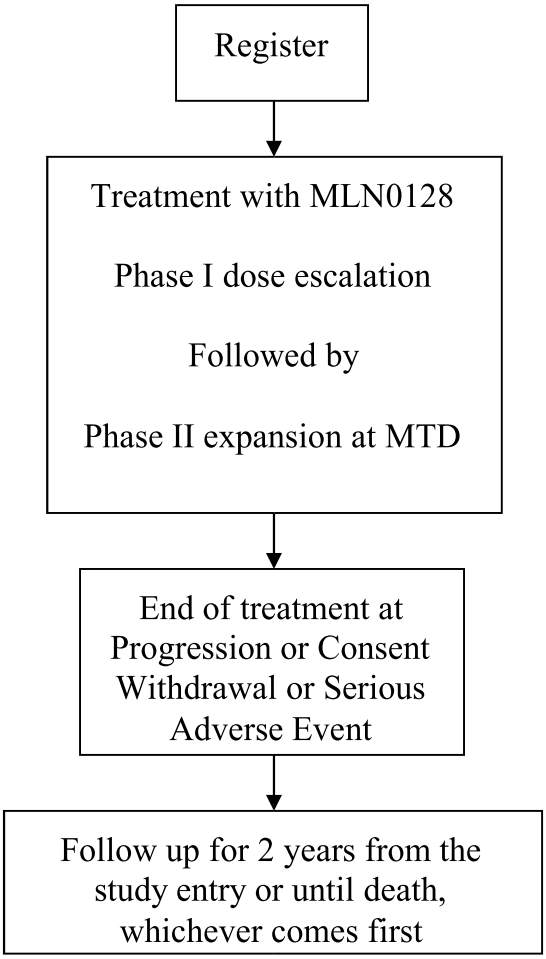

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This is a single arm, non-randomized, phase I/II, pilot/feasibility study, to determine the recommended phase II dose (RP2D) and toxicity and efficacy of MLN0128 in metastatic/recurrent Merkel Cell Carcinoma (MCC), an orphan disease. Between 6 and 34 patients could be entered into this trial, a maximum of 18 in the phase I and a maximum of 16 in the phase II portion of the trial. The phase I design will be standard 3+3. The starting dose will be 3 mg QD. Each cohort will be evaluated for tolerability after completing 1 cycle of treatment before proceeding to escalation (4 mg QD or 5 mg QD) or de-escalation (2 mg QD or 2mg 5 days a week). Escalation/de-escalation will not proceed beyond 5 mg QD or below 2 mg 5 days a week respectively. The phase II portion of the study will be conducted according to a two-stage phase II design. The phase II part of the study will use the RP2D determined during the phase I part of the study.

1.2 Primary Objectives

- Phase I: To determine the recommended phase II dose (RP2D)
- Phase II: To evaluate response rate (ORR)

1.3 Secondary Objectives

- To evaluate overall survival (OS)
- To evaluate progression-free survival (PFS)
- To evaluate safety/adverse events
- Identification of biomarkers predictive of response to therapy with MLN0128

2. BACKGROUND

2.1 Study Disease

Although uncommon, Merkel Cell Carcinoma (MCC) incidence has tripled in US from 1986 to 2001. It is an orphan and devastating disease, usually affecting elderly patients. No standard of care is available for patients with recurrent or metastatic disease. Given histologic and biologic similarities between MCC and Small Cell Lung Cancer, platinum/etoposide combination therapy is commonly used. Although response rates can be as high as 60%, median duration of response is 8 months (less than 3 months for those with partial response) [1]. Response rates to second and third line therapies are substantially lower (40% and 20%, respectively), with most patients dying within a year with metastatic disease. In addition, toxic death rate from chemotherapy for this patient population has been described as 4-8% [1].

More recently, a human polyomavirus (MCV) was implicated in the pathogenesis of MCC. It is constituted by 5,387 base pairs, encoding for the large T (LT) antigen and small T (ST) antigen, which act differently and sinergistically to promote cell proliferation and transformation.

Shuda et al. [2] showed that MCV ST antigen reduced turnover of hyperphosphorylated 4E-BP1, which in turn increased eIF4E activity. Expression of a constitutively active 4E-BP1 that cannot be phosphorylated reversed MCV ST–induced cell transformation, which showed that the proliferative effects of MCV ST are caused by targeting downstream components of the AktmTOR pathway. These findings indicate that MCV ST targets cap-dependent translation though a mechanism that contributes to Merkel cell tumorigenesis.

Lin et al. [3], using tissue microarray and immunohistochemistry, found that mTOR pathway was activated as indicated by positive staining of phosphorylation-4E-BP1, phosphorylation-S6K, and phosphorylation-mTOR regardless of MCV status. Two primary human MCC cell lines from two patients with lymph node metastases were established, demonstrating mTOR pathway upregulation and decreased autophagy in both MCC cells. Inhibition of mTOR pathway decreased cell proliferation and induced autophagy and cell death in MCC cells. Furthermore, cell death induced by mTOR inhibitors was independent of caspase activation and attenuated by an autophagy inhibitor, suggesting a rationale for potential new therapeutic targets.

Finally, Nardi et al. [4] retrospectively profiled 60 primary MCC samples using a SNaPshot-based tumor genotyping assay to screen for common mutations in 13 cancer genes. Six of 60 were found to have PIK3CA gene activating mutations. Sanger sequencing of the primary MCC tumors detected one additional PIK3CA mutation (R19K) that had not been previously described in cancer. MCV was detected in 38 (66%) MCC cases. With one exception, the presence of MCV and activating mutations in PIK3CA appeared mutually exclusive. We observed that signaling through the PI3K/pAKT pathway was active in one MCV-positive and in all MCV-negative MCC cell lines, as evidenced by AKT phosphorylation.

Based on the above data, we propose a phase I/II study evaluating the activity of MLN0128 in patients with metastatic/recurrent MCC.

2.2 IND Agent

Millennium has developed MLN0128, 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 (formerly INK128) targets 2 distinct multiprotein complexes, mTORC1 and mTORC2. MLN0128 is being developed for both oncology and non-oncology indications. In oncology, MLN0128 is being investigated as a treatment for advanced solid tumors and hematologic malignancies, either as monotherapy or in combination with chemotherapy, other molecularly targeted therapies, or antihormonal agents. Non-oncology indications being investigated include fibrotic and inflammatory diseases in the lung or bronchioles such as idiopathic pulmonary fibrosis (IPF) and bronchiolitis obliterans syndrome (BOS). MLN0128 is also being developed in combination with MLN1117 (an oral phosphoinositide-3 kinase alpha isoform [PI3Kα] inhibitor) as a treatment for advanced nonhematologic

malignancies; information regarding this novel combination is provided to relevant investigators in the MLN0128 + MLN117 Investigator's Brochure (IB).

MLN0128 selectively and potently inhibits mTOR kinase (IC50 = 1.1 nM), inhibits mTORC1/2 signaling, and prevents cellular proliferation. The mTOR is a kinase that regulates cell growth, translational control, angiogenesis, and cell survival by integrating nutrient and hormonal signals. mTOR kinase plays a key role in several pathways that are frequently dysregulated in human cancer [5]. mTORC1 is best known as a key regulator of protein translation through phosphorylation of 4EBP1 (the eukaryotic translation Initiation Factor 4E-binding Protein 1) and ribosomal protein S6 (known as S6) kinase. mTORC2 is best known for its ability to fully activate protein kinase B (AKT) by phosphorylation on the S473 site, which regulates proliferation and survival pathways [6].

The mTOR complex (mTORC) is an important therapeutic target that is generally stable (ie, low tendency to mutate) and is a key intracellular point of convergence for a number of cellular signaling pathways. Inhibiting mTOR may inhibit abnormal cell proliferation, tumor angiogenesis, and abnormal cellular metabolism, thus providing the rationale for mTOR inhibitors as potential agents in the treatment of a number of indications including solid tumor and hematological malignancies, as either monotherapy or in combination with other chemotherapeutic agents. Like rapamycin, several newly approved rapalogs (temsirolimus and everolimus) are specific and allosteric inhibitors of mTORC1, and only partially inhibit mTORC1 signaling pathways. They do not directly inhibit mTORC2, which has shown to be an emerging target in cancer research. MLN0128 was developed to address the incomplete inhibition of the mTOR pathway by rapalogs.

2.3 Nonclinical Summary

2.3.1 Pharmacology

MLN0128 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 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.

2.3.2 Safety Pharmacology

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

2.3.3 Drug Metabolism and Pharmacokinetics

MLN0128 was rapidly absorbed after PO administration to mice, rats, dogs, and monkeys, with high oral bioavailability. [14C]MLN0128 was rapidly and widely distributed throughout the body in Long-Evans rats; radioactivity was eliminated from most tissues at 48 hours postdose.

MLN0128 displayed dose-proportional plasma exposures, a moderate propensity to cross the blood-brain barrier, and was modestly bound (70.5%) to human plasma proteins. MLN0128 distributed mainly to the plasma of human blood. There was no obvious concentration-dependent red blood cell (RBC) distribution of MLN0128 in human blood.

MLN0128 did not inhibit P-glycoprotein, but did inhibit breast cancer-resistance protein (BCRP), organic cation transporter (OCT)1 and (OCT)2.

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 did not induce CYP1A2, 2B6, and 3A4 activity and expression at concentrations up to 10 μM. MLN0128 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 in humans has a low potential for metabolic and transporterbased 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]).

2.3.4 Toxicology

The toxicologic profiles obtained in the Good Laboratory Practice (GLP)-compliant and non-GLPcompliant studies in rats and monkeys were generally consistent with pharmacologic inhibition of mTORC1/2 activity. Observed toxicities were mostly consistent between sexes. MLN0128 repeatdose 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 dose-limiting toxicities (DLTs) of MLN0128 in rats and monkeys were secondary to an exaggerated pharmacologic response and consisted of body weight loss and associated clinical observations that included 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 lungs, thymus, nonglandular stomach, and bone marrow.

The adverse effects in monkeys included 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; GI tract erosion and ulceration; skin 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 were generally reversible after a 14-day recovery period.

The findings in rat and monkey repeat-dose toxicology studies with MLN0128, including bone marrow and lymphoid depletion, GI 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.

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

MLN0128 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 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 does not present a genotoxic risk.

MLN0128 was negative for phototoxicity in the 3T3 fibroblast assay.

2.4 Summary of Effects in Humans in Advanced Solid Malignancies and Hematologic Malignancies

MLN0128 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 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 receptorpositive /human epidermal growth factor receptor 2 protein-negative) advanced or metastatic breast cancer (Ph1b/2 study C31001)

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

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

2.4.1 Safety and Efficacy in Oncology Studies

In the clinical development plan, the safety and tolerability profile of single-agent MLN0128 is being studied in an ongoing phase 1, first-in-human, dose-finding study in patients with advanced solid malignancies (Study INK128-001) and in a completed phase 1 study (Study INK128-002) in patients with MM and WM. A third study (INK128-003) is being conducted in patients with solid tumors to evaluate the preliminary safety and efficacy of the combination of MLN0128 with paclitaxel, with or without trastuzumab.

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 (see section 5.3.1.1 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.

2.4.2 Study INK128-001

Study INK128-001 is a phase 1, first-in-human, dose-escalation study of single-agent MLN0128 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 × 3d QW, and QD × 5d QW). 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 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 × 3d QW dosing, 10 mg for QD × 5d QW dosing, and 40 mg for QW dosing.

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 5.3.1.1. of the IB Ed8.

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%).
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 patients as of the clinical data cutoff date. Severity ≥Grade 3 TEAEs, regardless of causality, were reported in ≥5% of patient treated
s 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).

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.

2.4.3 Study INK128-002

Study INK-002 is a completed phase 1, open-label, dose-escalation study of oral MLN0128 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 in 1 of 2 regimens: 26 patients received QD doses (range, 2-7 mg) and 13 patients were dosed on a QD × 3d QW schedule (range, 9-12 mg). The MTD for the QD schedule was 4 mg. The MTD for the QD × 3d QW 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).
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.

Details of the subdural hemorrhage case, taken from the Final Clinical Study Report INK128-002, are as follows:

PATIENT NARRATIVE Study INK128-002			
		Patient Number:	2401103
		Study Drug regimen:	2 mg QD MLN0128
		Study Drug Start date: **Stop date:**	29DEC2010 31DEC2010
		Date of Death:	01JAN2011
Primary Reason(s) for Narrative: AE resulting in study discontinuation; On-study death			
Verbatim/Preferred Term:	SUBDURAL BLEED/Subdural haemorrhage		
Event Start date: **Days from 1st /prior dose:** **Event Stop date:**	31DEC2010 3/1 01JAN2011	**Serious (Y/N):** **Severity:** **Outcome:**	Y Grade 5 Death
Relationship to Study Drug:	Not Related	**Action Taken:**	Hospitalized; Discontinued
Narrative: The patient was assigned to receive 2 mg MLN0128 once daily (QD). On 31 December 2010 (within 1 day of his third [and final] dose of MLN0128), the patient was hospitalized due to subdural hemorrhage and subsequently died on 01 January 2011. Event details are provided in CIOMS MCN 2012-05040.			

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 × 3d QW dose group (resolved with sequelae).

No SAEs were considered to be related to MLN0128 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.

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%).

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 nonserious. 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.

The DLTs taken from the Final Clinical Study Report INK128-002 are as follows:

Dose-Limiting Toxicities during Cycle 1 – QD Schedule (Dose-escalation Evaluable Population)

Preferred term	MLN0128 2 mg QD n = 3	MLN0128 4 mg QD n = 6	MLN0128 6 mg QD n = 6	MLN0128 7 mg QD n = 4	Total QD Dosing N = 19
Patients with Cycle 1 DLT(s)	0	1	3	1	5
Blood creatinine increased	0	0	1	0	1
Fatigue	0	0	1	0	1
Nausea	0	0	1	0	1
Stomatitis	0	1	0	0	1
Urticaria	0	0	0	1	1

Vomiting	0	0	1	0	1

Source: Table 14.3.4.
Abbreviations: AE = adverse event; DLT = dose-limiting toxicity; QD = once daily.
At each level of summation (overall and preferred term), patients reporting > 1 AE were counted only once.

Dose-Limiting Toxicities during Cycle 1 – QD × 3d QW Schedule (Doseescalation Evaluable Population)

Preferred term	MLN0128 9 mg QD × 3d QW n = 6	MLN0128 12 mg QD × 3d QW n = 7	Total QD × 3d QW N = 13
Patients with Cycle 1 DLT(s)	1	3	4
Asthenia	0	1	1
Fatigue	1	0	1
Mucosal inflammation	0	1	1
Rash erythematous	1	0	1
Thrombocytopenia	0	1	1

Source: Table 14.3.4.
Abbreviations: AE = adverse event; d = day(s); DLT = dose-limiting toxicity; QD = once daily; QW = each week.
At each level of summation (overall and preferred term), patients reporting > 1 AE were counted only once.

2.4.4 Study INK128-003

Study INK128-003 is a phase 1, open-label, dose-escalation study of oral MLN0128 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 × 3d QW; and QD × 5d QW. With each regimen, paclitaxel 80 mg/m2 is dosed on Days 1, 8, and 15 of each cycle. Patients who test positive for the human epidermal growth factor receptor 2 protein (HER2+) receive the combination and also receive trastuzumab (8 mg QW).

A total of 57% of the treated patients are female, 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 on the QD × 3d QW schedule was selected for the dose expansion phase in breast cancer patients. The QD × 5d QW and QW schedules were abandoned before MTDs were declared, as they were viewed as less convenient relative to the QD × 3d QW 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 8 mg QD×3days per week HER2- treatment group relative to the MLN0128 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.

As of the clinical data cutoff date, 10 patients in this study had died within 30 days of their last dose of study drug. Of these patients, 6 died due to disease progression, 1 died due to enlarging tumor mass causing tracheal compression, 1 died due to pneumonia, and 2 died due to failure to thrive. None of the events were considered related to MLN0128.

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.

All patients treated in Study INK128-003 reported at least 1 TEAE. Regardless of causality, TEAEs in 53 patients (79%) were assessed as severity ≥ Grade 3. The most frequently reported events 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 and hyperglycemia (12% of patients each), and fatigue, hypokalemia, and vomiting (10% of patients each).

All but 1 patient had discontinued from M 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%).

A total of 21 TEAEs were reported as leading to study discontinuation. Events reported for more than 1 patient included fatigue (4 patients) and pneumonia, rash (including erythematous rash), failure to thrive, or vomiting (2 patients, each). A majority (52%) of the events were considered not related to MLN0128.

2.4.5 Study C31001

Study C31001 is a phase 1b/2 study of the safety and efficacy of MLN0128 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. As of the clinical data cutoff date, 16 patients had received ≥1 MLN0128 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 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.

2.4.6 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 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 if, in the opinion of the investigator, the patient is deriving clinical benefit, until they experience disease progression. Patients continuing treatment receive MLN0128 30 mg QW in 28-day cycles. As of the clinical data cutoff date, 19 patients had received ≥1 MLN0128 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.

2.4.7 Pharmacokinetics

Overall, pharmacokinetic (PK) data from Studies INK128-001, INK128-002, and INK128-003 indicate that MLN0128 exhibits fast oral absorption (first time to maximum plasma concentration [Tmax], generally between 1-4 hours after dosing); dose-linear PK, with a mean plasma half-life (t½) of approximately 8 hours; and that MLN0128 does not accumulate meaningfully in plasma when dosed as frequently as once daily and under any of 4 tested dosing regimens. The PK of MLN0128 was generally consistent, with no appreciable differences across the 3 clinical studies. Neither paclitaxel nor MLN0128 appeared to alter the PK of the other agent when co-administered.

A capsule containing milled active pharmaceutical ingredient (API) is available for clinical studies in 1 mg, 3 mg and 5 mg strengths. The milled API, may result in faster absorption profile with possibly higher maximum concentration (Cmax), which could result in a different safety profile compared to the previous unmilled API capsules. Therefore, Takeda has ongoing studies with the new milled API to determine the recommended phase 2 dose (RP2D) for single agent MLN0128 and in combination with paclitaxel.

2.5 Rationale

Recently, a human polyomavirus (MCV) was implicated in the pathogenesis of MCC. MCV is constituted by 5,387 base pairs, encoding for the large T (LT) antigen and small T (ST) antigen, which act differently and synergistically to promote cell proliferation and transformation [7].

A key step in cap-dependent translation is the binding of eukaryotic translation initiation factor 4E (eIF4E) to mRNA molecules having a 5′ 7-methylguanosine GTP cap [8]. Ribosome recruitment to capped mRNAs is initiated by the assembly of the multi-subunit eIF4F, composed of eIF4E, eIF4A, and eIF4G, on the cap. A key regulator of this process is the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), which sequesters eIF4E to prevent eIF4F formation on capped mRNA [9]. Induction of cap-dependent translation may play a role in tumor cell growth, since eIF4E overexpression causes rodent cell transformation [10,11].

Shuda et al [7] showed that MCV ST antigen reduced turnover of hyperphosphorylated 4E-BP1, which in turn increased eIF4E activity. Expression of a constitutively active 4E-BP1 that cannot be phosphorylated reversed MCV ST–induced cell transformation, which showed that the proliferative effects of MCV ST are caused by targeting downstream components of the AktmTOR pathway. These findings indicate that MCV ST targets cap-dependent translation though a mechanism that contributes to Merkel cell tumorigenesis.

Lin et al [8] using tissue microarray and immunohistochemistry, found that mTOR pathway was activated as indicated by positive staining of phosphorylation-4E-BP1, phosphorylation-S6K, and phosphorylation-mTOR regardless of MCV status. Two primary human MCC cell lines from two patients with lymph node metastases were established, demonstrating mTOR pathway upregulation and decreased autophagy in both MCC cells. Inhibition of mTOR pathway decreased cell proliferation and induced autophagy and cell death in MCC cells. Furthermore, cell death induced by mTOR inhibitors was independent of caspase activation and attenuated by an autophagy inhibitor, suggesting a rationale for potential new therapeutic targets.

Finally, Nardi et al [9] retrospectively profiled 60 primary MCC samples using a SNaPshot-based tumor genotyping assay to screen for common mutations in 13 cancer genes. Six of 60 were found to have PIK3CA gene activating mutations. Sanger sequencing of the primary MCC tumors detected one additional PIK3CA mutation (R19K) that had not been previously described in cancer. MCV was detected in 38 (66%) MCC cases. With one exception, the presence of MCV and activating mutations in PIK3CA appeared mutually exclusive. We observed that signaling through the PI3K/pAKT pathway was active in one MCV-positive and in all MCV-negative MCC cell lines, as evidenced by AKT phosphorylation.

MLN0128 is a novel, highly selective, orally bioavailable ATP-competitive inhibitor of the mTOR. The mTOR is a kinase that regulates cell growth, translational control, angiogenesis, and cell survival. MLN0128 selectively and potently inhibits mTOR kinase, inhibits mTORC1/2 signaling, and prevents cellular proliferation. mTORC1 is best known as a key regulator of protein translation through phosphorylation of 4EBP1 and ribosomal protein S6 kinase. mTORC2 is best known for its ability to fully activate AKT by phosphorylation on the S473 site, which regulates proliferation and survival pathways [6].

Based on the above data, we propose a run-in phase I prior to the phase II study, to evaluate the RP2D; and phase II to determine activity of MLN0128 in patients with metastatic/recurrent MCC. PK samples will be obtained on days 8, 15 and 28 in phase I.

2.6 Correlative Studies Background

All patients will have tumor tissue collected (upto 40 unstained slides or one tumor block). A vial of EDTA blood will also be obtained. Whole exome sequencing will be performed on tumor and normal genomic DNA of all patients. All patients will undergo Oncopanel testing which analyzes 300 cancer relevant genes. Patients with accessible tumors may undergo sequential biopsies prior to, at 4 weeks of therapy and upon progression. Analysis of p4EBP1, pSK6, pCAD, pMTOR and MCV LT/ST will be performed retrospectively to correlate with disease response.

PATIENTS WHO PROGRESS ON THERAPY WILL BE STRONGLY ENCOURAGED TO UNDERGO ANOTHER BIOPSY. WHOLE EXOME SEQUENCING WILL BE PERFORMED ON THIS SAMPLE TO ELUCIDATE POTENTIAL RESISTANCE MECHANISMS.

3. UPDATED MANUFACTURING PROCESS

A new MLN0128 capsule containing milled active pharmaceutical ingredient (API) is available for new clinical studies in 1 mg, 3 mg and 5 mg strengths.

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

4. CLINICAL SUMMARY OF SAFETY

4.1 Special Warnings and Precautions for Use

4.1.1 Insulin and Glucose Levels

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

A rise in fasting plasma glucose has been observed as early as 1 to 2 days following oral administration of MLN0128. Daily in-home glucose monitoring and early initiation of treatment of the hyperglycemia are essential. For subject self-monitoring of blood glucose, a finding of closer monitoring of serum glucose and possible intervention. Subjects with Grade 1 hyperglycemia (fasting serum glucose [FSG] > the upper limit of the normal range mg/dL) are treated with oral hypoglycemic agents (eg, metformin), and subjects with mg/dL) are treated aggressively with oral

fasting blood glucose ≥ 140 mg/dL, measured by glucometer would initiate

≤ 160

≥ Grade 2 hyperglycemia (FSG > 160

hypoglycemic agents and/or insulin as clinically indicated. Daily home monitoring and early treatment, have resulted in good control of glucose levels for the majority of MLN0128-treated subjects who developed hyperglycemia.

4.1.2 Cardiac Effects

Cardiac events (including QT interval corrected for heart rate prolongation and arrhythmias) have been infrequently observed in clinical studies of MLN0128. To date, there has been 1 report of ventricular fibrillation and cardiac arrest postdose that had a fatal outcome and was assessed as related to MLN0128. Routine cardiac monitoring with baseline electrocardiogram (ECG) or multigated acquisition (MUGA) scan and on-study ECGs and physical examination constitute the core cardiac safety monitoring in all MLN0128 studies.

For subjects showing any signs of cardiac instability after MLN0128 dosing, additional monitoring onsite before clinic discharge should be considered.

4.1.3 Renal Function

Elevations in creatinine (regardless of causality) have been observed in subjects receiving MLN0128, 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 prerenal 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 studies. Additionally, microscopic urinalysis, a 12 hour urine collection, spot urine electrolytes, protein and creatinine, and serum chemistry should be collected at any time when the serum creatinine is ≥ Grade 1, according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0, to further evaluate possible etiologies for the renal dysfunction.

4.1.4 Rash

Rash observed in clinical studies of MLN0128 tends to be maculopapular and pruritic and has ranged from Grade 1 to 3. For the most part, rash and pruritus improve with antihistamines, topical steroid creams, and/or dose interruption. Some subjects have required pulse systemic steroids, dose reduction, and/or study treatment discontinuation.

4.1.5 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 administration. Symptoms of pneumonitis will be closely monitored in all MLN0128 study subjects.

4.2 Interactions with other medications and other forms of interaction

Clinical drug-drug interaction studies have not been conducted with MLN0128. At this time, there are no known drug interactions. In vitro data, including cytochrome P450 induction/inhibition and transporter inhibition studies conducted for MLN0128, suggest a low risk for MLN0128 to precipitate a drug-drug interaction. Although potential drug-drug interactions with MLN0128 cannot be ruled out based on the known metabolism characteristics of MLN0128, the potential risk is considered low.

5. PARTICIPANT SELECTION

Inclusion Criteria

- Metastatic or recurrent MCC confirmed by histology
- Participants must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 20 mm with conventional techniques or as > 10 mm with spiral CT scan (see section 12 for the evaluation of measureable disease). Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented Age 18 years
- or older
- ECOG performance status ≤2 (Karnofsky >60%, see Appendix A)
- Participants must have normal organ and marrow function as defined below:
  leukocytes 3,000/mcL absolute ≥ neutrophil count 1,500/mcL
  platelets ≥100,000/mcL
  ≥9 g/dL
  hemoglobin total bilirubin within normal institutional limits AST(SGOT)/ALT(SGPT) 2.5 × institutional upper limit of normal creatinine within normal institutional limits, OR creatinine clearance 60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal fasting serum glucose fasting triglycerides • Female patients who: o Are postmenopausal for at least 1 year before the screening visit, OR o Are surgically sterile, OR
  - o If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 90 days after the last dose of study drug, or agree to completely abstain from heterosexual intercourse. Periodic abstinence (calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception

≤ 150 mg/dL
≤ 300 mg/dL

- Male patients, even if surgically sterilized (ie, status post-vasectomy), who:
  - o Agree to practice effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, or

- Agree to completely abstain from heterosexual intercourse. Periodic abstinence (calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal are not acceptable methods of contraception
- Agree not to donate sperm during the course of this study or 120 days after receiving their last dose of study drug.

- Treatment with strong CYP2C19, CYP3A4, and CYP2C9 inhibitors and/or inducers must be discontinued at least 1 week before administration of the first dose of study drug (see appendix B)
- Tissue for correlative studies must be available (paraffinized or frozen), but confirmation at screening is not needed. Archival tissue may be used instead of a fresh biopsy at baseline if it already exists.
- Ability to swallow oral medications and maintain an empty stomach state for 2 hours prior to the MLN0128 dose and for 1 hour following administration
- Ability to understand and the willingness to sign a written informed consent document before performance of any study related procedure not part of standard medical care

Exclusion Criteria

- Participants who have had chemotherapy or radiotherapy within 2 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier
- The subject has active brain metastases or epidural disease (Note: Subjects with brain metastases previously treated with whole brain radiation or radiosurgery or subjects with epidural disease previously treated with radiation or surgery who are asymptomatic and do not require steroid treatment for at least 2 weeks before starting study treatment are eligible).
- Participants who are receiving any other investigational agents within 14 days before the first dose of study drug
- 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 • Female patients who are both lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug
- Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of MLN0128
- Poorly controlled diabetes mellitus defined as HbA1c > 7%; subjects with a history of transient glucose intolerance due to corticosteroid administration are allowed in this study if all other inclusion/exclusion criteria are met
- History of any of the following within the last 6 months prior to study entry:
  - Ischemic myocardial event, including angina requiring therapy and artery revascularization procedures
  - Ischemic cerebrovascular event, including TIA and artery revascularization procedures

- Requirement for inotropic support (excluding digoxin) or serious (uncontrolled) cardiac arrhythmia (including atrial flutter/fibrillation, ventricular fibrillation or ventricular tachycardia)
- Placement of a pacemaker for control of rhythm
- New York Heart Association (NYHA) Class III or IV heart failure (See Appendix B)
- Pulmonary embolism

- Significant active cardiovascular or pulmonary disease at the time of study entry, including:
  - Uncontrolled high blood pressure (i.e., systolic blood pressure >180 mm Hg, diastolic blood pressure > 95 mm Hg)
  - Pulmonary hypertension
  - Uncontrolled asthma or O_2 saturation < 90% by ABG (Arterial Blood Gas) analysis or pulse oximetry on room air
  - Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention, or history of valve replacement
  - Medically significant (symptomatic) bradycardia
  - History of arrhythmia requiring an implantable cardiac defibrillator o Baseline prolongation of the rate-corrected QT interval (QTc) (e.g., repeated demonstration of QTc interval > 480 milliseconds, or history of congenital long QT syndrome, or torsades de pointes)
- Initiation of treatment with hematopoietic growth factors, transfusions of blood and blood products, or systemic corticosteroids (either IV or oral steroids, excluding inhalers) within 1 week before administration of the first dose of study drug (patients already receiving erythropoietin on a chronic basis for ≥ 4 weeks are eligible).
- Diagnosed or treated for another malignancy within 2 years before administration of the first dose of study drug, or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

6. REGISTRATION PROCEDURES

6.1 General Guidelines for DF/HCC and DF/PCC Institutions

Study team will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the QACT protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Notify the QACT Registrar of registration cancellations as soon as possible.

6.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin protocol therapy during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

- Obtain written informed consent from the participant prior to the performance of any protocol specific procedures or assessments.

- Complete the QACT protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical record and/or research chart. To be eligible for registration to the protocol, the participant must meet all inclusion and exclusion criterion as described in the protocol and reflected on the eligibility checklist.

  Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for a treatment protocol. Registration to both treatment and ancillary protocols will not be completed if eligibility requirements are not met for all studies.

- Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617632-2295. For Phase I protocols, attach participant dose level assignment confirmation from the sponsor.

- The QACT Registrar will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant when applicable.

- An email confirmation of the registration and/or randomization will be sent to the Overall PI, study coordinator(s) from the Lead Site, treating investigator and registering person immediately following the registration and/or randomization.

NOTE: Registration with the QACT can only be conducted during the business hours of 8:00 AM and 5:00 PM Eastern Standard Time Monday through Friday. Same day treatment registrations will only be accepted with prior notice and discussion with the DF/HCC Lead Institution.

7. TREATMENT PLAN

7.1 Treatment Regimen

MLN0128 milled API will be administered (phase I starting dose, 3mg and phase II starting at RP2D), orally, daily at the same time of the day, until disease progression, unacceptable toxicity or withdrawal of consent. Dose reduction beyond 2 mg is not allowed. Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 9. Appropriate dose modifications are described in Section 8. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The participant will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle.

7.2 Pre-Treatment Criteria

As long as the screening lab results meet eligibility criteria, some lab value variance may be allowed by Cycle 1 Day 1, as long as toxicity criteria are not met. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

7.3 Agent Administration

All protocol-specific criteria for administration of MLN0128 must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

MLN0128 capsule will be taken orally, once daily, approximately at the same time each day, on an empty stomach. The patients should be instructed to refrain from eating and drinking (except for water and any other prescribed medications), for two hours before and one hour after each dose. It is recommended that each dose of MLN0128 be given with 8 ounces (240 mL) of water.

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 dose within the time frame specified (+/- 8h of the QD or QD×3days per week schedule), 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.

In the phase I part of this study, the starting dose of 3 mg QD was chosen to account for the possibility of increased absorption with MLN0128 capsules based on preliminary MLN0128 milled API pharmacokinetic data. Each cohort should be evaluated for tolerability after completing 1 cycle of treatment before proceeding to escalation (4 mg QD or 5 mg QD) or deescalation (2 mg

QD). Escalation/de-escalation should not proceed beyond 5 mg QD or below 2 mg QD respectively (Table 1). Patients may not re-escalate dose after a dose reduction.

The phase II part of the study will use the phase II dose or RP2D determined during the phase I part of the study

7.3.1 Dose Escalation Criteria

Number of Subjects per Cohort with DLT During Treatment Period	Dose Escalation Decision
0 out of 3	Enter 3 subjects at the next dose level.
1 out of 3	Enter 3 more subjects at this dose level. If no additional DLT, proceed to the next dose level. If an additional DLT occurs (i.e. > 2 DLTs/6 subjects), dose escalation is stopped and the previous dose level is declared the MTD.
≥ 2	The previous dose level is declared MTD. There is no advancement to higher dose levels.

7.3.2 Dose Escalation for Phase I

Dose level	MLN0128 Dose
-1	2 mg QD
1 (starting dose)	3 mg QD
2	4 mg QD
3	5 mg QD

If severe emesis or mucositis prevents the patient from taking an MLN0128 dose, that dose will be skipped. If emesis occurs after study medication ingestion and whole capsule is visible in the vomitus, replacement capsule should be taken; otherwise the dose will not be re-administered, and patients should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Under no circumstance should a patient repeat a dose or double-up doses.

7.3.3 Dose-Limiting Toxicity:

Toxicity will be assessed using the NCI Common Toxicity Criteria for Adverse Events, version 4.0 http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf unless otherwise specified (e.g., hyperglycemia). A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications, and occurs < 28 days following the last dose of MLN0128, and meets any of the criteria listed below.

Whenever a patient experiences toxicity that fulfills the criteria for a DLT (or a potential DLT), treatment with MLN0128 will be interrupted (if not otherwise specified) and the toxicity will be followed up as described in section 7.3. 5. The criteria for dose-limiting toxicities are outlined below.

7.3.4 Criteria for Defining Dose-Limiting Toxicities

TOXICITY	ANY OF THE FOLLOWING CRITERIA
Hematologic [a]	•CTCAE grade 3 neutropenia for > 7 consecutive days
	CTCAE grade 3 thrombocytopenia for > 7 consecutive days
	CTCAE grade 4 thrombocytopenia
	CTCAE grade 3 thrombocytopenia with clinically significant bleeding
	Febrile neutropenia (ANC < 1.0 x 10^9/L, fever • 38.5°C)
Renal	Serum creatinine 2.0 x ULN to ” 3.0 x ULN for > 7 consecutive days
	> CTCAE grade 3 serum creatinine
Hepatic [b]	Total bilirubin 2xULN to ” 3.0 x ULN for > 7 consecutive days
	> CTCAE grade 3 total bilirubin
	CTCAE grade 3 AST or ALT for > 7 consecutive days
	CTCAE grade 4 AST or ALT
Endocrine	Grade 2 hyperglycemia (confirmed with a repeat FPG within 24 hours) that does not resolve to grade 1 or baseline within 14 consecutive days (after initiation of glimepiride, metformin or glibenclamide)
	•Grade 3 hyperglycemia (confirmed with a repeat FPG within 24 hours)
Metabolic/Laboratory	CTCAE grade 3 asymptomatic amylase and/or lipase, not reversible to CTCAE grade 2 for > 7 consecutive days
	CTCAE grade 4 asymptomatic amylase and/or lipase
Pancreatitis	•CTCAE grade 2
Cardiac	Cardiac toxicityCTCAE grade 3 or cardiac event that is symptomatic or requires medical intervention
	Clinical signs of cardiac disease, such as unstable angina or Myocardial infarction, or Troponin • CTCAE grade 3
Neurotoxicity	•1 CTCAE grade level increase

Mood alteration	CTCAE grade 2 mood alteration that does not resolve to grade 1 within 14 days despite medical treatment (for Anxiety only, if worsened from baseline) CTCAE grade 3 mood alteration
Dermatologic	Any phototoxicity CTCAE grade 2, or skin toxicity (rash) resulting in interruption of MLN0128 for > 21 consecutive days
Other adverse events	•CTCAE grade 3 adverse events (excluding CTCAE grade 3 elevations in alkaline phosphatase) CTCAE grade 4 and 5 toxicities for hematologic and non-hematologic toxicities, unless noted for specific exceptions

[a] • CTCAE grade 3 anemia will not be considered DLT unless judged to be a hemolytic process secondary to study drug. • CTCAE grade 3 lymphopenia will not be considered DLT unless clinically significant.

[b] For any grade 3 or 4 hepatic toxicity that does not resolve within 7 days to grade 1 (or grade 2 if liver infiltration with tumor present), an abdominal CT scan has to be performed to assess if it is related to disease progression.

A single patient is assumed not to tolerate the dose if he/she experiences at least one DLT. If a lower grade AE leads to a dose interruption of more than 7 doses of MLN0128, this AE will be considered as DLT.

If the 2nd occurrence of an initially non-dose limiting toxicity (e.g., grade 3 AST that resolved to grade 1 within 7 days at 1st occurrence) leads to a dose reduction (Section 8) within 28 days of the first dose of MLN0128, this will be considered a DLT.

7.3.5 Follow up to DLT

Patients who experience an AE that meets the definition of a DLT during or after completing Cycle 1 should have their study drug treatment interrupted. If the event resolves to Grade 1 or baseline values within 2 weeks of interrupting planned therapy, and in the opinion of the investigator the benefits of continuing treatment outweigh the risks posed by the toxicity, patients may continue study treatment with MLN0128 at a 20% to 33% dose reduction (ie, dose reduced from 5 mg to 4 mg [20%]; from 4 mg to 3 mg [25%]; from 3 mg to 2 mg [33%]; or if dose modification is required for patients receiving 2 mg QD, then the dosing frequency should be decreased to 5 days per week (28% reduction) instead of decreasing the daily dose administered. If study drug dosing is delayed for more than 14 consecutive days for MLN0128related toxicity, despite supportive treatment per standard clinical practice, the patient should be discontinued from the study treatment and complete the follow-up visit within 30 days of the last administration of MLN0128 and continue to be followed according to protocol.

7.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of MLN0128 with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Overall PI should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes, including CYP2C19, CYP3A4, and CYP2C9. Appendix B presents guidelines for identifying medications/substances that could potentially interact with the study agent.

7.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator Participants will be removed from the protocol therapy when any of these criteria apply. The reason

for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

A QACT Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the QACT website or obtained from the QACT registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Guilherme Rabinowits, MD at 617-632-3090 or page at 49015.

7.6 Duration of Follow Up

Participants will be followed for two years from study entry or until death, whichever occurs first.

7.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply: Lost

- to follow-up
- Withdrawal of consent for data submission Death
-

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

A QACT Treatment Ended/Off Study Form will be filled out when a participant comes off study. This form can be found on the QACT website or obtained from the QACT registration staff.

8. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
MLN0128 dosing should be withheld for ≥ Grade 2 renal insufficiency or ≥ Grade 3 MLN0128-related toxicities. The relatedness should be defined as set out in ICH E2A. If the event resolves to Grade ≤ 1 or baseline values within 28 days of interrupting therapy, the subject may resume study treatment at a dose reduction. If a dose modification is required for subjects receiving 2 mg, then the dosing frequency should be decreased to 5 days per week, instead of decreasing the daily dose administered. See table of dose adjustments below according to the schedule applied in this protocol. Patients may not re-escalate dose after a dose reduction. Table 1 a: Dose Reductions for Phase I

Dose Level	Dose

3	5 mg
2	4 mg
1	3 mg
-1	2 mg
-2	2 mg x 5 days per week
	Discontinue
Level 1 is the starting dose	

If patients in the phase I portion of the trial are tolerating their current study drug dose level and have completed 1 cycle at this level, intra-patient dose escalation will be allowed to a dose level for which there is 4 weeks of safety data demonstrating acceptable tolerability for at least 3 patients. This evaluation can also be obtained from DFCI protocol 14-223 (PHASE II STUDY OF MLN0128 IN THYROID CANCER), which has the same trial design and the same experimental agent under investigation, for thyroid cancer patients. Therefore, for example, if there have been 3 subjects on 4mg in 14-223 without DLTs, subjects on 15-223 are able to be dose escalated from 3mg to 4mg without waiting for the 4 mg cohort of 15-223 to be completed.

Patients will be able to enter the next higher dose level if the PI determines that there is a potential clinical benefit. This dose escalation will be approved by the PI after discussion with the treating oncologist, and then documented in the patient's visit note. These patients will be closely monitored with weekly visits for 4 weeks, with the following procedures performed at each weekly visit (+/- 3 days): PE, concurrent medication assessment, vital status, weight, AE assessment, performance status, and fasting lab tests which include CBC w/ diff, serum chemistry, phosphorus, LDH, PT/INR, PTT, and urinalysis. After completing the 4 week safety monitoring period, these patients will then resume the protocol required visit schedule.

Patients that have been introduced to a dose escalation stay registered in their original cohort, and are not part of the new cohort with regards to data collection in the 3+3 study design. Finally patients may be dose escalated more than once, as long as they follow the requirements listed above.

Table 1 b: Anticipated MLN0128 Dose Reductions for Phase II

Dose Level	Dose (X=RP2D) if X is 5 mg	Dose (X=RP2D) if X is 4 mg	Dose (X=RP2D) if X is 3 mg
1	X mg	X mg	X mg
-1	X-1 mg	X-1 mg	X-1 mg
-2	X-2 mg	X-2 mg	X-1 x 5 days per week
-3	X-3 mg	X-2 x 5 days per week	Discontinue
-4	X-3 x 5 days per week	Discontinue	

	Discontinue		
Level 1 is the starting dose			

If MLN0128 dosing is delayed for > 28 consecutive days for MLN0128-related toxicity despite supportive treatment per standard clinical practice or more than 2 dose reductions of MLN0128 is required in a subject, stop MLN0128 therapy, discontinue the subject from the study, and complete the follow-up visit within 30 days of the last administration of MLN0128.

See Section 8.1 for management of MLN0128 dosing for specific clinical events. The PI should be contacted prior to any dose modification in MLN0128 for any subject in the study. All dose reductions will be by one dose level down at a time, unless specified (there is no dose lower than 2 mg).

8.1 Management of Clinical Events

8.1.1 Management of Hyperglycemia

We will obtain fasting serum glucose (FSG) levels at clinic visits. Guidance for MLN0128 dose management in the event of hyperglycemia is provided in the table below.

Table 2: Management of Hyperglycemia

Grade	Description	Treatment	MLN0128 Dose Modification
1	Fasting blood sugar > ULN–160 mg/dL	Continue close monitoring of blood sugars. Initiate oral hypoglycemic agent.	None.
2	Fasting blood sugar > 160–250 mg/dL	Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None.
≥3	Fasting blood sugar > 250 mg/dL	Initiate oral hypoglycemic agent and/or insulin.	Hold drug until ≤ Grade 2. Resume MLN0128 based on timing of recovery: ≤ 1 week: resume at same dose and schedule; >1 but ≤ 2 weeks: reduce dose > 3 weeks: stop MLN0128 and discontinue subject from the study.

Prevention/Prophylaxis

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

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

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

a If dose modification is required for subjects receiving 2 mg, then the frequency of dosing should be decreased to 5 days/week, rather than decreasing the daily dose administered. In the event that any FSG reading performed at the site indicates hyperglycemia (> upper limit of normal [ULN] or ≥ 110 mg/dL), the study staff should first ascertain that the subject was fasting at the time of the blood draw (ie, nothing by mouth for at least 8 hours prior to blood being obtained), had continued to take their concomitant antiglycemic medications should the subject have underlying diabetes mellitus, and repeat the FSG as needed. If the repeat FSG continues to demonstrate hyperglycemia, investigators should initiate steps to aggressively manage the hyperglycemia per standard clinical practice. The following guidelines are provided to aid the investigator in initiating antiglycemic therapies.

Based on the clinical experience from MLN0128 trials, most episodes of hyperglycemia observed have been Grade 1 or 2 that have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since instituting a standard regimen for early treatment of hyperglycemia. All subjects developing hyperglycemia on the study should have their glucose closely monitored by study staff. The investigator may choose either to continue close monitoring of subjects who develop Grade 1 hyperglycemia (FSG > ULN ≤ 160 mg/dL) or, alternatively, consider initiating treatment with an oral hypoglycemic agent, such as metformin. All subjects with Grade ≥ 2 hyperglycemia (FSG > 160 mg/dL) must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated while continuing on MLN0128. The investigator should consult an endocrinologist if needed to aid in optimizing the subject's hyperglycemia treatment plan.

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

8.1.2 Management of Noninfectious 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 administration. Symptoms of pneumonitis will be closely monitored in all MLN0128 study subjects.

Guidance for MLN0128 dose management in the event of noninfectious pneumonitis is shown in the table below.

Table 3: Management of Non-infectious Pneumonitis

Grade	Description	Treatment	MLN0128 Dose Modification
1	Asymptomatic: Radiographic findings only	Rule out infection and closely monitor.	None.
2	Symptomatic: with Not interfering ADLs	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ Grade 1.	Interrupt MLN0128 treatment: When symptoms ≤ Grade 1, re-initiate MLN0128 treatment at a dose reduction Discontinue MLN0128 treatment if failure to recover within 4 weeks.
3	Symptomatic: Interfering with ADLs; Requires administration of O_2	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ Grade 1.	Interrupt MLN0128 treatment until symptoms resolve to ≤ Grade 1. Consider re-initiating MLN0128 treatment at a dose reduction If toxicity recurs at Grade 3, discontinue MLN0128 treatment.
4	Life-threatening: Ventilatory support indicated	Rule out infection and consider treatment with corticosteroids.	Discontinue MLN0128 treatment.

Abbreviations: ADL = activities of daily living ; O_2 = oxygen gas.
a If dose modification is required for subjects receiving 2 mg, then the frequency of dosing should be decreased to 5 days/week, rather than decreasing the daily dose administered.

8.1.3 Management of Hyperlipidemia

Guidance for MLN0128 dose management in the event of hyperlipidemia is shown in the table below.

Table 4: Management of Hyperlipidemia

Grade	Description	Treatment	MLN0128 Dose Modification
1	Cholesterol: > ULN - 300 mg/dL Triglycerides: > 150 - 300 mg/dL	None.	None.

Table 4: Management of Hyperlipidemia

Grade	Description	Treatment	MLN0128 Dose Modification
2	Cholesterol: > 300 – 400 mg/dL Triglycerides: > 300 - 500 mg/dL	Treat hyperlipidemia according to standard guidelines. Triglycerides ≥ 500 mg/dl should be treated urgently due to risk of pancreatitis.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to ≤ Grade 1. Reinitiate at same dose.
3	Cholesterol: > 400 - 500 mg/dL Triglycerides: > 500 - 1000 mg/dL	Same as for Grade 2.	Hold dose until recovery to ≤ Grade 1, then restart at a dose reduction
4	Cholesterol: > 500 mg/dL Triglycerides: > 1000 mg/dL	Same as for Grade 2.	Same as for Grade 3

Prevention/Prophylaxis

- Life-style modifications, as appropriate (balanced diet, limit consumption of alcoholic beverages, increase physical activity)

Abbreviations: dL = deciliters; mg = milligrams; ULN = upper limit of normal.
a If dose modification is required for subjects receiving 2 mg, then the frequency of dosing should be decreased to 5 days/week, rather than decreasing the daily dose administered.

8.1.4 Management of Oral Mucositis

Guidance for MLN0128 dose management in the event of oral mucositis is provided in the table below.

Table 5: Management of Oral Mucositis

Grade	Description	Treatment	MLN0128 Dose Modification
1	Asymptomatic or mild symptoms	Non-alcoholic mouth wash or 0.9% salt water rinse; Consider topical corticosteroids at earliest signs of mucositis.	None.

2	Moderate pain, not interfering with oral intake Modified diet indicated	Topical analgesic mouth treatments; Topical corticosteroids; Initiate antiviral or antifungal therapy, if indicated.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 dosing until recovery to < Grade 1. Reinitiate at same dose.
3	Severe pain, interfering with oral intake	Same as for Grade 2; Consider intra-lesional corticosteroids.	Hold dose until recovery to ≤ Grade 1, then restart at a dose reduction
4	Life-threatening consequences	Same as for Grade 2. Consider intra-lesional corticosteroids.	Discontinue treatment.

Prevention/Prophylaxis

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

a If dose modification is required for subjects receiving 2 mg, then the frequency of dosing should be decreased to 5 days/week, rather than decreasing the daily dose administered.

8.1.5 Management of Rash

Guidance for MLN0128 dose adjustment for the event of rash is provided in table below.

Table 6: Management of Rash

Grade	Description	Treatment	MLN0128 Dose Modification
2	Macules/papules covering ≤ 30% body surface area with or without symptoms	Consider treatment with topical steroid cream/ointment and/or oral antihistamines.	None.
≥ 3	Macules/papules covering ≥ 30% body surface area	Consider treatment with topical steroid	Hold until Grade ≤ 2; Resume MLN0128 based on

surface area with or without symptoms	cream/ointment, oral antihistamines, and/or pulsed steroids.	timing of recovery: ≤ 3 weeks: reduce dose ; > 3 weeks: stop MLN0128 and discontinue subject from the study.

a If dose modification is required for subjects receiving 2 mg, then the frequency of dosing should be decreased to 5 days/week, rather than decreasing the daily dose administered.

8.1.6 Management of Nausea and/or Vomiting

Guidance for MLN0128 dose adjustment for the event of nausea and/or vomiting is provided in the table below.

Table 7: Management of Nausea and/or Vomiting

Grade	Description	Treatment	MLN0128 Dose Modification
≤ 2	Loss of appetite with or without decreased oral intake; 1-5 episodes of vomiting within 24 hours	Maximize anti-emetic therapy; Consider IV fluid hydration.	None.
≥ 3	Inadequate oral intake; within 24 hours ≥ 6 episodes of vomiting	Maximize antiemetic therapy; Initiate tube feeding, IVF, or TPN.	Hold until ≤ Grade 1; Resume MLN0128 without dose modification.

Prevention/Prophylaxis
Prophylactic use of anti-emetic, anti-nausea, and anti-diarrheal medications are encouraged and may be used before each dose of MLN0128 as needed throughout the study.

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

8.1.7 Management of Cardiac Events

8.1.7.1 Management of Cardiac Instability

For subjects showing signs of cardiac instability after MLN0128 dosing, additional monitoring onsite before clinic discharge should be considered.

8.1.7.2 Management of Left Ventricular Dysfunction

Guidance for MLN0128 dose adjustment for the event of left ventricular dysfunction is provided in the table below.

Table 8: Management of Left Ventricular Dysfunction

Grade	Description	MLN0128 Dose Modification
1	Asymptomatic decline in LVEF > 15% from baseline values OR; LVEF > 10%-15% from baseline values and is below institution's LLN	No change; continue MLN0128 at same dose and schedule.
≥ 2	Symptomatic cardiac dysfunction/congestive heart failure	Discontinue treatment.

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

8.1.7.3 Management of QTc Prolongation

Guidance for MLN0128 dose adjustment for the event of QTc prolongation is provided in the table below.

Table 9: Management of QTc Prolongation

Grade	Description	Treatment	MLN0128 Dose Modification
2	480 ms < QTc < 501 ms	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication, etc.)	None; continue MLN0128 at the same dose and schedule.
≥ 3	QTc ≥ 501 ms	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 those subjects who had performed at intervals that the treating physician deems clinically appropriate repeated QTc measurements	MLN0128 should be interrupted. The decision whether to reinitiate MLN0128 treatment with or without dose reduction and additional monitoring in asymptomatic prolonged QTc ≥ 501 msec (Grade 3) that has until reverted to an acceptable interval, have previously fall or are below the threshold tolerated MLN0128, and appear interval that triggered the repeat to have benefitted from measurement. MLN0128 treatment with either disease control or response, will be agreed to by the investigator and the study doctor on a caseby-case basis.

Abbreviations: ECG = electrocardiogram; IV = intravenous; ms = milliseconds; QTc = QT interval corrected for heart rate
a A list of medications known to prolong QTc can be found at www.torsades.org and www.QTdrugs.org.

8.1.8 Management of Other Nonhematologic Toxicities (including Asthenia, Weakness and Fatigue)

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

Table 10 Management of Other Nonhematologic Toxicities (Including Asthenia, Weakness, and Fatigue)

Grade	Description	Treatment	Dose Modification
1	Mild; asymptomatic or mild symptoms; clinical observations only; intervention not indicated.	Initiate appropriate medical therapy and adjustment is required. or diagnostic monitor.	If tolerable, then no

Table 10 Management of Other Nonhematologic Toxicities (Including Asthenia, Weakness, and Fatigue)

Grade	Description	Treatment	Dose Modification
2	Moderate; minimal, noninvasive intervention indicated.	Initiate appropriate medical therapy and adjustment required. monitor.	If tolerable, no local or • If toxicity becomes intolerable, hold MLN0128 until recovery to ≤Grade 1, then reinitiate at same dose.
≥ 3	Severe or medically significant but not immediately lifethreatening; hospitalization or prolongation of hospitalization indicated		Hold MLN0128 until recovery to ≤ Grade 1. Reinitiate MLN0128 at dose reduced by 1 level

8.1.9 Management of Aspartate Aminotransferase/Alanine Aminotransferase Elevations

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

Table 11 Management of Aspartate Aminotransferase/Alanine Aminotransferase Elevations

Grade	Description	Treatment	Dose Modification
1	>ULN to 3×ULN	None	None
2 3	Asymptomatic with levels to 5 ULN; >3 ULN with least weekly or more the appearance of worsening frequently as indicated. fatigue, nausea, vomiting, or causes of transaminitis (eg, tenderness, fever, rash, or eosinophilia.	• Closely monitor LFTs at • Assess patient for other right upper quadrant pain past medical history, concomitant medications).	None
3	>5 to 20×ULN; >5×ULN	Same as for Grade 2.	Hold MLN0128 until ≤Grade 1; for >2 weeks Restart MLN0128 at the same dose;
4	>20×ULN	Same as for Grade 2.	Stop MLN0128 and discontinue patient from the study.

Prevention/Prophylaxis:
Ensure proper screening of patients for study participation.

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

Table 11 Management of Aspartate Aminotransferase/Alanine Aminotransferase Elevations

Grade	Description	Treatment	Dose Modification

8.2 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Other investigational agents or mTOR 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 related AE, ie, rash
- Anti-epileptic drugs for subjects with treated brain metastasis
- Anti-emetic drugs that are associated with a risk for QT prolongation, including ondansetron
- 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.

- Strong CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2C9. Consumption of grapefruit or grapefruit juice is not permitted during the study. Patients should not consume food or beverages containing the fruit or juice of grapefruits or Seville oranges within 7 days before the first dose of study drug and throughout the study (see appendix C).

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.

8.3 Permitted Concomitant Medications and Procedures

Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications is encouraged and may be used prior to first dose of MLN0128, and as needed throughout the study prior to each dosing and as clinically indicated per standard practice. When selecting an anti-emetic agent, drugs that do not have an effect on the QT interval, such as palonosetron, are preferred.

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 antiemetic 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. Neutralizing antacid preparations (acid neutralizers) and calcium supplements are not permitted during Cycle 1 on study drug administration days in the phase 1/1b portion of the study, but may be taken as needed on non-MLN0128 administration days. However, for all other cycles in the phase 1b portion of the study and throughout the phase 2 portion of the study, administration of neutralizing antacids and calcium preparations is permitted except from 2 hours before until 2 hours after MLN0128 administration. Some anti-gas preparations may also have antacid properties, and should also not be permitted from 2 hours before until 2 hours after study drug administration.
Strong CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2C9 should only be administered with caution, at the discretion of the investigator (see Appendix X).

8.4 Precautions and Restrictions

No dietary restrictions will be imposed on study patients other than avoiding the fruit or juice from grapefruit and Seville oranges within 1 week before first dose of study drug and throughout the study and daily fasting for glucose monitoring.

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

Pregnancy

It is not known what effects MLN0128 has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

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

Male patients, even if surgically sterilized (ie, status post-vasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through 90 days (3 months) after the last dose of study drug, or completely abstain from heterosexual intercourse.
- b-HGG testing for women of childbearing potential should be done prior to the initiation of each cycle.

9. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 9.1) and the characteristics of an observed AE (Section 9.2) will determine whether the event requires expedited reporting in addition to routine reporting.

9.1 Expected Toxicities

All the events included in this section are considered expected for the purpose of regulatory reporting and must remain unchanged. Adverse drug reactions that have a reasonably causal relationship to treatment with MLN0128 are presented in table below, listed according to Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term.

Gastrointestinal Disorders
Diarrhea
Nausea
Stomatitis
Vomiting

General Disorders and Administration Site Conditions
Asthenia
Fatigue
Mucosal inflammation

Metabolism and Nutrition Disorders
Anorexia
Decreased appetite
Hyperglycemia

Skin and Subcutaneous Tissue Disorders
Pruritus
Rash

9.2 Adverse Event Characteristics

- CTCAE term (AE description) and grade: 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.

- For expedited reporting purposes only:
  - AEs for the agent that is listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of ProtocolSpecific Expedited Adverse Event Reporting Exclusions.

- Attribution of the AE:
  - Definite – The AE is clearly related to the study treatment.
  - Probable – The AE is likely related to the study treatment.
  - Possible – The AE may be related to the study treatment.
  - Unlikely – The AE is doubtfully related to the study treatment.
  - Unrelated – The AE is clearly NOT related to the study treatment.

9.3 Routine Adverse Event Reporting

All Adverse Events must be reported in routine study data submissions to the Overall PI on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from the time of consent up to and including 30 days after administration of the last dost of MLN0128. Any SAE that occurs at any time after completion of MLN0128 treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to study drug must be reported to Millennium Pharmacovigilance (or designee). Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Since this is an investigator-initiated study, the sponsor-investigator Guilherme Rabinowits, MD, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's IRB. Regardless of expectedness or causality, all SAEs must also be reported to Millennium Pharmacovigilance or designee:

Fatal and Life Threatening SAEs: within 24 hours but no later than 4 calendar days of the sponsor-investigator's observation or awareness of the event.

All other serious (non-fatal/non life threatening) events: within 4 calendar days of the sponsorinvestigator's observation or awareness of the event. See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

The SAE report must include at minimum:
Event term(s) Serious criteria; Intensity of the event(s): Sponsor-investigator's or subinvestigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.Causality of the event(s): Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium.

Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsorinvestigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to study drug for each SAE will be determined by the investigator or subinvestigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide Millennium Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study drug product as soon as possible but no later than 4 calendar days of such communication.

SAE and Pregnancy Reporting Contact Information:
Cognizant
Fax Number: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com

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

9.3.1 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events:
If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee. The pregnancy must be followed for the final pregnancy outcome.

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

10. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 9.1. The DFCI INV 100 policy will be followed in handling the IP and the destruction of patient returns.

10.1 MLN0128

10.1.1 Description

A new MLN0128 capsule is available in 3 dose strengths, 1 mg, 3 mg, and 5 mg, each containing 1 mg, 3 mg, and 5 mg of MLN0128, respectively, in addition to the milled active pharmaceutical ingredient (API), the following inactive ingredients: microcrystalline cellulose (solid filler/diluents), magnesium stearate (lubricant) are found in the, and hard gelatin capsule. All 3 dose strengths are formulated into size 2 capsules, and each dose strength is differentiated by color, as listed below:

- MLN0128 capsules, 1 mg - white opaque color
- MLN0128 capsules, 3 mg – orange opaque color; and/or
- MLN0128 capsules, 5 mg – grey opaque color

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

10.1.2 Form

MLN0128 capsules are packaged in 60-cc HDPE bottles with polypropylene, child-resistant caps and induction seal. For all 3 dose strengths, each bottle contains 30 capsules.

10.1.3 Storage and Stability

MLN0128 should be stored at controlled room temperature 15°C to 30°C (59°F to 86°F). All study supplies must be kept in a restricted access area.

MLN0128 will be packaged and labeled according to all regulations. Sites must store according to the labeled conditions.

10.1.4 Handling

Because MLN0128 is an investigational agent, it should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin.

Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes,

copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

10.1.5 Availability

MLN0128 will be supplied free-of-charge, by Millennium Pharmaceuticals.

10.1.6 Preparation

MLN0128 study drug will be provided in 60 cc high-density polypropylene (HDPE) bottles with polypropylene, child-resistant caps and induction seal. Study drug will be dispensed with dosing instructions for home use, including the requirement that capsules are stored in their original containers and that capsules be swallowed whole and not opened, chewed, or manipulated in any way. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

MLN0128 is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling MLN0128 capsules.

10.1.7 Administration

MLN0128 will be administered once daily, approximately at the same time each day, on an empty stomach. The patients should be instructed to refrain from eating and drinking (except for water and any other prescribed medications), for two hours before and one hour after each dose. It is recommended that each dose of MLN0128 be given orally with 8 ounces (240 mL) of water. Missed or vomited dose should not be made up. If patient forgets MLN0128 dose until after 6:00 pm, he/she should wait until the next day. If the patient vomits MLNM0128 after taking and whole capsule is visible in the vomitus, replacement capsule should be taken, otherwise the dose should not be re-administered, and patient should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Under no circumstance should a patient repeat a dose or double-up doses.

10.1.8 Ordering

Dana-Farber Research Pharmacy will request supply of MLN0128 capsules form Millennium Pharmaceuticals, by submitting the order form.

10.1.9 Accountability

Accountability for MLN0128 at the study site is the responsibility of the sponsor-investigator. Study drug will be dispensed only to eligible patients by Dana-Farber Research Pharmacy. The appropriate study personnel will maintain records of study drug receipt and dispensing at DanaFarber Research Pharmacy. A careful record of the inventory and disposition of the agent will be maintained, using the NCI Drug Accountability Record Form (DARF).

10.1.10 Destruction and Return

Unused supplies and any expired supplies of the agent will be destroyed on site, by the DanaFarber Research Pharmacy.

11. BIOMARKER STUDIES

We plan to analyze the p4EBP1, PSK6, pCAD and Merkel cell polyomavirus (MCV) Large T antigen (LT) and small T antigen (ST) of patients' biopsy-tumors pre-treatment and correlate with treatment benefit. Original archival biopsy can be used instead of the fresh biopsy at baseline, if enough tissue is available, otherwise those with easily accessible tumor tissue from minimally invasive biopsy sites (e.g. superficial nodes, cutaneous lesions, bone biopsies, superficial soft tissue, abdominal ascites and pleural effusions) will be eligible for these biopsies. Formalin fixed paraffin embedded (FFPE) samples will be scored for p4EBP1, PSK6, pCAD and MCV LT and ST. Clinical efficacy of MLN0128 treatment will then be correlated to high and low expressing levels pre-treatment. Upon progression of disease, patients will be asked to provide another biopsy (if easily accessible, through minimally invasive procedure) to repeat the above correlative studies. This biopsy will be optional and not a requirement to participate on this study.

MCC sample processing

All MCC tumor specimens have been handled by our clinical research coordinator, in Dermatology. A protocol is already in place to request tumor blocks and whole blood for research purposes. This might be the best way to coordinate this study with earlier MCC studies. MCC specimens will have reviewed by BWH Dermatopathology for confirmation of MCC diagnosis including review or performance of specialized Immunohistochemistry (IHC) stains for CK20.
FFPE blocks of MCC tumor specimens will be requested and delivered to the DF/HCC Specialized Histopathology Services Core facility at Brigham and Women's Hospital. The BWH core or another laboratory will perform IHC from MCC specimens and will prepare sections or cores to extract DNA.

IHC

Staining will be performed in non-CLIA format by BWH core. Five unstained 4-micron sections will be obtained. Slides will be stained with antibodies for the above targets.

Whole exome sequencing

To better understand the biology of the disease, we plan to perform whole exome sequencing of available tumor tissue. Whole-exome sequencing is a diagnostic test for patients with nonspecific or unusual disease presentations of possible genetic cause and for patients with clinical diagnoses of different and unrelated genetic conditions. The purpose is also to study how DNA, genes, proteins, and other molecules in the tumor may affect response to treatment. In case archival biopsy sample is not available, patients would be asked for an optional fresh tumor biopsy sample during screening and at progression. Whole exome sequencing will be performed/coordinated at Broad Institute. The goal is to obtain 100-500ng of genomic DNA from FFPE blocks. To obtain sufficient amount of DNA, we need one of the following:

a) 5-10 unstained 10 micron FFPE slides (10 ideal)
b) 2-3 30 micron scrolls (3 ideal)
c) 2 x 1mm cores or equivalent (3 x 0.6mm cores, 1 x 2mm core, etc)

In addition, one tube of whole blood (frozen at – 80°C or fresh) needed for isolation of normal blood.

12. STUDY CALENDAR

Screening evaluations are to be conducted within 4 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

With the exception of EKGs, assessments may be done within 24-48 hours of dosing with MLN0128 administration. Cycle 1, Day 1 labs do not need to re-meet eligibility criteria for the trial.

Each treatment cycle is 28 days long. Patients will visit the clinic on Days 1, 8, 15 and 22 in cycle 1 and 2, on Days 1 and 15 in cycle 3 and 4 and on Day 1 in all subsequent cycles.

Assessments must be performed prior to administration of study agent. Study assessments and agent should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

If patients in the phase I portion of the trial are tolerating their current study drug dose level and have completed 1 cycle at this level, intra-patient dose escalation will be allowed to a dose level for which there is 4 weeks of safety data demonstrating acceptable tolerability for at least 3 patients. This evaluation can also be obtained from DFCI protocol 14-223 (PHASE II STUDY OF MLN0128 IN THYROID CANCER), which has the same trial design and the same experimental agent under investigation, for thyroid cancer patients. Therefore, for example, if there have been 3 subjects on 4mg in 14-223 without DLTs, subjects on 15-223 are able to be dose escalated from 3mg to 4mg without waiting for the 4 mg cohort of 15-223 to be completed.

Patients will be able to enter the next higher dose level if the PI determines that there is a potential clinical benefit. This dose escalation will be approved by the PI after discussion with the treating oncologist, and then documented in the patient's visit note. These patients will be closely monitored with weekly visits for 4 weeks, with the following procedures performed at each weekly visit (+/- 3 days): PE, concurrent medication assessment, vital status, weight, AE assessment, performance status, and fasting lab tests which include CBC w/ diff, serum chemistry, phosphorus, LDH, PT/INR, PTT, and urinalysis. After completing the 4 week safety monitoring period, these patients will then resume the protocol required visit schedule.

Patients that have been introduced to a dose escalation stay registered in their original cohort, and are not part of the new cohort with regards to data collection in the 3+3 study design. Finally patients may be dose escalated more than once, as long as they follow the requirements listed above.

	Screening	Cycle 1 & 2				Cycle 3-4		Cycle 5+	EOT	FU until first progression[i]
	≤4 weeks of treatment	D1	D8	D15	D22	D1	D15	D1		
Informed Consent	X									
Demographics	X									
Medical History	X									
Concurrent Meds	X	X	X	X	X	X	X	X	X	
Physical Exam[a]	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	
Height	X									
Weight	X	X	X	X	X	X	X	X	X	
Performance Status	X	X	X	X	X	X	X	X	X	
CBC w/ diff, plts	X	X	X	X		X		X	X	
Phosphorus	X	X	X	X		X		X	X	
LDH	X	X	X	X		X		X	X	
HbA1c[b]	X	X				X		X		
Serum Chemistry	X	X	X	X		X		X	X	
PT/INR, PTT	X	X		X		X		X	X	
O2 Saturation	X									

B-HCG	X	X				X		X	X	
EKG[f]	X								X	
PET/CT[c]; CT[c];	X	X				X		X	X	X
MRI[c]										
Tumor Measurements[d]	X	X				X		X		X
MLN0128		X								
Adverse Events[e]		X	X	X	X	X	X	X	X	
Fasting serum glucose[g]	X	X	X	X	X	X	X	X	X	
In-home daily fasting glucose monitoring[h]		X	X	X	X	X	X	X	X	
Fasting lipid profile	X	X				X		X	X	
Urinalysis	X	X		X		X	X	X	X	

a) Physical exam is symptom directed
b) HbA1c is done every 3 months until first progression, death, or 24 months from study entry, whichever occurs first (Screening, C1D1, C3D1, C6D1, C9D1...etc.)
c) The same imaging modality should be used throughout the study. Scans are done every 2 cycles until first progression, death, or 24 months from study entry whichever occurs first.
d) Tumor measurements should be done after each scan
e) Patients will be assessed on every cycle for adverse events until first progression, death, or 24 months from study entry, whichever occurs first
f) EKGs are done only at screening and EOT.
g) Fasting serum glucose will be measured at each clinic visit. 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.
h) In-home glucose monitoring is not required on days when fasting glucose is 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. If glucose levels stay low (<150) for 2 consecutive months, glucose monitoring can be changed to once a week.
i) After EOT, tumor assessments/scans are to continue every 2 months until first progression, death, or 24 months from study entry, whichever happens first.

AFTER FIRST PROGRESSION, PARTICIPANTS WILL BE FOLLOWED BY PHONE ONLY, EVERY 3 MONTHS (+/- 2 WEEKS) FOR 24 MONTHS FROM STUDY ENTRY OR UNTIL DEATH, WHICHEVER OCCURS FIRST.

13. MEASUREMENT OF EFFECT

13.1 Antitumor Effect – Solid Tumors

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

Response and progression will be evaluated in this study using the new international criteria proposed by the 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 the RECIST criteria.

13.1.1 Definitions

Evaluable for Target Disease response. Only those participants 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 target disease response. These participants will have their response classified according to the definitions stated below.

(Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

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

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered nonmeasurable.

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 noncystic lesions are present in the same participant, these are preferred for selection as target lesions.

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

measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

13.1.3 Methods for Evaluation of Disease

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

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

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm 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.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are

clearly defined and surrounded by aerated lung; however, CT is preferable.

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

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should

be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET/CT Imaging.

Patient Preparation

Patients should avoid any strenuous exercise for 24 hours prior to the PET scan and fast for no less than 4 hours prior to the injection of FDG. Patients must have a fasting blood glucose level $\leq$ 200 mg/dL prior to FDG injection. An attempt should be initially made to control the blood glucose level, which will require the rescheduling of the injection. If the glucose level cannot be controlled (i.e. > 200 mg/dL), the patient will not be included in the FDG-PET/CT imaging. Patients should be adequately hydrated with plain water. Weight (kg), height (cm), and blood glucose (mg/dL) will be measured and recorded prior to the injection of FDG. Sedation (alprazolam, 0.5-1 mg, po, 30 minutes pre-FDG injection) is allowed, but not mandatory and should be used consistently by the patient for all scans. Filgrastim, pegfilgrastim, and epoetin are known to affect FDG uptake, and their use by the patient should be recorded. Patients should wait in a warm room to avoid false positive brown fat FDG uptake. Patients will lie supine in a quiet room during the FDG uptake period. FDG will be synthesized and prepared in accordance with the institution's standard procedures or obtained from a commercial supplier.

FDG Dosing and Administration

The administered activity of FDG should be based on the PET/CT system manufacturer's recommendation. The recommended FDG dose is 0.14-0.21 mCi/kg. The actual FDG dose should be a bolus of 8-20 mCi, followed by a saline flush (per institutional procedure). Preinjection FDG Syringe dose, FDG dose injected and Post-injection FDG dose residual and corresponding time should be documented.

FDG-PET/CT Imaging Acquisition

Whole body PET/CT acquisition at both pre-therapy (baseline) and on follow ups MUST start 70 (± 10) minutes after FDG injection. The timing should stay the same for followup PET/CT scans from the baseline (no more than a ± 10 minute difference). It is critical that follow-up PET/CT scans will be performed in an identical way to the baseline scan, with the same scanner, same scan direction (skull to thighs or thighs to skull), and consistent arm positioning (arms up or arms down). Preferably, schedule the patient for both baseline and follow-up scans at the same time of day (AM or PM) to improve reproducibility. The field of view is to encompass the region between the scalp and toes. Patient will be scanned supine with arms positioned comfortably above the head, if possible. Oral and/or IV contrast is optional. Patient should empty his/her bladder immediately before the acquisition of images. For the emission scanning, the acquisition should be performed in 2D or 3D mode in accordance with the manufacturer's recommendations. The emission

scan must be corrected for scatter, random events, and dead-time losses using the manufacturer's recommended procedure. The image reconstruction will be performed using the manufacturer recommended parameters. Images should be attenuation corrected using CT data (note that if IV contrast is used, blood FDG SUV may be altered; therefore attenuation correction must be done without contrast).

13.1.4 Response Criteria

13.1.4.1 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 progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

13.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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

13.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

13.1.4.4 Evaluation of Best Overall Response

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

For Participants 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/NonPD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/NonPD/not evaluated	No	PR	
SD	Non-CR/NonPD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

*	See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
**	Only for non-randomized trials with response as primary endpoint.
***	In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants 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 Participants with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

13.1.5 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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.

13.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

14. DATA REPORTING / REGULATORY REQUIREMENTS

14.1 Data Reporting

14.1.1 Method

The QACT will collect, manage, and perform quality checks on the data for this study.

14.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

15. STATISTICAL CONSIDERATIONS

15.1 Study Design/Endpoints

Phase I Component

The MTD of MLN0128 will be determined using a standard 3+3 dose escalation design with three doses (3, 4, and 5 mg QD) and six patients treated at the proposed MTD. In the dose escalation design, 3 patients will be initially treated at the lowest dose level. If more than one patient experiences DLT at the lowest dose, the agent will be de-escalated to the 2 mg QD dose. If no DLT occurs in the first 3 patients at dose level 1, accrual to the next dose will begin, again with 3 patients. If at any dose one DLT occurs in the first 3 patients, 3 additional patients will be treated at that dose level and the dose either escalated or deemed the MTD if none of the additional 3 patients experiences DLT. If one or more of the additional 3 patients experiences DLT, the MTD will have been exceeded and the MTD will be defined to be the next lower dose. If at any time 2 or more patients experience DLT at a dose level, the MTD will have been exceeded. Patients will be treated through the two cycles for DLT assessment.

With this escalation strategy, the table below gives the probability of escalation as a function of the true underlying DLT rate for a variety of true rates. There will be 6 patients treated at the MTD before moving to the phase II component of the study. That is, if only 3 patients had been treated at the recommended dose, a second cohort of 3 patients will be added. The phase I component of

this study will therefore accrue a potential total of 18 patients. See also section 7.3 for additional details on the dose escalation design, proposed dosing and definition of DLT.

True rate of DLT	10%	20%	30%	40%	50%	60%	70%
Probability of escalation	.91	.71	.49	.31	.17	.08	.03

Phase II Component

The primary objective of this trial is to assess MLN0128 activity in patients with recurrent/metastatic MCC. MLN0128 will be considered an active drug for recurrent/metastatic MCC if there is evidence that the true objective response rate is at least 40% (against a null of 10% in this heterogeneous population). We will adopt a two-stage design in this study whereby at the first stage 6 patients are entered. If one or more responses are seen amongst the first 6 patients, an additional 10 treated patients will be entered. A total number of responses of 4 or more out of 16 patients will be sufficient evidence to reject the null hypothesis. We will consider MLN0128 to be an active drug in this patient population.

With this design, the probability of concluding the proposed treatment is promising is 0.91 if the true but unknown response rate is 40% (power) but 0.06 if the true disease control rate is 10% (type I error). The probability of stopping early under the null hypothesis is 53%. The operating characteristics of this design are calculated using the exact binomial distribution.

Progression-free (PFS), disease control rate (DCR) and overall survival (OS) of patients receiving MLN0128 for MCC will be described using the method of Kaplan and Meier. Survival and 90% confidence intervals for OS and PFS will be reported, although the precision for these estimates is expected to be low given the small sample size, hence these analyses will be largely descriptive.

Toxicity is an important secondary endpoint. Assuming the trial moves to the second stage, with 16 treated patients there is at least 56% probability of observing one or more rare (5% true probability) events, and over 90% probability of observing toxicities that have a true occurrence of at least 14%. A 90% two-sided exact binomial confidence interval on any given adverse event rate will be no wider than 45 percentage points.

Continuous Toxicity Monitoring: Due to anticipated treatment-related toxicities, continuous monitoring of serious treatment-related toxicities will be performed. The study will be terminated early if excessive incidence of treatment related toxicity is observed.

15.2 Sample Size, Accrual Rate and Study Duration

The planned sample size is 6-34 patients total. The anticipated annual accrual is approximately 6 patients. The anticipated period of active accrual is expected to be 24-36 months depending upon the enrollment required for the phase I component.

16. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

17. ADMINISTRATIVE REQUIREMENTS

17.1 Product Complaints

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

For Product Complaints, call 1-844-ONC-TKDA (1-844-662-8532) e-mail: GlobalOncologyMedinfo@takeda.com

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance (refer to Section 14.2).

18. REFERENCES

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all selfcare, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B INFORMATION ON POSSIBLE DRUG INTERACTIONS

MLN0128 is metabolized by CYP2C19, CYP3A4, and CYP2C9.

There are no known strong specific CYP2C9 inhibitors or inducers. Examples of moderate inhibitors of CYP2C9 are fluconazole and miconazole; moderate inducers of CYP2C9 are carbamazepine and rifampin. These agents show some degree of overlap with their modulation of CYP3A4 and CYP2C19 activity and should hence be considered with similar caution.

Strong inhibitors of CYP2C19 include fluconazole, fluvoxamine, omeprazole, and ticlopidine. Strong inhibitors of CYP3A4 include ketoconazole, itraconazole, ritonavir, mibefradil, indinavir, and clarithromycin. Strong inducers of CYP3A4 include phenobarbital, phenytoin, carbamazepine, St. John's wort, and rifampin (also a moderate CYP2C19 inducer).

Strong Inhibitors and Strong Inducers of CYP2C19, and CYPE3A4

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

Note that these lists are not exhaustive.

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

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

Sources: ganfyd.org/index.php?title=Inhibitors_of_CYP3A4 and medicine.iupui.edu/clinpharm/ddis/