Title: A phase I/II study of MLN0128 in metastatic anaplastic thyroid cancer and incurably poorly differentiated or radioiodine refractory differentiated thyroid cancer

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Agent: MLN0128 (SAPANISERTIB/CB-228/TAK-228)

SCHEMA OF THE STUDY

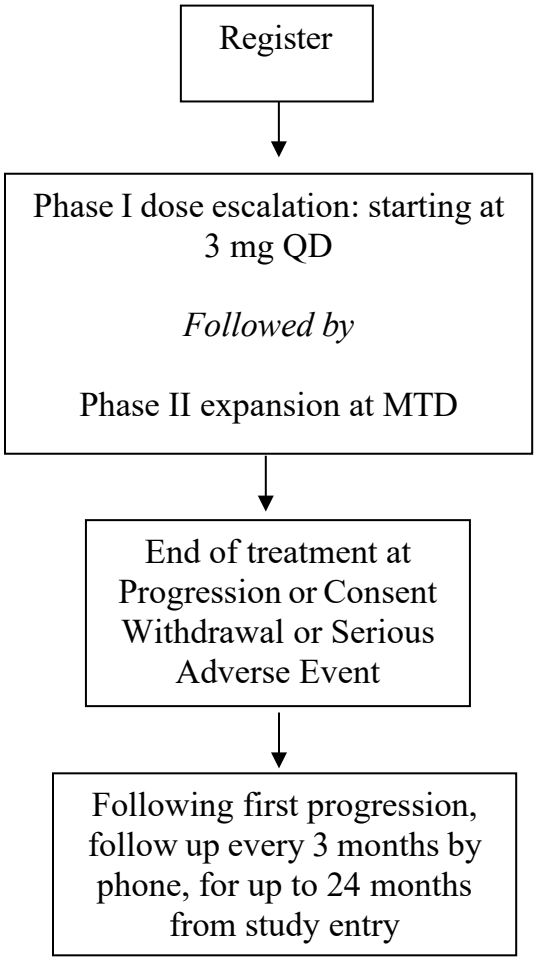


TABLE OF CONTENTS

1. OBJECTIVES

1.1 Study Design

This is a non-randomized phase I/II study to determine the recommended phase II dose (RP2D) and study the efficacy of MLN0128 (SAPANISERTIB/CB-228/TAK-228) . . Between 43 and 53 patients could be entered into this trial. The phase I design, which has completed, was a standard 3+3 design. The starting dose was 3 mg. Each cohort was 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 was not to proceed beyond 5 mg QD or below 2 mg 5 days a week, respectively. The phase I design enrolled patients with thyroid cancer as defined in section 3.0 below. The phase II part of the study uses the RP2D determined during the phase I part of the study: 5mg.
The original phase II cohort was designed to enroll only patients with anaplastic thyroid cancer (ATC) as defined in section 3.0 below. The cohort for patients with ATC continues to enroll between 23-25 patients. . With this amendment, a second phase II cohort of up to 23-24 patients with differentiated thyroid cancer (DTC), as defined in section 3.0 below are to be enrolled. Each respective cohort includes those patients from the phase I portion treated at the MTD.

1.2 Primary Objectives

- Phase I: To determine the recommended phase II dose (RP2D)
- Phase II: To evaluate the proportion progression free at 4 months in patients with anaplastic thyroid cancer.

1.3 Secondary Objectives

- To evaluate safety/adverse events
- To evaluate proportion progression-free at 6 months in patients with DTC.
- To evaluate response rate (ORR)
- To evaluate overall survival (OS)
- Identification of biomarkers predictive of response to therapy with MLN0128 (SAPANISERTIB/CB-228/TAK-228)

2. BACKGROUND

2.1 Study Disease

Anaplastic thyroid cancer is a rare tumor originating from the thyroid gland. It is one of the deadliest malignancies and is characterized by aggressive growth, and early lymphogenous and hematogenous metastasis. Even though it accounts for only 2% of all thyroid carcinomas, it is responsible for 14-39% of all cancer deaths. Median survival is estimated at 4-9 months and fewer than 20% of patients live beyond one year (1).

No established treatment options exist for patients with metastatic disease. Rare responses to anti-VEGF TKI's are reported but this class of drugs is generally not considered effective (2).

Poorly differentiated and RAI refractory metastatic incurable disease carries a dismal prognosis. Tyrosine kinase inhibitors such as sorafenib and lenvatinib are FDA approved based on statistically significant impact on progression free survival (PFS) in pivotal phase III studies; however, a difference in overall survival was not observed between treatment and placebo cohorts (Brose, Schlumberger et al. 2015, Schlumberger, Tahara et al. 2015).

No standard options exist for patients who fail TKI treatment or who do not tolerate or are not candidates for treatment due to significant toxicities of these drugs. mTOR inhibitors such as everolimus have significant activity in these patients as we and others have demonstrated in phase 2 trials (Lim, Chang et al. 2013, Schneider, de Wit et al. 2017, Hanna, Busaidy et al. 2018).

2.2 IND Agent

MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) (formerly INK128) targets 2 distinct multiprotein complexes, mTORC1 and mTORC2.

MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (3). 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 (4).

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 (SAPANISERTIB/CB-228/TAK-228) was developed to address the incomplete inhibition of the mTOR pathway by rapalogs.

MLN0128 (SAPANISERTIB/CB-228/TAK-228) is being developed for both oncology and non-oncology indications. In oncology, MLN0128 (SAPANISERTIB/CB-228/TAK-228) is being investigated as a treatment for advanced solid tumors and hematologic malignancies, either as monotherapy or in combination with chemotherapy, other molecularly targeted therapies, or antihormonal agents. 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).

2.3 Nonclinical Summary

2.3.1 Pharmacology

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

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

2.3.2 Safety Pharmacology

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

2.3.3 Drug Metabolism and Pharmacokinetics

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

MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) did not induce CYP1A2, 2B6, and 3A4 activity and expression at concentrations up to 10 μM. MLN0128 (SAPANISERTIB/CB-228/TAK-228) displayed low potential for inhibition and is not a time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5.

Oral administration of MLN0128 (SAPANISERTIB/CB-228/TAK-228) in humans has a low potential for metabolic and transporter-based drug-drug interactions (DDIs), especially given

clinical exposures observed to date after administration of the highest anticipated therapeutic dose to be used in the clinic in oncology indications (total maximum plasma concentration [Cmax] of 0.48 μM [free Cmax of 0.14 μM] at 30 mg once weekly [QW]).

2.3.4 **Toxicology**

The toxicologic profiles obtained in the Good Laboratory Practice (GLP)-compliant and non-GLP-compliant studies in rats and monkeys were generally consistent with pharmacologic inhibition of mTORC1/2 activity. There were no apparent sex differences in observed toxicities.

The dose-limiting toxicities (DLTs) of MLN0128 (SAPANISERTIB/CB-228/TAK-228) in rats and monkeys were secondary to an exaggerated pharmacologic response and consisted of body weight loss and associated clinical observations that included gastrointestinal (GI) distress and decreased activity, appetite, and body temperature. 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, and alveolar histiocytosis. The microscopic findings observed in the testes and epididymides 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; and skin ulceration/epidermal hyperplasia. 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 (SAPANISERTIB/CB-228/TAK-228) , 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 (SAPANISERTIB/CB-228/TAK-228) .

MLN0128 (SAPANISERTIB/CB-228/TAK-228) was negative for genotoxicity in an in vitro bacterial mutagenesis (Ames) assay, an in vivo rat micronucleus assay, and an in vivo rat comet assay. An in vitro chromosomal aberration assay with MLN0128 (SAPANISERTIB/CB-228/TAK-228) in human peripheral blood lymphocytes (PBLs) was positive for chromosomal aberrations in the presence and absence of metabolic activation.

However, the weight of evidence from the combined results of a negative mutagenicity assay and negative genotoxicity assessments in 2 in vivo assays in 3 tissues (bone marrow, liver, and duodenum) demonstrate that MLN0128 (SAPANISERTIB/CB-228/TAK-228) does not present a genotoxic risk.

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

Preliminary findings in ongoing rat and rabbit embryofetal studies indicated teratogenic, fetotoxic, and abortive effects with MLN0128 (SAPANISERTIB/CB-228/TAK-228) . Embryofetal lethality and/or teratogenic effects have been reported with the TORC1 inhibitors rapamycin and the rapalogs.

2.3.5 **Summary of Effects in Humans in Advanced Solid Malignancies and Hematologic Malignancies**

MLN0128 (SAPANISERTIB/CB-228/TAK-228) is in clinical development as a single agent in 2 phase 1 studies in patients with advanced solid malignancies and hematologic malignancies (multiple myeloma [MM] and
Waldenström macroglobulinemia [WM]); 1 of these studies has been completed. It is also being investigated in combination with paclitaxel (with or without trastuzumab) in a phase 1b study in patients with advanced solid tumors.

As of the clinical data cutoff (09 December 2013), a total of 248 patients had received ≥ 1 dose of study drug across the 3 oncology studies. In general, observed toxicities have been assessed primarily as severity Grade 1 or 2, and have been manageable with supportive care and/or dose interruption or reduction. A total of 15 deaths reported to the clinical database as of data cutoff occurred within 30 days of the last study drug dose; of these events, 1 (cardiac arrest; Study INK0128-001) was considered related to MLN0128 (SAPANISERTIB/CB-228/TAK-228) (see Section 5.3.1.1 of the IB).

2.3.6 **Safety and Efficacy in Oncology Studies**

In the clinical development plan, the safety and tolerability profile of single-agent MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) with paclitaxel, with or without trastuzumab.

2.3.7 **Study INK128-001**

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

As of 09 December 2013, a total of 166 patients had been enrolled and 142 of these had received at least 1 dose of MLN0128 (SAPANISERTIB/CB-228/TAK-228) . The median age at baseline was 60 years (range 24-89 years). Most (93%) patients are white, and 57% are female.

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 2013, a total of 4 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 and 3 were due to disease progression. The event of ventricular fibrillation and cardiac arrest was the only case considered related to study drug.

As of the clinical database cutoff date, treatment-emergent SAEs had been reported for 58 patients (41%) in this study. The most commonly reported preferred terms overall were mucosal inflammation in 5 patients (4%), asthenia and pneumonia in 4 patients (3%) each, and abdominal pain, stomatitis, and renal failure in 3 patients (2%) each.

Overall, ≥ 1 TEAE was reported for 139 (98%) of the 142 treated patients. Across the dosing groups, hyperglycemia was reported most frequently (65% of patients). The second most frequent TEAE was nausea (63% of patients), followed by vomiting (54%).

In general, TEAEs have been mostly Grade 1 or 2 and manageable with supportive care, and/or interruption or dose reduction of study drug. Across all dosing groups, at least 1 TEAE severity Grade 3 or higher had been reported for 64% of treated patients as of the clinical data cutoff date. Severity ≥ Grade 3 TEAEs that were reported in 6% or more of patients as of the data cutoff, regardless of causality, were hyperglycemia (13% of patients), asthenia (8%), anemia (7%), and hypophosphatemia and lymphopenia (6% of patients each).

Of the 142 patients treated in Study INK128-001 as of the clinical data cutoff, 74 (52%) discontinued because of disease progression, 29 (20%) discontinued because of 1 or more AEs, 15 (11%) withdrew consent, and 8 (6%) were lost to follow-up, used a prohibited medication, or discontinued for other reasons.

A total of 40 AEs led to study discontinuation among 29 patients. A total of 21 events (53%, including 11 nonserious AEs) were reported as severity Grade 3, and 4 SAEs were Grade 5 (fatal). No Grade 4 events were reported. The majority (63%) of events had resolved as of the data cutoff date.

A total of 9 preferred terms were reported as leading to discontinuation for more than 1 patient, including rash, which was reported in 6 patients (including 2 AEs of maculopapular and 1 erythematous rash AE), mucosal inflammation (4 patients), and asthenia (3 patients). Events reported in 2 patients included hyperglycemia, nausea, performance status decreased, pruritus, and renal failure/renal failure acute.

As of 09 December 2013, dose-limiting toxicities have included hyperglycemia, asthenia, fatigue, mucositis, and rash. SAEs attributed to MLN0128 (SAPANISERTIB/CB-228/TAK-228) have included hyperglycemia, asthenia, mucosal inflammation, stomatitis, esophagitis, nausea, anemia, renal failure, cardiac arrest, and ventricular fibrillation.

2.3.8 **Study INK128-002**

Study INK-002 is a completed phase 1, open-label, dose-escalation study of oral MLN0128 (SAPANISERTIB/CB-228/TAK-228) administered as a single agent in patients with relapsed or refractory hematologic malignancies (MM or non-Hodgkin lymphoma, including WM). A total of 39 patients received MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) .

[redacted]

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 (SAPANISERTIB/CB-228/TAK-228) treatment, with the exception of 3 events that were reported in 1 patient. This patient experienced Grade 2 pneumonia on Day 58 that resolved without sequelae on Day 60. On Day 121, the same patient experienced SAEs of pneumonia (Grade 2) and hypoxia (Grade 3). The 3 events improved

by Day 125 and were resolved as of Day 142. All 3 events were considered by the investigator to be related to MLN0128 (SAPANISERTIB/CB-228/TAK-228) .

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.

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 (SAPANISERTIB/CB-228/TAK-228) 2 mg QD n = 3	MLN0128 (SAPANISERTIB/CB-228/TAK-228) 4 mg QD n = 6	MLN0128 (SAPANISERTIB/CB-228/TAK-228) 6 mg QD n = 6	MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (Dose-escalation Evaluable Population)

Preferred term	MLN0128 (SAPANISERTIB/CB-228/TAK-228) 9 mg QD × 3d QW n = 6	MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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.

2.3.9 **Study INK128-003**

Study INK128-003 is a phase 1, open-label, dose-escalation study of oral MLN0128 (SAPANISERTIB/CB-228/TAK-228) administered in 4-week cycles in combination with paclitaxel in patients with advanced solid malignancies (lung, ovarian, endometrial, breast, pancreatic, prostate, etc).

As of the clinical data cutoff date, 69 patients had been enrolled. Of these patients, 67 had received ≥ 1 MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) 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. The dose expansion phase of this study remains ongoing.

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 (SAPANISERTIB/CB-228/TAK-228) .

As of the clinical data cutoff date, 55 SAEs had been reported among 29 patients (43%) in this study.

The most commonly reported SAEs included pneumonia in 6 patients (9%), dehydration in 4 patients (6%), and small intestinal obstruction in 3 patients (4%).

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 in 53 patients (79%) 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).

Of the 63 patients (94%) in Study INK128-003 who had discontinued MLN0128 (SAPANISERTIB/CB-228/TAK-228) treatment as of the clinical data cutoff, 34 (51%) discontinued because of disease progression, 15 (22%) because of patient decision, and 14 (22%) because of 1 or more TEAEs.

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 (SAPANISERTIB/CB-228/TAK-228) .

As of 09 December 2013, the MLN0128 (SAPANISERTIB/CB-228/TAK-228) dosing regimens (and dose ranges) studied in INK128-003 are QDx3d QW (6-10 mg), QDx5d QW (7 mg), and QW (30 and 40 mg). MLN0128 (SAPANISERTIB/CB-228/TAK-228) is administered in combination with paclitaxel (80 mg/m2) administered on Days 1, 8, and 15 of each 28-day cycle. The dose escalation phase of this study has completed and the administration of MLN0128 (SAPANISERTIB/CB-228/TAK-228) plus paclitaxel with or without trastuzumab is being evaluated in the expansion phase. Observed DLTs include fatigue, mucosal inflammation, rash, nausea, diarrhea, leukopenia, neutropenia, and thrombocytopenia. SAEs observed with the MLN0128 (SAPANISERTIB/CB-228/TAK-228) + paclitaxel are dehydration, diarrhea, vomiting, and mucositis.

Due to changes in the manufacturing process which may result in increased absorption of MLN0128 (SAPANISERTIB/CB-228/TAK-228) from capsules, there will be a run-in phase I prior to the phase II of the study. Patients with poorly differentiated thyroid cancer, RAI refractory differentiated thyroid cancer with prior treatment with a TKI will be allowed to participate in the run-in phase I part in addition to the incurable anaplastic thyroid cancer cases. The phase II part of the study will enroll incurable anaplastic thyroid cancer cases only.

2.3.10 **Pharmacokinetics**

Overall, pharmacokinetic (PK) data from Studies INK128-001, INK128-002, and INK128-003 indicate that MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) was generally consistent, with no appreciable differences across the 3 clinical studies. Neither paclitaxel nor MLN0128 (SAPANISERTIB/CB-228/TAK-228) appeared to alter the PK of the other agent when co-administered. Given the changes in maufacturing and different drug availability, PK samples will be collected in phase I on C1D8; at 0 (before MLN0128 (SAPANISERTIB/CB-228/TAK-228) dose) and 2, 4 and 8 hours after the MLN0128 (SAPANISERTIB/CB-228/TAK-228) dose. See PK sample processing details in Appendix D.

2.3.11 **Rationale**

We have recently completed accrual for an investigator initiated phase II study in patients with

differentiated thyroid cancer with the mTOR inhibitor everolimus, a rapamycin analogue. This study also included an exploratory cohort of 7 patients with anaplastic thyroid cancer (Hanna, Busaidy et al. 2018). Among these 7 cases, one patient had a near complete response which lasted for 18 months, another patient has ongoing disease stability for 16 months with approximately 20% shrinkage of the tumor burden and a third patient had a mixed response. Analysis of the patient with the near complete response revealed a nonsense mutation in the tumor suppressor TSC2 which acts through suppression of the mTOR complex 2 (mTORC2). When the patient progressed after 18 months, we obtained another biopsy which shows a new mutation within the rapamycin binding site of mTOR (F2108L). Cell culture experiments with transfection of wild type versus mutated mTOR show that cells were resistant to rapamycin but sensitive to Torin 2, an allosteric mTOR inhibitor similar to ML0128 (Wagle, Grabiner et al. 2014).

We were also able to show that Torin2, but not rapamycin was able to inhibit phosphorylation of S6K, a downstream effector of mTOR, providing further evidence that acquired resistance to rapamycin does not extend to other mTOR inhibitors and suggesting that ML0128 could be useful in cases that have acquired resistance to rapamycin analogues such as everolimus. We also performed exome sequencing on tumor material from the patient with a mixed response which revealed an activating mutation of PI3K. Primary cell cultures from the same patient showed that while everolimus showed some anti-tumor effects initially, these effects diminished over several days while Torin2 induced cell death effectively and permanently at low doses. Another patient with metastatic anaplastic thyroid cancer who is currently undergoing treatment with off label everolimus recently had restaging scans at 3 months of therapy showing 10% reduction in the size of the lesions. Sequencing demonstrated 2 separate missense mutations within the PI3K gene.

In a retrospective series of 27 anaplastic TC cases, we found that TSC2 missense mutations occur in 15%, loss of TSC2 occur in 19%. Missense mutations of PI3K were demonstrated in 22%. Since approximately 50% of all cases had abnormalities of either TSC2 or PI3K and based on the strong response signal to everolimus that we have observed in treatment of anaplastic thyroid cancer cases on our everolimus study and off protocol, we anticipate that between 30 and 50% of cases should respond to treatment with MLN0128 (SAPANISERTIB/CB-228/TAK-228) .

The same phase II study also included differentiated RAI refractory thyroid cancer and medullary thyroid cancer that had progressed within 6 months prior to enrollment. Both patient groups had significant clinical benefit with a median PFS of 12 months for differentiated thyroid cancer and several patients who had no disease progression within 12 months in the exploratory medullary thyroid cancer group. These and data from 2 other phase 2 studies led to compendia listing of everolimus in RAI refractory differentiated thyroid cancer.

Based on these findings, we anticipate that ML0128 may be beneficial in many cases of anaplastic thyroid cancer cases, a disease in which no active treatment standard exists.
Given the activity with everolimus in RAI refractory thyroid cancer, subjects wth metastatic, incurable differentiated RAI refractory and poorly differentiated thyroid cancer were enrolled during the phase 1 part of this trial. As of this amendment, a phase II cohort of these patients who have previously failed or who can not tolerate FDA approved standard TKI's such as sorafenib or lenvatinib and for whom no standard options exist plan to be enrolled.

2.3.12 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 on all patients. Patients with accessible tumors will undergo sequential biopsies prior to and at 2 weeks of therapy. Genetic information will be used to identify biomarkers that predict response to therapy. Kinome analysis will be performed to assess molecular pathway activation in response to mTOR inhibition to elucidate possible escape mechanisms that could account for resistance and provide a rationale for combination therapy in the future. Patients with mutations and deletions of TSC2 will be evaluated separately and descriptive statistics including confidence intervals will be used to evaluate prgoression free survival (PFS); because the sample size of this sub-population is anticipated to be small, no further statistical analysis is planned.

3. PARTICIPANT SELECTION

3.1 Inclusion Criteria

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

1. Male or female patients 18 years or older
2. Any number of prior chemotherapy or targeted agents including rapamycin analogues are allowed
3. For the Phase II part of the study, newly diagnosed OR refractory/metastatic anaplastic thyroid cancer confirmed by histology, incurable by surgery, radiotherapy or chemoradiotherapy alone or in combination OR, new for Protocol Amendment 16, newly diagnosed patients with incurable poorly differentiated OR radioiodine refractory differentiated thyroid cancer that is refractory to TKI treatment. Patients who cannot tolerate a TKI or are not candidates for a TKI at the discretion of the PI are also eligible.
4. Note that phase I portion is complete as of this Amendment. For the Phase I part of the study, eligible patients must have incurable poorly differentiated thyroid cancer; ORanaplastic thyroid cancer; OR radioiodine refractory differentiated thyroid cancer that is refractory to a TKI; OR patients who cannot tolerate a TKI are also eligible. Histological confirmation of poorly differentiated, undifferentiated or anaplastic histology is required for untreated cases, but is not required for the refractory cases.
5. Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension
6. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0-2 (see appendix A)
7. No active intracranial metastases
8. 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.
9. Ability to swallow oral medications and maintain an empty stomach state for 2 hours prior to the MLN0128 (SAPANISERTIB/CB-228/TAK-228) dose and for 1 hour following administration
10. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

11. Adequate organ function, as specified below, within ≤ 4 weeks prior to study entry:
    a) Bone marrow reserve consistent with: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L; platelet count ≥ 100 x 10^9/L; hemoglobin ≥ 9 g/dL;
    b) Hepatic: total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN), transaminases (aspartate aminotransferase/serum glutamic oxaloacetic transaminase-AST/SGOT and alanine aminotransferase/serum glutamic pyruvic transaminase-ALT/SGPT) ≤ 2.5 x institutional ULN (≤ 5 x institutional ULN if liver metastases are present);
    c) Renal: creatinine within normal institutional limits, OR creatinine clearance ≥60 mL/min, based either on Cockroft-Gault estimate or based on urine collection (12 or 24 hour), for participants with creatinine levels above institutional normal;
    d) Metabolic: fasting serum glucose (≤ 130 mg/dL) and fasting triglycerides ≤ 300 mg/dL;
12. Female patients who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, 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
13. Male patients, even if surgically sterilized (ie, status post-vasectomy), who:
    - Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, or
    - Agree to completely abstain from heterosexual intercourse
14. 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 C)

3.2 Exclusion Criteria

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

1. Female patients who are both lactating and breastfeeding or have a positive serum pregnancy test during the screening period
2. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol
3. Treatment with any investigational products within 14 days before the first dose of study drug
4. Failed to recover from the reversible effects of prior anticancer therapies with the exception of alopecia
5. Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of MLN0128 (SAPANISERTIB/CB-228/TAK-228)
6. 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;
7. 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

8. 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
    - 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)
9. 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).
10. Other clinically significant co-morbidities, such as uncontrolled pulmonary disease, active central nervous system disease, active infection, or any other condition that could compromise participation of the patient in the study.
11. 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. For patients with anaplastic thyroid cancer or otherwise particularly aggressive disease (as determined by the investigator), the washout period for chemotherapy/radiotherapy and/or targeted agents is at the investigator's discretion.
12. Presence of active brain metastases or epidural disease
    - Subjects with brain metastases are eligible if previously treated with whole brain radiation or radiosurgery, and do not require steroid treatment for at least 2 weeks before starting study treatment
    - Subjects with epidural disease are eligible if previously treated with radiation or surgery, are asymptomatic, and do not require steroid treatment for at least 2 weeks before starting study treatment.
13. 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.

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. 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 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. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

- DF/HCC Standard Operating Procedure for Human Subject Research Titled *Decentralized Subject Protocol Registration* (SOP #: REGIST-101B) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at DF/HCC by the Study Coordinator. [redacted] Following registration, participants should begin protocol therapy as soon as possible, and the Study Coordinator should be notified of the anticipated treatment start date. Issues that would cause treatment delays should be discussed with the Overall PI. If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the research nurse or data manager and faxed ([redacted]) or e-mailed to the Study Coordinator:

- Copy of relevant lab tests, scan reports, and pathology reports as described per the eligibility checklist
- Signed participant consent form

- HIPAA authorization form
- Completed and signed Eligibility Checklist

The research nurse or data manager at the participating site will then call or e-mail the Study Coordinator to verify eligibility. To complete the registration process, the Coordinator will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Decentralized Subject Protocol Registration* (SOP #: REGIST-101B) and register the participant on the protocol. The coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The coordinator will also call the research nurse or data manager at the participating site to verbally confirm registration.

5. TREATMENT PLAN

5.1 Treatment Regimen

Treatment will be administered on an outpatient basis. MLN0128 (SAPANISERTIB/CB-228/TAK-228) will be administered orally, daily for 28 consecutive days of a treatment cycle. The participant will be requested to maintain a medication diary of medication. The medication diary will be returned to clinic staff at the end of each cycle. Treatment with MLN0128 (SAPANISERTIB/CB-228/TAK-228) will continue until progression or withdrawal of consent.

Reported adverse events and potential risks of MLN0128 (SAPANISERTIB/CB-228/TAK-228) are described in Section 6. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

5.2 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.

5.3 Agent Administration

MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) be given with 8 ounces (240 mL) of water.

In the phase I part of this study, the starting dose of 3 mg was chosen to account for the possibility of increased absorption with MLN0128 (SAPANISERTIB/CB-228/TAK-228) capsules based on preliminary MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 de-escalation (2 mg QD).

Escalation/de-escalation should not proceed beyond 5 mg QD or below 2 mg QD respectively (Table 1).

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

Dose Escalation Criteria for Phase I

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.
	If during testing of dose level 1 (3mg QD), the above rules call for dose de-escalation to dose level -1 (2mg QD), then 3 patients will be entered at 2mg QD. If there are no DLT's, then 2mg will be declared the MTD (since no further dose de-escalation is allowed) and entry into expansion cohort will begin (this is the same logic if testing escalates up to dose level 3 (5mg QD) and there are no DLTs observed in the first 3 patients). If DLT is observed in the first 3 patients at 2mg QD, then the above rules will be followed for further testing in the 2mg QD cohort prior to decisions about any patients being entered into an expansion cohort or not.

Dose Escalation for Phase I

Dose level	**MLN0128 (SAPANISERTIB/CB-228/TAK-228) Dose**
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 (SAPANISERTIB/CB-228/TAK-228) 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.

5.3.1 **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 (SAPANISERTIB/CB-228/TAK-228) , 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 (SAPANISERTIB/CB-228/TAK-228) will be interrupted (if not otherwise specified) and the toxicity will be followed up as described in section 5.3.3. The criteria for dose-limiting toxicities are outlined below.

5.3.2 **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
	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 (SAPANISERTIB/CB-228/TAK-228) for > 21 consecutive days
Other adverse events	CTCAE grade 3 adverse events (excluding CTCAE grade 3 elevations in alkaline phosphatase)

[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 (SAPANISERTIB/CB-228/TAK-228) , 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 6) within 28 days of the first dose of MLN0128 (SAPANISERTIB/CB-228/TAK-228) , this will be considered a DLT.

5.3.3 **Follow up to DLT**

Patients who experience an AE that meets the definition of a DLT 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 (SAPANISERTIB/CB-228/TAK-228) 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 MLN0128 (SAPANISERTIB/CB-228/TAK-228) -related 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 (SAPANISERTIB/CB-228/TAK-228) and continue to be followed according to protocol until first disease progression or death whichever occurs fist. Patients may, however, hold drug over 14 consecutive days if PI approval is received.

5.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 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 C presents guidelines for identifying medications/substances that could potentially interact with the study agent.

5.5 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 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. Patients who discontinue protocol treatment for reasons other than disease progression will continue to be followed according to protocol until first disease progression or death whichever occurs first, or if first disease progression has been documented, will be followed until death or 24 months post study entry whichever occurs first.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the PI, Kartik Sehgal, MD [redacted]

5.6 Duration of Follow Up

Participants will be followed for first progression and survival. After first progression, participants will be followed for survival by phone only, every 3 months (+/- 2 weeks) for 24 months from study entry or until death whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event and continue to be followed according to protocol until first disease progression or death whichever occurs fist.

5.7 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 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.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following tables. 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.

Patients who experience an AE that meets the definition of a DLT 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 (SAPANISERTIB/CB-228/TAK-228) .

For the phase I part of the study, treatment will continue 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 MLN0128 (SAPANISERTIB/CB-228/TAK-228) -related 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 (SAPANISERTIB/CB-228/TAK-228) and continue to be followed according to protocol (see section.10.0). Patients may, however, hold drug over 14 consecutive days if PI approval is received.

Dose will be modified according to the same criteria in Phase I and II and dose levels will follow as specified in table 1a and 1 b below.

MLN0128 (SAPANISERTIB/CB-228/TAK-228) dosing should be withheld for ≥ Grade 2 renal insufficiency or ≥ Grade 3 MLN0128 (SAPANISERTIB/CB-228/TAK-228) -related toxicities. If the event resolves to Grade ≤ 1 or baseline values within 14 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 QD, 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. If

MLN0128 (SAPANISERTIB/CB-228/TAK-228) dosing is delayed for > 14 consecutive days for MLN0128 (SAPANISERTIB/CB-228/TAK-228) -related toxicity despite supportive treatment per standard clinical practice or more than 2 dose reductions of MLN0128 (SAPANISERTIB/CB-228/TAK-228) is required in a subject, stop MLN0128 (SAPANISERTIB/CB-228/TAK-228) therapy, discontinue the subject from the study, and complete the follow-up visit within x days of the last administration of MLN0128 (SAPANISERTIB/CB-228/TAK-228) . Patients may, however, hold drug over 14 consecutive days if PI approval is received.

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. 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: Dose Reductions for Phase II (based on RP2D = 5 mg)

Dose Level	Dose (RP2D = 5 mg) mg
1	5 mg
-1	4 mg
-2	3 mg
-3	2 mg
-4	2 mg x 5 days per week
	Discontinue
Level 1 is the starting dose	

See Section 6.1 for management of MLN0128 (SAPANISERTIB/CB-228/TAK-228) dosing for specific clinical events. The PI should be contacted prior to any dose modification in MLN0128 (SAPANISERTIB/CB-228/TAK-228) for any subject in the study. All dose reductions will be by one dose level down at a time. However,

depending on the PI/treating physician's discretion, the dose reduction may be by two dose levels down at a time.

6.1 Management of Clinical Events

6.1.1 Management of Hyperglycemia

In addition to obtaining fasting serum glucose (FSG) levels at clinic visits, all subjects will be given a glucometer to monitor their daily pre-dose fasting blood glucose (FBG) levels at home. Subjects will be instructed to notify the study staff immediately with any abnormal readings (ie, ≥ 150 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia. If no irregularities in the fasting blood glucose level are observed during a minimum of 2 consecutive months, then the frequency of in-home fasting glucose testing may be reduced to once weekly if the investigator approves. Subjects will continue to notify the investigator of fasting blood glucose levels that exceed 150 mg/dL and, if blood glucose levels are not well-controlled, or if the subject requires either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of fasting blood glucose levels will be reinstated to daily. Weekly glucose monitoring may stop after 1 year on study drug, at the discretion of the treating physician. Subjects will continue to have fasting glucose collected at each monthly clinic visit.
Guidance for MLN0128 (SAPANISERTIB/CB-228/TAK-228) dose management in the event of hyperglycemia is provided in the table below.

Table 2: Management of Hyperglycemia

Grade	Description	Treatment	MLN0128 (SAPANISERTIB/CB-228/TAK-228) Dose Modification
1	Fasting blood sugar > ULN–160 mg/dL	Continue close monitoring of blood sugars. Initiate oral hypoglycemic agent.	None.
2	Fasting blood sugar > 160–250 mg/dL	Initiate oral hypoglycemic agent and/or insulin if not well controlled on oral agent.	None.
≥3	Fasting blood sugar > 250 mg/dL	Initiate oral hypoglycemic agent and/or insulin.	Hold drug until ≤ Grade 2. Resume MLN0128 (SAPANISERTIB/CB-228/TAK-228) based on timing of recovery: ≤ 1 week: resume at same dose and schedule; >1 but ≤ 2 weeks: reduce dose > 2 weeks: stop MLN0128 (SAPANISERTIB/CB-228/TAK-228) and discontinue subject from the study.

Prevention/Prophylaxis

- Follow fasting serum glucose levels during clinic visits.
- Monitor home glucometer test results.
- Check HbA1c levels every 3 months during therapy.
- Life-style modifications, as appropriate (balanced diet, limit alcohol consumption, increase physical activity).
- Most episodes of Grade 1 and 2 hyperglycemia respond quickly to oral metformin.

- Early initiation of therapy is recommended to prevent higher grade hyperglycemia.
- Fasting blood glucose levels ≥ 150 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention.

Abbreviations: dL = deciliters; mg = milligrams; ULN = upper limit of normal.
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 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) . 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.

6.1.2 Management of Noninfectious Pneumonitis

Guidance for MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) Dose Modification
1	Asymptomatic: Radiographic findings only	Rule out infection and closely monitor.	None.
2	Symptomatic: Not interfering with ADLs	Rule out infection and consider treatment with corticosteroids until symptoms improve to ≤ Grade 1.	Interrupt MLN0128 (SAPANISERTIB/CB-228/TAK-228) treatment: When symptoms ≤ Grade 1, re-initiate MLN0128

Table 3: Management of Non-infectious Pneumonitis

Grade	Description	Treatment	MLN0128 (SAPANISERTIB/CB-228/TAK-228) Dose Modification
			(SAPANISERTIB/CB-228/TAK-228) treatment at a dose reduction Discontinue MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) treatment until symptoms resolve to ≤ Grade 1. Consider re-initiating MLN0128 (SAPANISERTIB/CB-228/TAK-228) treatment at a dose reduction If toxicity recurs at Grade 3, discontinue MLN0128 (SAPANISERTIB/CB-228/TAK-228) treatment.
4	Life-threatening: Ventilatory support indicated	Rule out infection and consider treatment with corticosteroids.	Discontinue MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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.

6.1.3 Management of Hyperlipidemia

Guidance for MLN0128 (SAPANISERTIB/CB-228/TAK-228) dose management in the event of hyperlipidemia is shown in the table below.

Table 4: Management of Hyperlipidemia

Grade	Description	Treatment	MLN0128 (SAPANISERTIB/CB-228/TAK-228) Dose Modification
1	Cholesterol: > ULN - 300 mg/dL Triglycerides: > 150 - 300 mg/dL	None.	None.
2	Cholesterol: > 300 – 400 mg/dL Triglycerides: > 300 - 500 mg/dL	Treat hyperlipidemia according to standard guidelines. Triglycerides ≥ 500 mg/dl should be treated urgently due to risk of pancreatitis.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 (SAPANISERTIB/CB-228/TAK-228) dosing until recovery to ≤ Grade 1. Reinitiate at same dose.
3	Cholesterol: > 400 - 500 mg/dL Triglycerides: > 500 - 1000 mg/dL	Same as for Grade 2.	Hold dose until recovery to ≤ Grade 1, then restart at a dose reduction
4	Cholesterol: > 500 mg/dL Triglycerides: > 1000 mg/dL	Same as for Grade 2.	Discontinue treatment.

Table 4: Management of Hyperlipidemia

Grade	Description	Treatment	MLN0128 (SAPANISERTIB/CB-228/TAK-228) Dose Modification
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.

6.1.4 Management of Oral Mucositis

Guidance for MLN0128 (SAPANISERTIB/CB-228/TAK-228) dose management in the event of oral mucositis is provided in the table below.

Table 5: Management of Oral Mucositis

Grade	Description	Treatment	MLN0128 (SAPANISERTIB/CB-228/TAK-228) Dose Modification
1	Asymptomatic or mild symptoms	Non-alcoholic mouth wash or 0.9% salt water rinse; Consider topical corticosteroids at earliest signs of mucositis.	None.
2	Moderate pain, not interfering with oral intake Modified diet indicated	Topical analgesic mouth treatments; Topical corticosteroids; Initiate antiviral or antifungal therapy, if indicated.	Maintain dose if tolerable. If toxicity becomes intolerable, interrupt MLN0128 (SAPANISERTIB/CB-228/TAK-228) dosing until recovery to ≤ Grade 1. Reinitiate at same dose.
3	Severe pain, interfering with oral intake	Same as for Grade 2; Consider intra-lesional corticosteroids.	Hold dose until recovery to ≤ Grade 1, then restart 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.

6.1.5 Management of Rash

Guidance for MLN0128 (SAPANISERTIB/CB-228/TAK-228) dose adjustment for the event of rash is provided in table below.

Table 6: Management of Rash

Grade	Description	Treatment	MLN0128 (SAPANISERTIB/CB-228/TAK-228) Dose Modification

≤ 2	Macules/papules covering ≤ 30% body surface area with or without symptoms	Consider treatment with topical steroid cream/ointment and/or oral anti-histamines.	None.
≥ 3	Macules/papules covering > 30% body surface area with or without symptoms	Consider treatment with topical steroid cream/ointment, oral antihistamines, and/or pulsed steroids.	Hold until ≤ Grade 2; Resume MLN0128 (SAPANISERTIB/CB-228/TAK-228) based on timing of recovery: ≤ 2 weeks: reduce dose ; > 2 weeks: stop MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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.

6.1.6 Management of Nausea and/or Vomiting

Guidance for MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) Dose Modification
≤ 2	Loss of appetite with or without decreased oral intake; 1-5 episodes of vomiting within 24 hours	Maximize anti-emetic therapy; Consider IV fluid hydration.	None.
≥ 3	Inadequate oral intake; ≥ 6 episodes of vomiting within 24 hours	Maximize anti-emetic therapy; Initiate tube feeding, IVF, or TPN.	Hold until ≤ Grade 1; Resume MLN0128 (SAPANISERTIB/CB-228/TAK-228) without dose modification.
Prevention/Prophylaxis Prophylactic use of anti-emetic, anti-nausea, and anti-diarrheal medications are encouraged and may be used before each dose of MLN0128 (SAPANISERTIB/CB-228/TAK-228) as needed throughout the study.			

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

6.1.7 Management of Cardiac Events

6.1.7.1 Management of Cardiac Instability

For subjects showing signs of cardiac instability after MLN0128 (SAPANISERTIB/CB-228/TAK-228) dosing, additional monitoring onsite before clinic discharge should be considered.

6.1.7.2 Management of Left Ventricular Dysfunction

Guidance for MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) Dose Modification
1	Asymptomatic decline in LVEF > 15% from baseline values OR;	No change; continue MLN0128 (SAPANISERTIB/CB-228/TAK-228) at same dose and schedule.

	LVEF > 10%-15% from baseline values and is below institution's LLN	
≥ 2	Symptomatic cardiac dysfunction/congestive heart failure	Discontinue treatment.

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

6.1.7.3 Management of QTc Prolongation

Guidance for MLN0128 (SAPANISERTIB/CB-228/TAK-228) dose adjustment for the event of QTc prolongation is provided in the table below.

Table 9: Management of QTc Prolongation

Grade	Description	Treatment	MLN0128 (SAPANISERTIB/CB-228/TAK-228) Dose Modification
2	480 ms < QTc < 501 ms	Evaluate for other possible causes (eg, electrolyte disturbance, concomitant medication, etc.)	None; continue MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 performed at intervals that the treating physician deems clinically appropriate until repeated QTc measurements fall or are below the threshold interval that triggered the repeat measurement.	MLN0128 (SAPANISERTIB/CB-228/TAK-228) should be interrupted. The decision whether to reinitiate MLN0128 (SAPANISERTIB/CB-228/TAK-228) treatment with or without dose reduction and additional monitoring in those subjects who had asymptomatic prolonged QTc ≥ 501 msec (Grade 3) that has reverted to an acceptable interval, have previously tolerated MLN0128 (SAPANISERTIB/CB-228/TAK-228) , and appear to have benefitted from MLN0128 (SAPANISERTIB/CB-228/TAK-228) treatment with either disease control or response, will be agreed to by the investigator and the study doctor on a case-by-case basis.

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

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

6.2 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 (SAPANISERTIB/CB-228/TAK-228) 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

- Strong CYP3A4 and CYP2C19 inducers and/or inhibitors and moderate inhibitors of CYP2C9 (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.

Subjects should not consume food or beverages containing the fruit or juice from grapefruits or Seville oranges within 7 days before first dose of study drug and throughout the study.

6.3 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 (SAPANISERTIB/CB-228/TAK-228) , and as needed throughout the study prior to each dosing and as clinically indicated per standard practice.

6.4 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 (SAPANISERTIB/CB-228/TAK-228) 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.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The list of reported and/or potential AEs (Section 6) and the characteristics of an observed AE (Section 7.1) will determine whether the event requires routine reporting.

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

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

7.1 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(s) that are 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 Protocol-Specific 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.

7.2 Expedited Adverse Event Reporting

Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.4 Expedited Reporting to Hospital Risk Management

Overall PI will report to the local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the PI on the toxicity case report forms.

7.5.1 Serious Adverse Event Definition

Serious AE (SAE) means any untoward medical occurrence that at any dose: Results in death.Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification in the paragraph below on planned hospitalizations).Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions). Is a congenital anomaly/birth defect.Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent. Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining

regulatory reporting obligations.

7.5.2 Procedures for Reporting Serious Adverse Events:

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 [redacted] from the time of consent up to and including 30 days after administration of the last dose of MLN0128 (SAPANISERTIB/CB-228/TAK-228) . Any SAE that occurs at any time after completion of MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 [redacted] 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 Kartik Sehgal, 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 [redacted]

- 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 sponsor-investigator's observation or awareness of the event. See below for contact information for the reporting of SAEs [redacted]

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

Follow-up information on the SAE may be requested [redacted] Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies [redacted] 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 sub-investigator

by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

Sponsor-investigator must also provide [redacted] 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.

[redacted]

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

7.5.2.1 Guidelines for Participating Institutions

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the same manner described above, and again below:

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

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

Criteria for SAEs remain the same as described in protocol section 7.5.1.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures.

7.5.3 **Procedures for Reporting Drug Exposure During Pregnancy and Birth Events:** If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form [redacted] The pregnancy must be followed for the final pregnancy outcome [redacted]

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form [redacted] Every effort should be made to

follow the pregnancy for the final pregnancy outcome.

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

8. 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 6. The DFCI INV 100 policy will be followed in handling the IP and the destruction of patient returns.

8.1 MLN0128 (SAPANISERTIB/CB-228/TAK-228)

8.1.1 Description

MLN0128 (SAPANISERTIB/CB-228/TAK-228) will be supplied as capsules for oral administration. The study drug is available in 3 dose strengths, 1 mg, 3 mg, and 5 mg, each containing 1 mg, 3 mg, and 5 mg of MLN0128 (SAPANISERTIB/CB-228/TAK-228) , 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 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 (SAPANISERTIB/CB-228/TAK-228) capsules, 1 mg - white opaque color
- MLN0128 (SAPANISERTIB/CB-228/TAK-228) capsules, 3 mg – orange opaque color; and/or
- MLN0128 (SAPANISERTIB/CB-228/TAK-228) capsules, 5 mg – grey opaque color

8.1.2 Form

MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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.

8.1.3 Storage and Stability

MLN0128 (SAPANISERTIB/CB-228/TAK-228) should be stored at controlled room temperature 15°C to 30°C (59°F to 86°F). All study supplies must be kept in a restricted access area.

MLN0128 (SAPANISERTIB/CB-228/TAK-228) will be packaged and labeled according to all regulations. Sites must store according to the labeled conditions.

8.1.4 Handling

Because MLN0128 (SAPANISERTIB/CB-228/TAK-228) is an investigational agent, it should be handled with due care. In case of contact with broken capsules, raising dust should be avoided

during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin.

Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (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.

8.1.5 **Availability**

[redacted]

8.1.6 **Preparation**

MLN0128 (SAPANISERTIB/CB-228/TAK-228) study drug will be provided in 60 cc high-density polypropylene (HDPE) bottles with polypropylene, child-resistant caps and induction seal. Study drug will be dispensed with dosing instructions for home use, including the requirement that capsules are stored in their original containers and that capsules be swallowed whole and not opened, chewed, or manipulated in any way. Materials provided by the sponsor should be dispensed to patients with clear administration instructions from the investigator.

MLN0128 (SAPANISERTIB/CB-228/TAK-228) is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling MLN0128 (SAPANISERTIB/CB-228/TAK-228) capsules.

8.1.7 **Administration**

MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 (SAPANISERTIB/CB-228/TAK-228) be given orally with 8 ounces (240 mL) of water. Missed or vomited dose should not be made up. If patient forgets MLNM0128 dose until 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. See table 1 for dosing schedule for phase I part of the study.

8.1.8 **Ordering**

[redacted]

[redacted]

8.1.9 **Accountability**

Accountability for MLN0128 (SAPANISERTIB/CB-228/TAK-228) 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 Dana-Farber Research Pharmacy. A careful record of the inventory and disposition of the agent will be maintained, using the NCI Drug Accountability Record Form (DARF).

8.1.10 **Destruction and Return**

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

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

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 on all responders. All other patients will undergo Oncopanel testing which analyzes 300 cancer relevant genes. Genetic information will be correlated with radiographic response data as well as survival data to identify potential biomarkers to predict response. These data may be useful to design future biomarker driven studies.

Patients with accessible tumors will undergo sequential biopsies prior to and at 2 weeks of therapy. This would be optional but encouraged. Kinome analysis will be performed [redacted] to assess molecular pathway activation in response to mTOR inhibition to elucidate possible escape mechanisms that could account for resistance and provide a rationale for combination therapy in the future.

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.

10. STUDY CALENDAR

Baseline (screening) evaluations are to be conducted within 4 weeks prior to study entry. Scans must be done $\leq$4 weeks prior to study entry. 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 (SAPANISERTIB/CB-228/TAK-228) administration.

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

Treatment cycles will continue until progression or consent withdrawal. Following first progression, patients will be followed for survival only by phone, every 3 months for 24 months from study entry or until death whichever occurs first. All treatment procedures will be done in an outpatient clinic. Patients will visit the clinic on a monthly basis (Day 1 of each cycle) for as long as they receive treatment. There will be one follow up visit within 30 days of coming off treatment.

Assessments must be performed prior to administration of study agent. Study assessments and agent should be administered +/- 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. 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 10: Study assessments

	Screening	Cycle 1				Cycle 2		Cycle 3+	EOT	FU until first progression[i]
	≤4 weeks of treatment	D1		D15		D1	D15	D1		
Informed Consent	X									
Demographics	X									
Medical History	X									
Concurrent Meds	X	X		X		X	X	X	X	
Physical Exam[a]	X	X		X		X	X	X	X	
Vital signs	X	X		X		X	X	X	X	
Height	X									
Weight	X	X		X		X	X	X	X	
Performance Status	X	X		X		X	X	X	X	
CBC w/ diff, plts	X	X		X		X		X	X	
Phosphorus	X	X		X		X		X	X	
LDH	X	X		X		X		X	X	
HbA1c[b]	X	X				X		X		
Serum Chemistry	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]; MRI[c]	X	X				X		X	X	X
Tumor Measurements[d]	X	X				X		X		X
MLN0128 (SAPANISERTIB/CB-228/TAK-228)		X								
Adverse Events[e]		X		X		X	X	X	X	
Fasting serum glucose[g]	X	X		X		X	X	X	X	
In-home daily fasting glucose monitoring[h]		X		X		X	X	X	X	
Fasting lipid	X	X				X		X	X	

profile										
Urinalysis	X	X		X		X	X	X	X	

a) Physical exam is symptom directed
b) HbA1c is done at Screening, C1D1, C2D1, C3D1, and then every 3 months until first progression, death, or 24 months from study entry, whichever occurs first (Screening, C1D1, C2D1, 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 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. Weekly monitoring can end after 1 year on study drug at the discretion of the treating physician.
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.

Biological Sample Collection:

Sample Type	Screening/Baseline	After 2 weeks of treatment	Progression
Blood (whole blood with EDTA)	X	X	X
Archived tumor	X	X**	
Fresh Biopsy*	X	X**	X

* Patients with accessible tumors, optional but encouraged. There will be an additional clinic visit for these patients, on Cycle 1Day15 (+/- 3 days), for a fresh biopsy. Archival tissue may be used in lieu of the fresh biopsy at baseline

** Biopsy after 2 weeks of treatment is optional, both for patients who had archival tissue at baseline or fresh biopsy at baseline.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect

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 every 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) http://ctep.cancer.gov/protocolDevelopment/docs/Recist_Guideline.pdf (*Eur J Ca* 45:228-247, 2009).

11.2 Progression-free survival

Progression-free survival is measured from the date of study entry to tumor progression or death from any cause whichever occurs first. Patients without documented disease progression will be censored at the date last disease assessment.

11.3 Survival

Survival is measured from the date of study entry to death from any cause. Patients without confirmed death at time of study analysis will be censored at date last known alive.

12. DATA REPORTING / REGULATORY REQUIREMENTS

The QACT will collect, manage, and perform quality checks on the data for this study. Adverse event lists, guidelines, and instructions for AE reporting can be found in Sections 6 and 7.

12.1 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.

12.2 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix E.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the study agent directly from the supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13. STATISTICAL CONSIDERATIONS

Original Design when trial Opened:

This trial was originally designed as a phase II trial only with a primary endpoint of proportion progression-free at 4 months for patients with metastatic anaplastic thyroid cancer (ATC).

Phase I Cohort (ATC and DTC):
Due to changes in the manufacturing process which has resulted in increased absorption of MLN0128 (SAPANISERTIB/CB-228/TAK-228) from capsules, a run-in phase I prior to the phase II of the study is needed. Due to the poor prognosis and short median survival of patients with incurable anaplastic thyroid cancer, patients with poorly differentiated thyroid cancer, RAI refractory differentiated thyroid cancer who failed prior treatment with a TKI, will be allowed to participate in the run-in phase I portion in addition to the incurable metastatic anaplastic thyroid cancer cases so that a more comprehensive longer term adverse event profile can be documented.

Phase I Design: (As of the writing of this Amendment, the phase I portion is complete and the MTD/RP2D is 5mg).

This portion of the trial follows a standard 3+3 phase I design. The primary endpoint is to determine the MTD. Patients will be started at a given dose and escalated according to the information outlined in section 5.3.

The table below gives the probabilities of the dose escalation scheme outlined in section 5.3.

True Rate of DLT	Probability of Escalation
20%	.71
30%	.49
40%	.31
50%	.17
60%	.08

For example, if the true rate of DLT is 20% at a given dose, there is a 71% probability of escalating

to a higher dose.

At most, 28 patients are estimated to be accrued in the phase I portion of the trial. This is based on studying 3 dose levels with at most 6 patients per level plus an additional 10 at the MTD (these 10 accrued to ensure that the adverse event rate at the MTD is acceptable). The estimation of adverse events will be based on studying these 10 additional patients. The width of the 90% confidence interval for the estimation of the adverse event rate will be no more than 56%.

Patients with metastatic anaplastic thyroid cancer who are treated at the MTD in the phase I portion will be included in the phase II portion.

Phase II Original Cohort of patients with ATC only.
Statistical Design for patients with ATC:

For the phase II portion of this trial, given the short median survival of this patient population (patients with ATC) and the expectation of the mechanism of this drug to more frequently induce disease stability (while allowing for at least 2 disease assessments post baseline), the primary endpoint of the phase II portion of the study is to evaluate the proportion progression-free at 4 months.

A Simon two-stage design will be used to minimize the number of patients exposed to this regimen and the specific sample size and operating characteristics were chosen to be able to show that the proportion progression-free at 4 months is greater than 11%.

In the first stage, accrual will continue until 13 evaluable patients (eligible patients who begin protocol therapy) are entered. If there are ≤1 patient whose disease is progression-free at 4 months, accrual to the trial will be closed with the conclusion that there is little evidence that the proportion progression-free at 4 months would reach 33%. The probability that the trial will close early is 57% if the true proportion progression-free is 11%.

If there are ≥2 patients among 13 evaluable patients whose disease is progression-free at 4 months, the trial will continue to accrue patients until a total of 23 evaluable patients are entered. If there are ≥5 patients whose disease is progression-free at 4 months among 23 evaluable patients, further testing of this regimen will be considered. The probability of concluding the regimen is effective is 90% if the true proportion progression-free is 33%. The probability of concluding the regimen is effective is 10% if the true proportion progression-free is 11%. Allowing 2 patients to not begin protocol treatment or be classified as ineligible or withdraw and refuse follow up prior to 4 months, a total of 25 patients will be entered.

Patients with metastatic ATC who are treated at the MTD in the phase I portion are included in this phase II cohort.

As of the writing of this amendment, this cohort of patients with ATC continues to accrue.

Phase II Amendment for Cohort of patients with DTC.
Rational for cohort of patients with DTC:

Given the activity with agents such as everolimus in RAI refractory thyroid cancer, subjects wth metastatic, incurable differentiated RAI refractory and poorly differentiated thyroid cancer were enrolled during the phase 1 part of this trial (see above). As of this amendment, a similar phase II cohort of these patients who have previously failed or who can not tolerate FDA approved standard TKI's such as sorafenib or lenvatinib and/or are not candidates for these treatments due to significant toxicities of these drugs and for whom no standard options exist, plan to be enrolled in an exploratory cohort.

Statistical Design for patients with DTC:

To keep the overall number of patients accrued to this trial within the overall original clinical trial budget, n=23 patients are proposed to be entered into this cohort of patients with DTC, therefore, only large differences would be able to be detected with reasonable operating characteristics. Given that overall outcome is slightly better for this population with DTC, relative to patients with ATC, the target endpoint is proportion progression-free at 6 months.

Results from the DECISION trial showed a median PFS of 10.8 months for patients who received sorafenib, corresponding to a a 6 month proportion progression-free of approximately 68% (under an exponential distribution). A Simon two-stage design will be used and the specific sample size and operating characteristics were chosen to be able to show that the proportion progression-free at 6 months is greater than 45%.

In the first stage, accrual will continue until 12 evaluable patients (eligible patients who begin protocol therapy) are entered. If there are ≥6 patients among 12 evaluable patients whose disease is progression-free at 6 months, the trial will continue to accrue patients until a total of 23 evaluable patients are entered. If there are ≥14 patients whose disease is progression-free at 6 months among 23 evaluable patients, further testing of this regimen will be considered. The probability of stopping the trial after the first stage is 53% if the true 6 month rate is 45%. The probability of concluding the regimen is effective is 87% if the true proportion progression-free is 70% and 9% if the true proportion progression-free is 45%.

Patients with DTC who were treated at the MTD in the phase I portion (n=7) are included in this phase II cohort.

Analyses and Accrual Estimates:
The primary efficacy population includes all eligible patients who begin protocol treatment. The proportion progression-free rates will be summarized as a proportion with a corresponding exact 95% binomial confidence interval (if the trial closes to accrual after the first stage) or a corresponding 95% two-stage confidence interval if the trial closes to accrual after the second stage. Safety will be assessed via the CTCAE vs 4 and frequencies of adverse events will be summarized. The progression-free survival and overall survival will be estimated using the Kaplan-Meier method and 95% confidence intervals for the median or time-specific event time will be summarized.

With an estimated monthly accrual of 1 to 2 patients with DTC and given that n=7 patients with

DTC have been entered and treated at the MTD, the first stage of the DTC cohort is estimated to complete accrual in 6-8 months. Patients who are treated at the MTD in the phase I portion with ATC and DTC will be included in the first stage of the phase II cohorts respectivly. As is customary with this type of design, accrual will be suspended after the first stage in order to assess outcome, however, this is also dependent on the actual observed accrual rate and the number of patients confirmed progression-free while the first stage of the trial is accruing.

14. 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.

15. REFERENCES

1. O'Neill JP, Shaha AR: Anaplastic thyroid cancer. Oral Oncol 49:702-6, 2013
2. Perri F, Lorenzo GD, Scarpati GD, et al: Anaplastic thyroid carcinoma: A comprehensive review of current and future therapeutic options. World J Clin Oncol 2:150-7, 2011

Brose, M. S., et al. (2015). "Sorafenib for patients with differentiated thyroid cancer--authors' reply." Lancet **385**(9964): 228-229.

Hanna, G. J., et al. (2018). "Genomic Correlates of Response to Everolimus in Aggressive Radioiodine-refractory Thyroid Cancer: A Phase II Study." Clin Cancer Res **24**(7): 1546-1553.

Purpose: Targeting mutations leading to PI3K/mTOR/Akt activation are of interest in thyroid cancer. We evaluated the efficacy of everolimus in aggressive, radioactive iodine-refractory (RAIR) thyroid cancer and correlated tumor mutational profiling with response. Exploratory medullary and anaplastic thyroid cancer cohorts were included.Experimental Design: This single-arm, multi-institutional phase II study was conducted from 2009 to 2013 in patients with incurable RAIR thyroid cancer who had radiographic progression six months prior to enrollment. The primary endpoint was progression-free survival (PFS) with a median follow-up of 31.8 months. The study is closed to enrollment but treatment and follow-up are ongoing. A targeted next-generation sequencing platform was used for mutational analysis.Results: Thirty-three patients with differentiated thyroid cancer (DTC), 10 with medullary thyroid cancer (MTC), and 7 with anaplastic thyroid cancer (ATC) enrolled. For the DTC cohort, median PFS was 12.9 months (95% CI, 7.3-18.5) with a 2-year PFS of 23.6% (95% CI, 10.5-39.5). Median OS was not reached; 2-year OS was 73.5% (95% CI, 53.8-85.8). Among ATC patients, 1 had a partial response and was progression-free until 17.9 months after study entry and one had disease stability for 26 months, respectively. The genomically profiled cohort enriched for PI3K/mTOR/Akt alterations. PI3K/mTOR/Akt-mutated ATC subgroups appeared to benefit from everolimus. Treatment-related adverse events were as anticipated.Conclusions: Everolimus has significant antitumor activity in thyroid cancer. While genomic profiling does not currently

guide therapeutic selection in thyroid cancer patients, these data have important implications when considering the use of an mTOR inhibitor in an era of precision medicine. Clin Cancer Res; 24(7); 1546-53. (c)2018 AACR.

Lim, S. M., et al. (2013). "A multicenter, phase II trial of everolimus in locally advanced or metastatic thyroid cancer of all histologic subtypes." Ann Oncol **24**(12): 3089-3094.

BACKGROUND: This phase II study investigated the efficacy and safety of everolimus, an inhibitor of mammalian target of rapamycin (mTOR), in locally advanced or metastatic thyroid cancer. PATIENTS AND METHODS: Patients with thyroid cancer of any histology that was resistant or not appropriate for (131)I received everolimus 10 mg daily orally until unacceptable toxicity or disease progression. The primary end point was disease control rate [partial response (PR) + stable response >/=12 weeks]. Secondary end points included response rates, clinical benefit (PD + durable stable disease (SD)], progression-free survival (PFS), overall survival, duration of response, and safety. RESULTS: Thirty-eight of 40 enrolled patients were evaluable for efficacy. The disease control rate was 81% and two (5%) patients achieved objective response; their duration of response was 21+ and 24+ weeks. Stable disease (SD) and progressive disease was reported in 76% and 17% of patients, respectively. Seventeen (45%) patients showed durable SD (>/=24 weeks) and clinical benefit was reported in 19 (50%) patients. Median PFS was 47 weeks [95% confidence interval (CI) 14.9-78.5]. Calcitonin, CEA, and thyroglobulin concentrations were >/=50% lower than baseline in three (30%) and four (44%) patients with medullary thyroid cancer and five (33%) patients with PTC, respectively. The most common treatment-related adverse events were mucositis (84%), anorexia (44%), and aspartate transaminase/alanine transaminase elevation (26%). CONCLUSIONS: Everolimus had a limited activity with low response rate in locally advanced or metastatic thyroid cancer. Reasonable clinical benefit rate and safety profile may warrant further investigation. CLINICALTRIALSGOV NUMBER: NCT01164176.

Schlumberger, M., et al. (2015). "Lenvatinib versus placebo in radioiodine-refractory thyroid cancer." N Engl J Med **372**(7): 621-630.

BACKGROUND: Lenvatinib, an oral inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, fibroblast growth factor receptors 1 through 4, platelet-derived growth factor receptor alpha, RET, and KIT, showed clinical activity in a phase 2 study involving patients with differentiated thyroid cancer that was refractory to radioiodine (iodine-131). METHODS: In our phase 3, randomized, double-blind, multicenter study involving patients with progressive thyroid cancer that was refractory to iodine-131, we randomly assigned 261 patients to receive lenvatinib (at a daily dose of 24 mg per day in 28-day cycles) and 131 patients to receive placebo. At the time of disease progression, patients in the placebo group could receive open-label lenvatinib. The primary end point was progression-free survival. Secondary end points included the response rate, overall survival, and safety. RESULTS: The median progression-free survival was 18.3 months in the lenvatinib group and 3.6 months in the placebo group (hazard ratio for progression or death, 0.21; 99% confidence interval, 0.14 to 0.31; P<0.001). A progression-free survival benefit associated with lenvatinib was observed in all prespecified subgroups. The response rate was 64.8% in the lenvatinib group (4 complete responses and 165 partial responses) and 1.5% in the placebo group (P<0.001). The median overall survival was not reached in either group. Treatment-related adverse effects of any grade, which occurred in more than

40% of patients in the lenvatinib group, were hypertension (in 67.8% of the patients), diarrhea (in 59.4%), fatigue or asthenia (in 59.0%), decreased appetite (in 50.2%), decreased weight (in 46.4%), and nausea (in 41.0%). Discontinuations of the study drug because of adverse effects occurred in 37 patients who received lenvatinib (14.2%) and 3 patients who received placebo (2.3%). In the lenvatinib group, 6 of 20 deaths that occurred during the treatment period were considered to be drug-related. CONCLUSIONS: Lenvatinib, as compared with placebo, was associated with significant improvements in progression-free survival and the response rate among patients with iodine-131-refractory thyroid cancer. Patients who received lenvatinib had more adverse effects. (Funded by Eisai; SELECT ClinicalTrials.gov number, NCT01321554.).

Schneider, T. C., et al. (2017). "Everolimus in Patients With Advanced Follicular-Derived Thyroid Cancer: Results of a Phase II Clinical Trial." J Clin Endocrinol Metab **102**(2): 698-707.

Background: Mammalian target of rapamycin (mTOR) upregulation has been reported to be involved in the pathogenesis of thyroid tumors, and treatment with the mTOR inhibitor everolimus has shown promising results in endocrine tumors. We conducted a prospective phase II clinical trial to determine the efficacy and safety of everolimus in patients with advanced follicular-derived thyroid cancer. Patients and Methods: Twenty-eight patients with progressive metastatic or locally advanced radioactive refractory differentiated thyroid cancer and 7 patients with anaplastic thyroid cancer were included and received everolimus 10 mg orally once daily. The primary endpoint was disease control rate [complete (CR) + partial response (PR) + stable disease (SD) > 24 weeks]. Secondary endpoints included progression-free survival (PFS), overall survival (OS), toxicity, and mutational and pharmacokinetic-related outcomes. Results: Median follow-up duration was 38 months (2-64). Seventeen patients (65%) showed SD, of which 15 (58%) showed SD >24 weeks. No CR or PR was observed. Median PFS and OS were 9 [95% confidence interval (CI): 4 to 14] and 18 (95% CI: 7 to 29) months, respectively. Survival was negatively influenced by the presence of bone metastases. Toxicity was predominantly grade 1/2 and included anemia (64%), cough (64%), stomatitis (61%), and hyperglycemia (61%). Duration of SD was related to everolimus exposure. The presence of somatic gene variants related to mTOR signaling did not clearly stratify for responses. Conclusion: Everolimus has clinically relevant antitumor activity in patients with advanced differentiated thyroid cancer. Given the observed disease control rate and the relatively low toxicity profile, further investigation of everolimus in sequential or combination therapy in these patients is warranted.

Wagle, N., et al. (2014). "Response and acquired resistance to everolimus in anaplastic thyroid cancer." N Engl J Med **371**(15): 1426-1433.

Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), is effective in treating tumors harboring alterations in the mTOR pathway. Mechanisms of resistance to everolimus remain undefined. Resistance developed in a patient with metastatic anaplastic thyroid carcinoma after an extraordinary 18-month response. Whole-exome sequencing of pretreatment and drug-resistant tumors revealed a nonsense mutation in TSC2, a negative regulator of mTOR, suggesting a mechanism for exquisite sensitivity to everolimus. The resistant tumor also harbored a mutation in MTOR that confers resistance to allosteric mTOR inhibition. The mutation remains sensitive to mTOR kinase inhibitors.

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 self-care, 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 self-care. 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: New York Heart Association Classification of Cardiac Disease

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

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

APPENDIX C: List of Relevant Cytochrome P450 Inhibitors and Inducers

MLN0128 (SAPANISERTIB/CB-228/TAK-228) is metabolized by CYP2C19, CYP3A4, and CYP2C9.

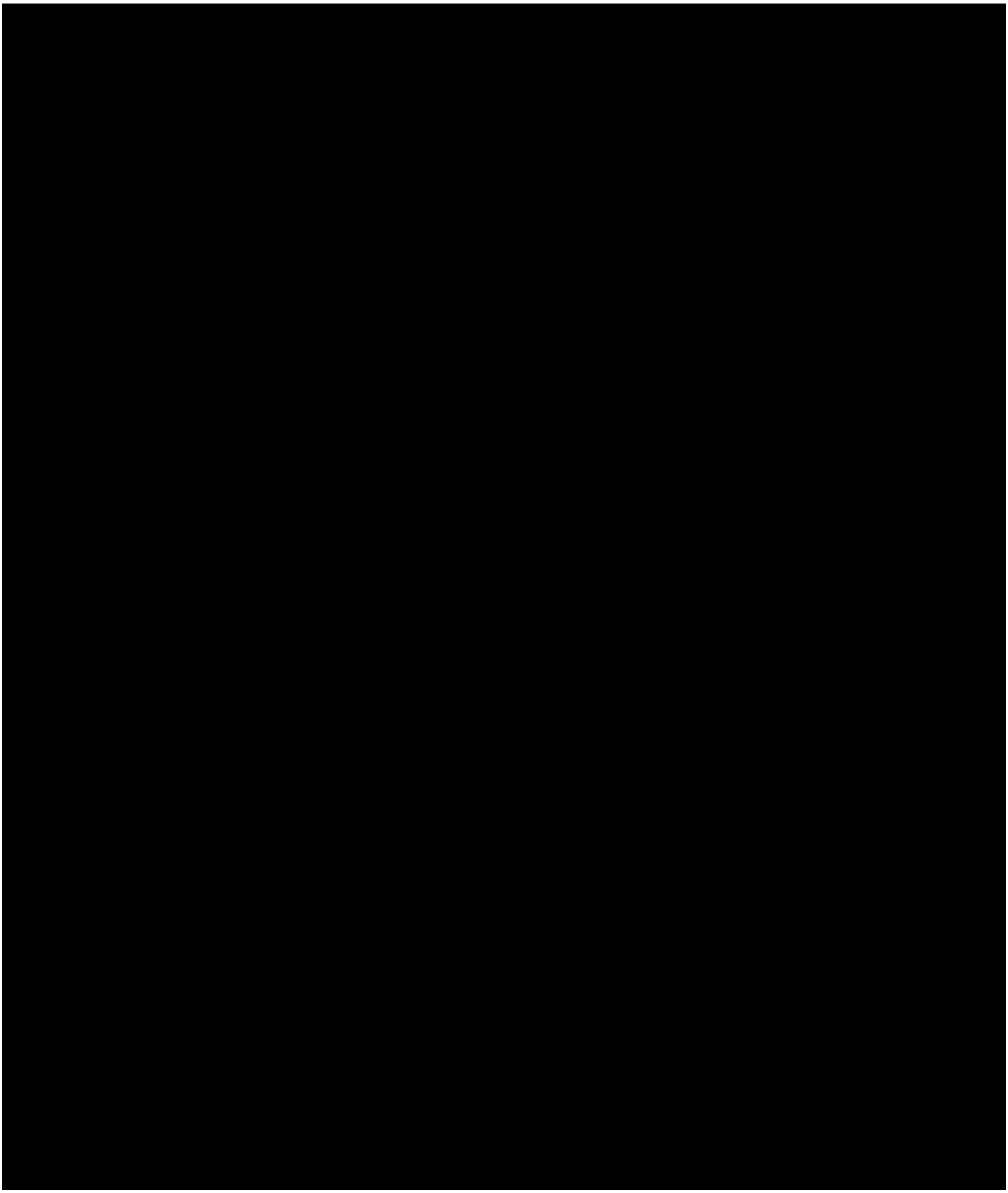
There are no known strong specific CYP2C9 inhibitors or inducers. Examples of moderate inhibitors of CYP2C9 are fluconazole and miconazole; moderate inducers of CYP2C9 are carbamazepine and rifampin. These agents show some degree of overlap with their modulation of CYP3A4 and CYP2C19 activity and should 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 CYP2C9, CYP2C19, and CYPE3A4

Strong Inhibitors	Strong Inducers
indinavir	carbamazepine
nelfinavir	phenobarbital
ritonavir	phenytoin
clarithromycin	rifabutin
itraconazole	St. John's wort
ketoconazole	troglitazone
nefazodone	secobarbital
fluconazole	rifampin
saquinavir	
telithromycin	
fluvoxamine	
telithromycin	
fluvoxamine	
mibefradil	
omeprazole	
ticlopidine	
Fruits and juice	
Star fruit and juice	
pomegranate fruit and juice	
grapefruit and juice	
Seville oranges and juice	
papaya fruit and juice	

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



APPENDIX E: Multi-Center Data and Safety Monitoring Plan