Update #09

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO ALLIANCE A091304

A PHASE I/RANDOMIZED PHASE II STUDY OF MLN0128 (TAK-228) VS. PAZOPANIB IN PATIENTS WITH LOCALLY ADVANCED/UNRESECTABLE AND/OR METASTATIC SARCOMA

[X]	**Update:**	[ ]	**Status Change:**
[ ]	Eligibility changes	[ ]	Pre-Activation
[ ]	Therapy / Dose Modifications / Study Calendar changes	[ ]	Activation
[ ]	Informed Consent changes	[ ]	Closure
[X]	Scientific / Statistical Considerations changes	[ ]	Suspension / temporary closure
[ ]	Data Submission / Forms changes	[ ]	Reactivation
[X]	Editorial / Administrative changes		
[X]	Other: Updated Pazopanib CAEPR		

The CAEPR and Risk List changes included in this update to A091304 have been made in response to the NCI Request for Amendment from Dr. Fernanda Arnaldez. A revised CAEPR for pazopanib with new risks has been added to the protocol. Therefore, the model consent form has been revised to incorporate these new risks, consistent with the NCI Model Consent Template instructions. There are no changes to the risk/benefit ratio.

Expedited review is allowed. IRB approval (or disapproval) is required within 90 days. Please follow your IRB of record guidelines.

UPDATES TO THE PROTOCOL:

Cover Page

Kristin Poe has replaced Jenna Baker as the Data Manger. All contact information has been updated.

Phase II Schema - Effective with Update #05

Footnote *** has been added beneath the table. It reads "**Note:** Effective 12/21/2018, patients will no longer be able to crossover to MLN0218 (TAK-228)." A reference to footnote *** has been added in the RE-REGISTER box.

Section 4.6 [Re-Registration at the Time of Progression (Step 2, if applicable) (Phase II only)]

A note has been added as a new first paragraph that reads: "Note: Effective 12/21/2018, patients will no longer be able to crossover to MLN0128 (TAK-228)."

Section 9.4.1 (Comprehensive Adverse Events and Potential Risks List [CAEPR] for Pazopanib [GW786034, NSC 737754])

-This section has been revised to include the updated pazopanib CAEPR (Version 2.8, January 31, 2019) provided by CTEP. Changes from Version 2.7 to Version 2.8 include the following:

- Added New Risk:
  - Also Reported on Pazopanib Trials But With Insufficient Evidence for Attribution: Muscle cramp.
- Deleted Risk:
  - Also Reported on Pazopanib Trials But With Insufficient Evidence for Attribution: Acute coronary syndrome; Musculoskeletal and connective tissue disorder - Other (muscle spasms).
- Provided Further Clarification:
  - Eye disorders - Other (eye/retinal hemorrhage) *(CTCAE 4.0 language)* is now reported as Eye disorders - Other (eye hemorrhage, retinal hemorrhage).
  - Female genital tract fistula *(CTCAE 4.0 language)* is now reported as Reproductive system and breast disorders - Other (female genital tract fistula).
  - Skin and subcutaneous tissue disorders - Other (hair color change/hair depigmentation) *(CTCAE 4.0 language)* is now reported as Hair color changes.
  - Vascular disorders - Other (arterial thromboembolic event) *(CTCAE 4.0 language)* is now reported as Arterial thromboembolism.
  - Gastrointestinal disorders - Other (oropharyngeal pain), previously listed under the GASTROINTESTINAL DISORDERS SOC *(CTCAE 4.0 language)*, is now reported as Oropharyngeal pain and is now listed under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.
  - Investigations - Other (blood lactate dehydrogenase increased) (CTCAE 4.0 language) is now reported as Blood lactate dehydrogenase increased.

- The following were erroneously retained with the previous updated pazopanib CAEPR (Version 2.7, June 2, 2017), but they have been removed with Update #09:
  - Also Reported on Pazopanib Trials But With Insufficient Evidence for Attribution: Cardiac disorders – Other (Torsades de Pointes); Eye disorders – Other (eye/retinal hemorrhage) Infection; Ejection fraction decreased; Intracranial hemorrhage; Hematuria; Vaginal hemorrhage.

Section 13.3.2 (Statistical Design)

The second sentence has been modified for accuracy.

Section 13.3.4 (Analysis Plan)

Two new sentences have been added to the end of the first bullet to provide more detail about the futility analysis. They begin "More specifically, the decision…" and "If P is greater than…," respectively.

UPDATES TO THE PHASE I MODEL CONSENT:

No changes have been made to the Phase I MCF.

UPDATES TO THE PHASE II MODEL CONSENT:

What possible risks can I expect from taking part in this study?

Based on the updated CAEPR described above, the following changes have been made to the NCI condensed risk profile for pazopanib:

- Added New Risk:

    - Rare: Blood clot in artery which may cause swelling, pain, shortness of breath or change of color in extremity.
- Deleted Risk:
    - Rare: Bleeding of the eye which may cause blurred vision with a chance of blindness.
- Provided Further Clarification:
    - High blood pressure which may cause blurred vision (under Common) is now reported as High blood pressure which may cause headaches, dizziness, blurred vision (under Common).
    - Bleeding from multiple sites including the nose or vagina (under Occasional) is now reported as Bleeding from multiple sites including the nose or vagina which may cause blurred vision with a chance of blindness (under Occasional).
    - Anemia, kidney problems which may require dialysis (under Rare) is now reported as Anemia, kidney problems which may cause tiredness, bruising, swellings, or may require dialysis (under Rare).

A replacement protocol document and model consent form have been issued.

This protocol remains permanently closed to new patient accrual.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

ALLIANCE A091304

A PHASE I/RANDOMIZED PHASE II STUDY OF MLN0128 (TAK-228) VS. PAZOPANIB IN PATIENTS WITH LOCALLY ADVANCED/UNRESECTABLE AND/OR METASTATIC SARCOMA

NCI-supplied agent: MLN0128 (TAK-228) (NSC #768435, IND #121931); IND holder: CTEP
Commercial agent: Pazopanib (IND Exempt)

ClinicalTrials.gov Identifier: NCT02601209

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Participating Organizations:
ALLIANCE / Alliance for Clinical Trials in Oncology (lead)
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
NRG / NRG Oncology
SWOG / SWOG

Study Resources:

Expedited Adverse Event Reporting http://eapps-ctep.nci.nih.gov/ctepaers/	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

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Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (where applicable) Data Manager
Questions related to data submission, RAVE or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review	Alliance Regulatory Inbox regulatory@allianceNCTN.org
Questions regarding CTEP-AERS reporting:	Pharmacovigilance Inbox pharmacovigilance@alliancenctn.org
Questions regarding specimens/specimen submissions:	appropriate Alliance Biorepository

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. *Include this statement if applicable:* Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Website is located at https://www.ctsu.org.

A PHASE I/RANDOMIZED PHASE II STUDY OF MLN0128 (TAK-228) VS. PAZOPANIB IN PATIENTS WITH LOCALLY ADVANCED/UNRESECTABLE AND/OR METASTATIC SARCOMA

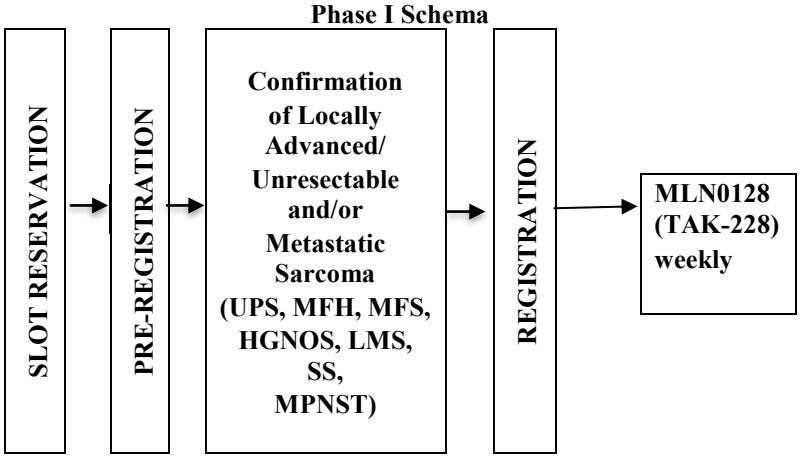
Pre-Registration Eligibility Criteria (see Section 3.2)
Central pathology review submission (See §3.2.1)
Eligibility Criteria (see Section 3.3)
Documentation of disease subtypes listed in Section 3.3.1 by central review
Locally advanced or metastatic disease
Measurable disease and/or nonmeasureable as defined in Section 11.0
Prior treatment: Progression on at least one prior systemic chemotherapy for advanced, unresectable or metastatic disease. See Section 3.3.4 for additional information and exclusions.
Not pregnant and not nursing.
Age ≥ 18 years
ECOG Performance Status ≤ 1
Patients may not have any history of the diseases, conditions or disorders described in Section 3.3.8.
Concomitant medications: concomitant treatment with strong inhibitors of CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration. Chronic concomitant treatment with strong CYP3A4 inducers is not allowed.

Required Initial Laboratory Values

Absolute neutrophil count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	< 1.5 x ULN
Total Bilirubin	≤ 1.5 x ULN*
AST / ALT	≤ 3 x ULN*
UPC	≤ 1*
TSH	WNL

*See Section 3.3.9

Phase I Schema

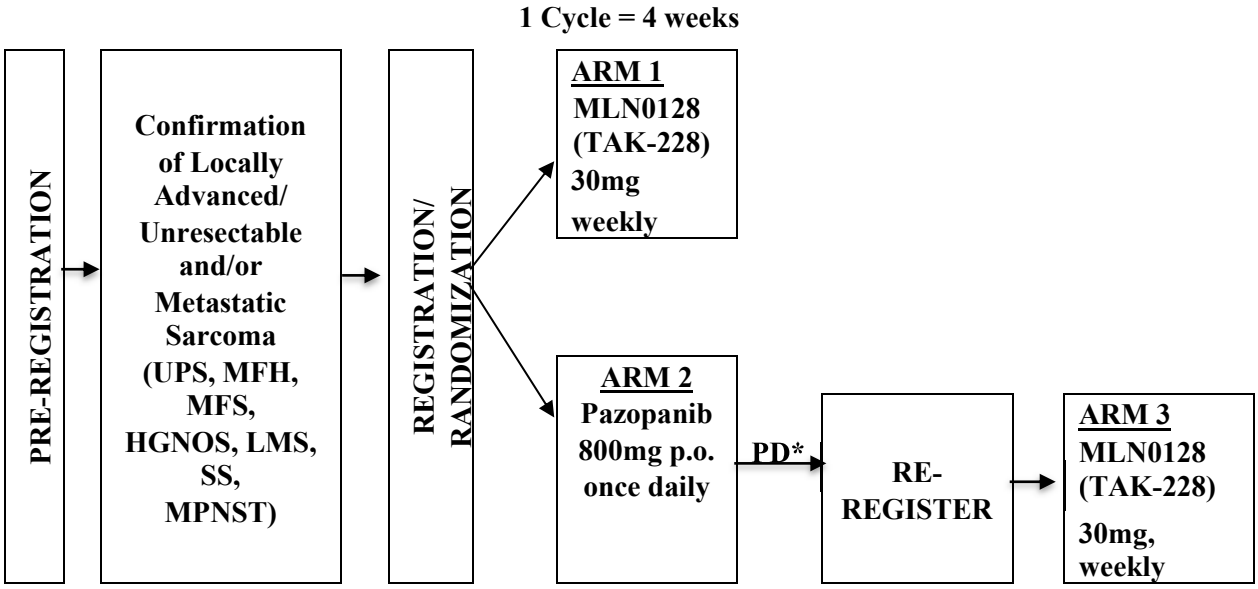


The Phase I portion of this study will assess safety and tolerability of the new milled formulation of MLN0128 (TAK-228). The Phase I portion is a standard 3+3 design which includes dose level 0, 1, 2 for entry and dose modifications as per protocol. Patients may remain on treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

Please Note: For the phase I portion of this study, patient enrollment will be facilitated using the Slot-Reservation System in conjunction with the Registration system on Oncology Patient Enrollment Network (OPEN). Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to insure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to pre-register the patient for central pathology review. Once eligibility has been confirmed centrally, then proceed to register patient onto the appropriate dose level.
Toxicity call attendance is required during the Phase I portion of the trial. See Section 7.1 for more information...

Phase II Schema – Prior to Update #05

Prior to discussing protocol entry with prospective patients, site staff must go to the A091304 study page on the CTSU web site to check histologic cohort status and accrual. See Section 4.4 for more information.



* Patients who progress on Arm 2 will have the option to crossover to receive MLN0128 (TAK-228). Patients who opt to crossover must be re-registered to the study. Patients must initiate treatment with MLN0128 (TAK-228) within 28 days of the CT demonstrating progression.

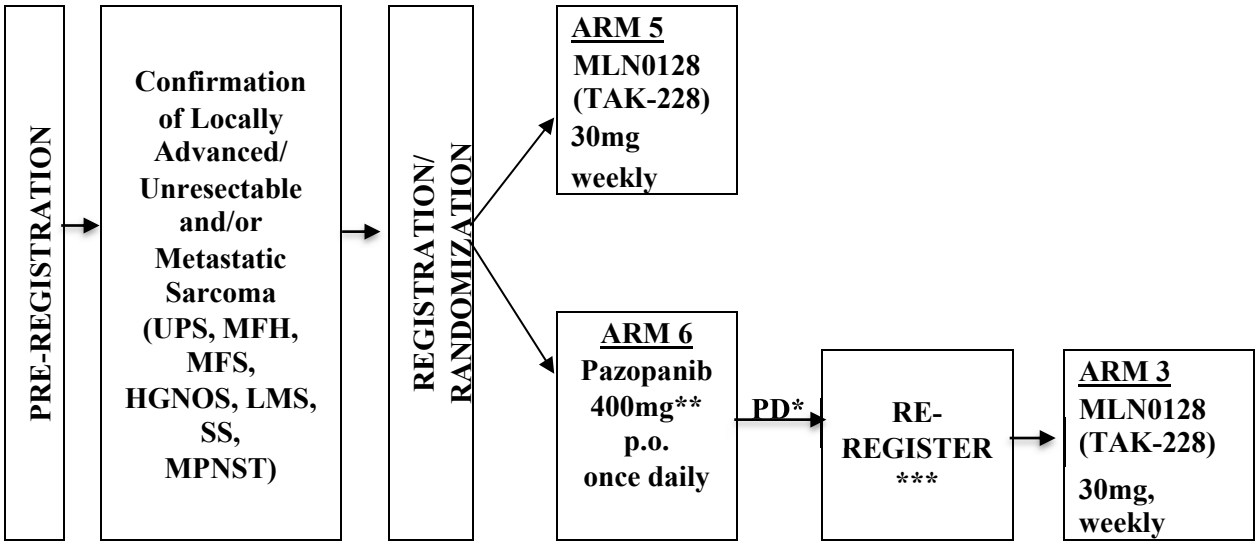
Treatment is to continue until disease progression or unacceptable adverse event. Patients discontinuing their initial treatment for reasons other than progressive disease and within 15 months of randomization will continue following the Study Calendar for disease assessments until progressive disease is documented. Upon progression, patients will be followed for survival for two years post-randomization or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Phase II Schema – Effective with Update #05

Prior to discussing protocol entry with prospective patients, site staff must go to the A091304 study page on the CTSU web site to check histologic cohort status and accrual. See Section 4.4 for more information.

1 Cycle = 4 weeks



* Patients who progress on Arm 6 will have the option to crossover to receive Arm 3 MLN0128 (TAK-228). Patients who opt to crossover must be re-registered to the study. Patients must cross over within 6 weeks of documented progression and need to have a CT scan within 28 days of starting MLN0128 to serve as a baseline.

** Effective with Update #05 pazopanib will be started at 400mg, titrated to a dose of 800 mg per section 7.2.

***__Note:__ Effective 12/21/2018, patients will no longer be able to crossover to MLN0128 (TAK-228)

Treatment is to continue until disease progression or unacceptable adverse event. Patients discontinuing their initial treatment for reasons other than progressive disease and within 15 months of randomization will continue following the Study Calendar for disease assessments until progressive disease is documented. Upon progression, patients will be followed for survival for two years post-randomization or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

Table of Contents

1.0 BACKGROUND

Sarcoma is a heterogeneous group of malignancies that are of mesenchymal and neural origin. There are approximately 60-80 specific subtypes of bone and soft tissue sarcoma [1]. Sarcomas are relatively rare neoplasms with an approximate incidence of 30 per million or about 13,000 cases diagnosed in the United States each year [2]. Sarcomas can arise in individuals of all ages; they represent approximately 1 percent of adult and 15 percent of pediatric malignancies. Surgery is the only treatment for adult patients that can be offered with curative intent. Chemotherapy, and more so radiation, are useful adjuncts in localized disease, but neither has shown to contribute to a survival benefit. When curative surgery cannot be delivered or when patients present with locally advanced or metastatic disease, survival rates in sarcoma plummet drastically despite the use of standard cytotoxics with estimated five-year survival rates of approximately 20% [3].

Historically, sarcomas have been broken down into two specific subgroups; those with simple karyotypes that are often defined by reciprocal or simple translocations and/or specific gene amplifications (e.g. Ewing's sarcoma, synovial sarcoma, GIST) and those with complex karyotypes with multiple chromosomal aberrations (e.g. liposarcoma, leiomyosarcoma, osteosarcoma) [4, 5]. The introduction of large-scale molecular and genomic studies has begun to shed light on the numerous diseases that are generally referred to as 'sarcomas' [6, 7]. We now view sarcoma as a complex group of many individual, molecularly unique neoplasms; all of which require individual attention and personally designed treatment paradigms.

1.1 Signaling in Sarcoma

The mTOR pathway regulates growth and maintains homeostasis in mesenchymal cells [8]. Under normal cellular conditions, the mTOR pathway is responsive to signals that can influence cell growth such as exogenous growth factors and changes in the levels of nutrition, energy, and oxygen. Dysregulation of the mTOR pathway can lead to uncontrolled cellular proliferation and the avoidance of programmed cell death. The updated results of a Phase II trial of AP23573 (ridaforolimus, formerly deforolimus) in patients with advanced soft tissue sarcoma (STS) has been published [9]. Ridaforolimus is a novel non-prodrug mTOR inhibitor (rapamycin analogue). The Phase II study which evaluated 212 patients with soft tissue and bone sarcomas met its primary endpoint by achieving a clinical benefit ratio [CBR – complete response (CR) + partial response (PR) + stable disease (SD) > 24 weeks] of 29%. The 6-month Progression Free Survival (PFS) rate in all study participants was 23%. A cohort analysis showed that the CBR rate was 30% in bone sarcomas, 33% in leiomyosarcomas (LMS), 30% in liposarcomas, and 23% in all other sarcomas. Therefore, all groups except for the 'all other STS' group met the study's primary endpoint of a CBR >25%. No CR's were achieved and four patients (2.0%) achieved a PR. The median OS rate of the entire cohort was 40 weeks. In a subset analysis presented at ASCO, the median OS of those participants who achieved a CBR was 67.6 weeks [10]. The investigators concluded that a CBR may be a surrogate marker for OS. These results prompted the initiation of the SUCEED trial (Sarcoma Multi-Center Clinical Evaluation of the Efficacy of Deforolimus), a double-blinded, placebo-controlled trial in patients with metastatic sarcoma who had a favorable response to chemotherapy. The SUCCEED trial evaluated the efficacy of maintenance ridaforolimus with a primary PFS endpoint. The SUCCEED trial had achieved its primary endpoint with an approximate 3.1 week improvement in median PFS over placebo. Ridaforolimus was not granted FDA approval based on these data.

In general, the activity of ridaforolimus in sarcoma is encouraging. Evaluation and noted responses as defined by a CBR do suggest activity of the mTOR pathway in the pathogenesis and propagation of sarcoma. However, lack of true response as defined by conventional size based overall response rates suggest that inhibition of mTORC1 is not sufficient to drastically impact a patient's clinical outcome. This is most likely due to incomplete blockade of the PI3K/AKT/mTOR pathway and/or upregulation of survival/bypass pathways that accelerate the

cellular growth of tumors [11, 12]. For example, blockade of mTORC1 alone paradoxically activates AKT through various feedback mechanisms including upregulation of the Insulin Growth Factor 1 Receptor (IGF1R) [13]. This is of critical interest in sarcoma as the Insulin Growth Factor Pathway (IGF) has also been implicated in the pathogenesis of these tumors [14-16].

Several phase II studies evaluating inhibition of the IGF pathway in sarcoma have been reported [17, 18]. The first trial evaluated AMG-479, an antibody to IGF1R, in patients with relapsed/recurrent Ewing's Sarcoma Family of Tumor (ESFT) [17]. This included patients with Ewing's sarcoma (ES), primitive neuroectodermal tumors (PNET), Askin's tumor and desmoplastic small round cell tumors (DSRCT). The trial reported on 35 patients, two had a PR and 4 had SD>24 weeks. This led to an overall response rate (ORR, CR+PR) of 6% and a CBR of 17%. Of note, the median PFS was 7.9 weeks in ES and 19 weeks in DSRCTs. A second trial reported on the activity of R1507, an antibody to IGF1R, in another Phase II trial in patients with ESFT [18]. This trial reported on 109 patients, with an ORR of 10%, a median duration of tumor response of 29 weeks and a median overall survival rate of 7.6 mos. Although these trials showed significant activity in a few patients, the overall response rate was discouraging and suggests that resistance may be mediated by downstream effectors not associated with or not properly targeted by inhibitors of the IGF1R pathway.

Much like the use of mTOR inhibitors in sarcoma, preclinical and clinical work is ongoing in order to determine the subset of patients who respond to IGF1R inhibition and why. In addition, as the mTOR and IGF pathway are closely related, evaluation of combined mTOR/IGF1R inhibition has also been performed in an effort to overcome mechanisms of resistance and provide more comprehensive pathway inhibition. A large multicenter study evaluating the combination of everolimus (mTOR inhibitor) and cixutumumab (IGF1R inhibitor) in patients with locally advanced, metastatic, recurrent soft tissue or bone sarcoma (NCT01016015) was reported [18]. Overall, the trial was positive, meeting predefined 12-week PFS endpoints in three cohorts of patients that included IGF1R+ (IHC) soft tissue sarcomas (12 wk. PFS 31%), IGF1R+ (IHC) bone sarcomas (12 wk. PFS 35%) and IGF1R- (IHC) bone and soft tissue sarcomas (12 wk. PFS 39%). These results were encouraging and exceeded prior PFS rates noted with single agent IGF1R or mTOR inhibitors in sarcoma [17-19]. However, Overall Response Rate by RECIST was once again only 5% [20].

1.2 MLN0128 (TAK-228)

MLN0128 (TAK-228) (Millennium/Takeda) is a selective and highly potent ATP competitor of both mTORC1 and mTORC2 [21].MLN0128 (TAK-228) has been shown in preclinical breast models (in vitro and in vivo) to overcome resistance to anti-HER2 agents that are mediated by secondary upregulation of the PI3K/AKT pathway [22]. As a preclinical tool, MLN0128 (TAK-228) provides an opportunity to investigate efficacy of dual mTORC1/mTORC2 inhibition in sarcoma as compared to combined IGF1R/mTOR inhibition and allows for further pathway evaluation to determine which mediators of the PI3K/AKT/mTOR axis drive tumor growth despite inhibition of mTOR and AKT. As a clinical tool, MLN0128 (TAK-228) competitively inhibits both mTORC1 and mTORC2 with high affinity. This should avoid primary and overcome secondary drug resistance that develops from blockade of Receptor Tyrosine Kinases (RTKs) that mediate signaling through the PI3K/mTOR pathway and selective mTORC1 inhibitors alone.

Mechanism of Action

MLN0128 (TAK228) selectively and potently inhibited mTOR kinase, demonstrating 50% inhibition at the concentration of 1.1 nM (IC50). Relative to mTOR, MLN0128 (TAK228) was

>100-fold less potent as an inhibitor of Class I (PI3 kinase isoforms α, β, γ, δ (Table 1), class II (PI3KC2α and PI3K2Cβ), and Class III (VPS34) PI3K family members, as well as PI3Kα and PI3Kβ.

MLN0128 (TAK228) (1 mcM) also inhibited (>80%) biochemical activity of five kinases (mTOR, DNA-PK, PDGFRα, Flt3, and CK1 epsilon kinases) out of a panel of 222 protein kinases. MLN0128 (TAK228) inhibited ligand binding of 10 receptor and intracellular protein kinases including (ACVR1, BMPR1B, CSF1R, CSNK1D, CSNK1E, DDR1, MEK1, MEK2 PDGFRβ, and RIPK2) out of a panel of 402 distinct kinases. MLN0128 (TAK228) displayed cellular inhibition of TORC1 and TORC2 pathways with IC50 less than 10 nM.

In Vivo Studies:

Pharmacokinetic (PK) studies of MLN0128 (TAK228) have been investigated in a number of animal models, including mice, rats, dogs, and monkeys.

Drug Metabolism and Pharmacokinetics: TAK-228 was rapidly absorbed after PO administration to mice, rats, dogs, and monkeys, with high oral bioavailability. 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. TAK-228 did not inhibit P-glycoprotein, but did inhibit breast cancer-resistance protein (BCRP), organic cation transporter (OCT)1 and OCT2.

The main isozymes responsible for phase 1 metabolism appear to be cytochrome P450 (CYP) 2C9, 2C19, and 3A4. TAK-228 did not induce CYP1A2, 2B6, and 3A4 activity and expression at concentrations up to 10 □M. TAK-228 displayed low potential for inhibition and is not a time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5.

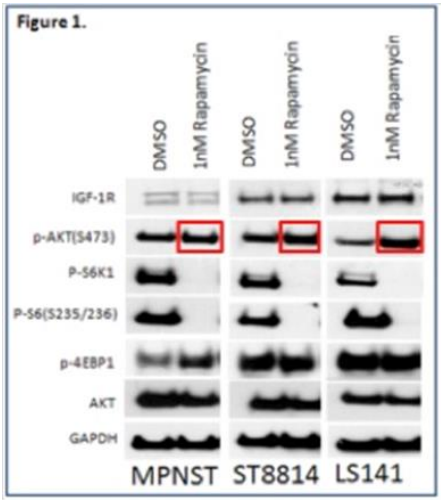
Toxicology: Adverse events of TAK-228 in rats and monkeys included body weight loss, decreased activity, increased glucose and insulin levels, alterations in white blood cells, bone marrow and lymphoid depletion, thymic necrosis, oligospermia, testes degeneration/atrophy, nonglandular stomach epithelial degeneration/ulceration/hyperplasia, pancreatic islet degeneration and fibrosis, lens fiber degeneration with cataract correlate, adrenal cortex hypertrophy, pituitary atrophy secondary to body weight loss, liver hepatocellular vacuolation, retinal dysplasia with or without optic nerve atrophy, and alveolar histiocytosis. 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. TAK-228 was negative for phototoxicity in the 3T3 fibroblast assay.

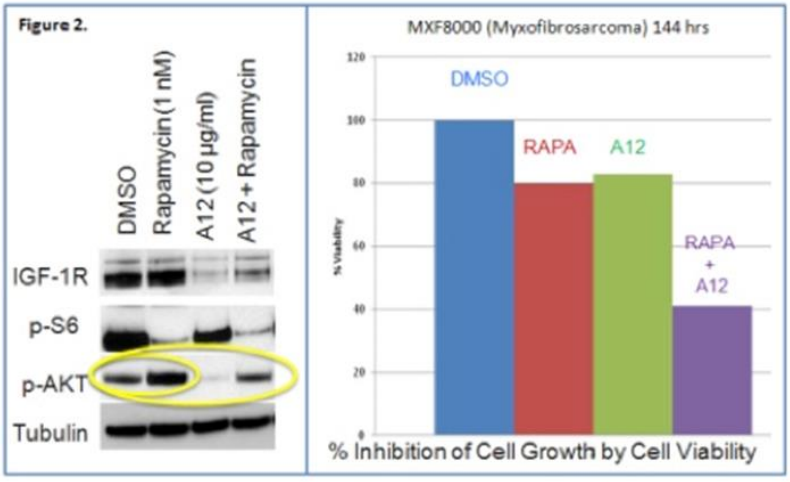
Safety Pharmacology: TAK-228 has a low potential to affect the human ether-a-go-go related gene (hERG) potassium ion channel and did not affect cardiovascular (CV) parameters in vivo in telemeterized monkeys.

1.3 Preclinical Data in Sarcoma Models

Data from in vitro and in vivo sarcoma models from the laboratory of PI GK Schwartz confirm that both primary and acquired resistance to single agent mTORC1 inhibitors in sarcoma is potentially mediated by upregulation of aberrant pAKT signaling (Figure 1; MPNST and ST88 [MPNST], LS141 [Liposarcoma]).

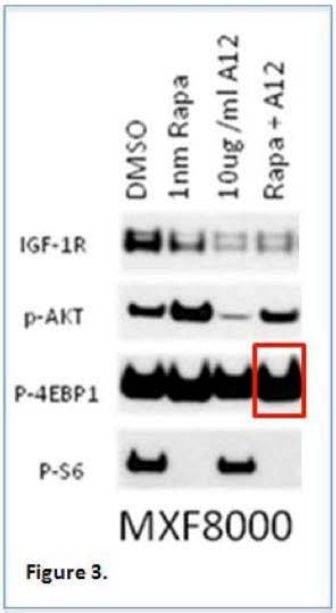
Dual IGF1R and mTORC1 inhibition suppresses total PI3K/AKT/mTOR signaling and overcomes drug resistance as mediated by aberrant pAKT as encountered with the single agents respectively (Figure 2; MXF8000 myxofibrosarcoma). This, in part, is due to the IGF1R inhibitors ability to abrogate the increase in pAKT signaling that is caused by mTORC1 inhibition alone. In addition, proliferation assays show at least additive effects on proliferation for the combination as opposed to either single agent alone.

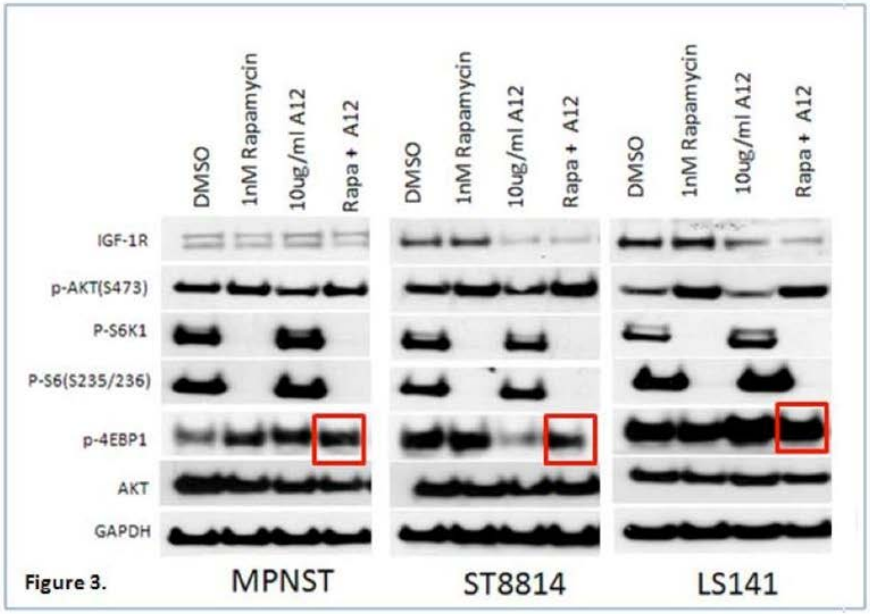




This data led to the now completed Phase II trial of everolimus and cixutumumab that was described above. Pre and post-treatment biopsies performed at Memorial Sloan Kettering Cancer Center (MSKC) on this study demonstrated inhibition of pIGF1R, pAKT, and pS6. However, in spite of this, patients with apparent pathway inhibition still progressed on drug, suggesting continued input to this pathway from an effector(s) not captured in assays performed on tissue samples taken from the study participants.

Follow-up work done at MSKCC on the sarcoma cell lines including a myxofibrosarcoma (MXF8000) cell line that was derived from a patient who rapidly progressed on the clinical trial suggest that dual mTORC1/IGF1R inhibition does not cause complete and sustained PI3K/AKT/mTOR pathway inhibition as 4EBP1 signaling is shown to be maintained through exposure to the combination (Figure 3).





Ideally, a stronger and more direct inhibitor of this axis is required to achieve predicted clinical results.MLN0128 (TAK-228) is a selective and highly potent ATP competitor/inhibitor of both mTORC1 and mTORC2 [21]. Direct inhibition of mTORC1 and mTORC2 provides a unique

opportunity to target the PI3K/AKT/mTOR pathway in sarcoma while suppressing de novo and secondary resistance generated through AKT activation and has the potential of providing more sustained pathway inhibition. In addition, it affords the ability to target PI3K/AKT/mTOR signaling at a single critical point, decreasing the likelihood of aberrant input from the numerous effectors involved in the signaling cascade of this complex pathway.

A growth response curve of MLN0128 (TAK-228) was generated against a large panel of well-characterized sarcoma cell lines. A representative panel of growth inhibition achieved with a 6-day proliferation assay is depicted (Figure 4, CHP100 [Ewing's Sarcoma], SaSO2 [osteosarcoma]). As noted, the concentration that achieved 50% growth inhibition in all of the cell lines was less than 50nm of drug. This confirms activity of the PI3K/AKT/mTOR pathway in these sarcoma cell lines and the significant activity of MLN0128 (TAK-228), a selective mTORC1/mTORC2 inhibitor in sarcoma.

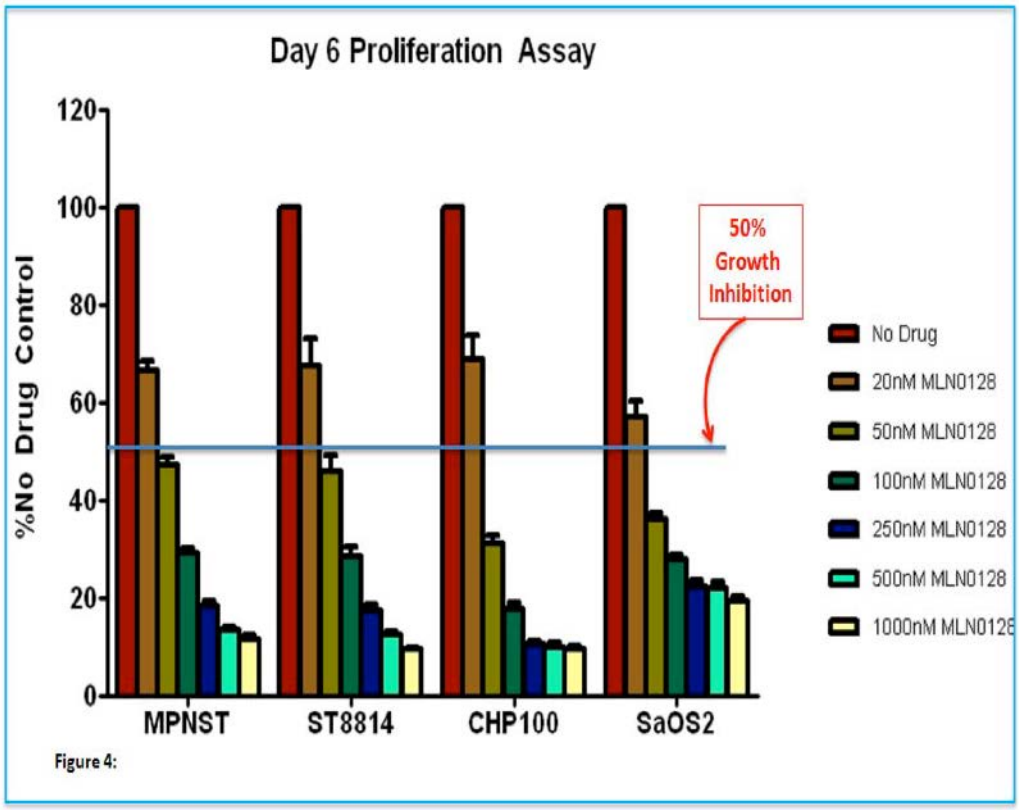
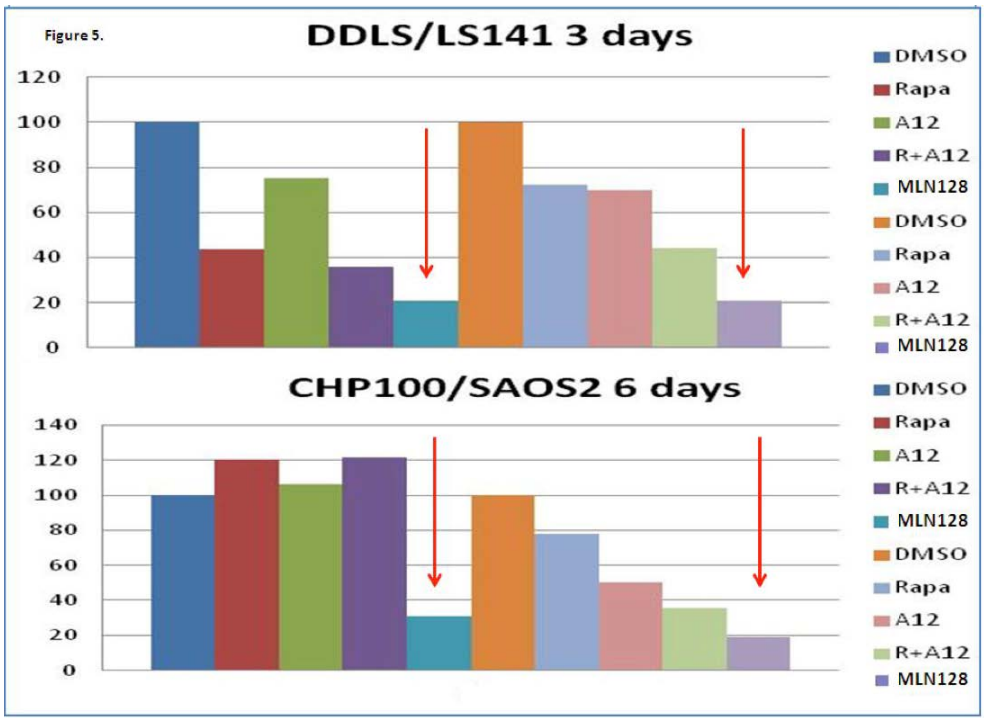
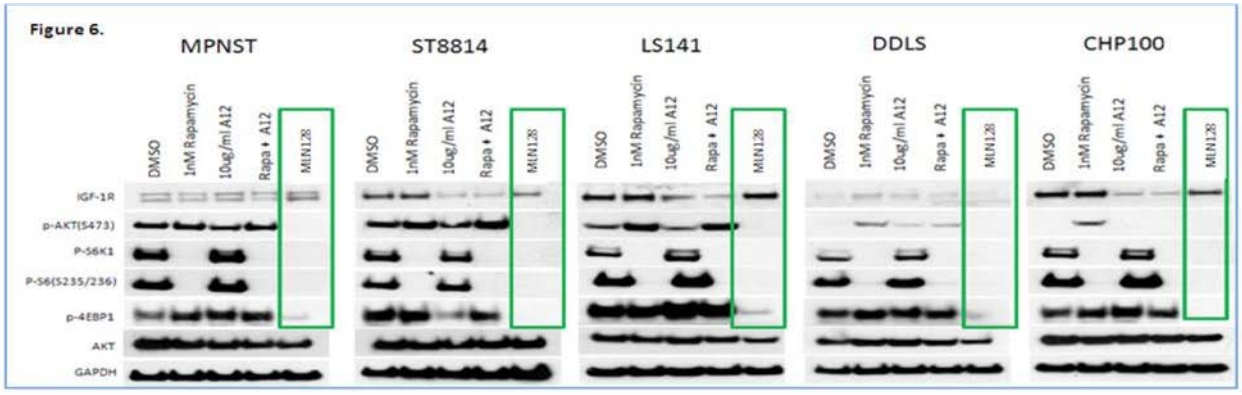


Figure 4:

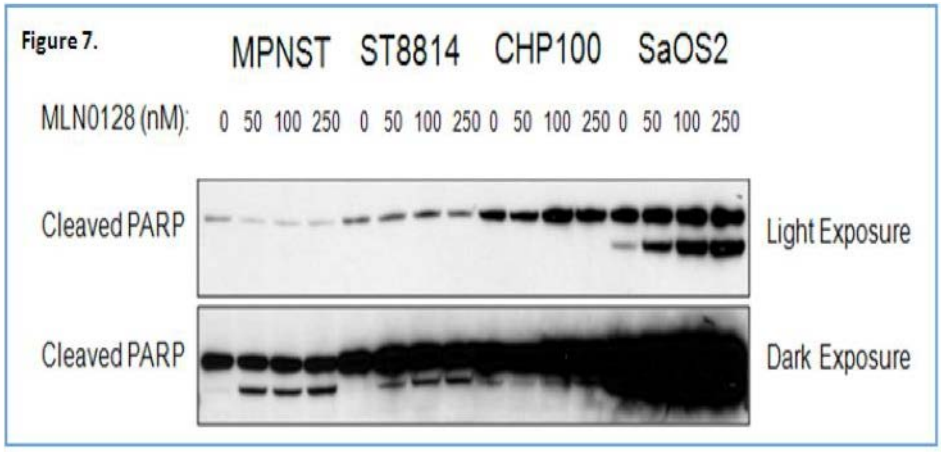
Comparative experiments in a large panel of sarcoma cell lines were also performed with the use of a single agent mTORC1 inhibitor (rapamycin), single agent IGF1R inhibitor (A12), combined mTORC1/IGF1R inhibitors and MLN0128 (TAK-228). Representative results at 3 and 6 days are depicted (Figure 5; DDLS (Liposarcoma). In each cell line, it is clear that single agent MLN0128 (TAK-228) has superior activity than mTORC1, IGF1R and dual mTORC1/IGF1R inhibition.



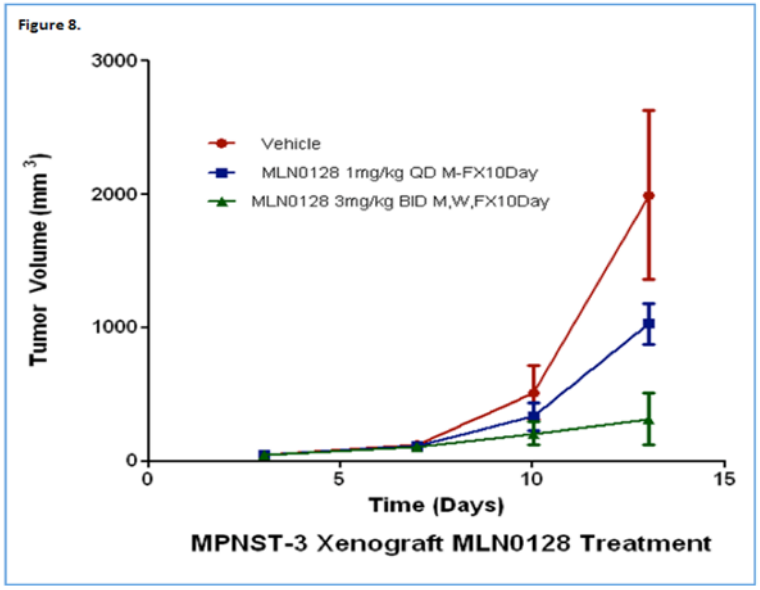
To investigate the molecular effects of MLN0128 (TAK-228) in the sarcoma cell lines, western blot analysis of protein lysates obtained before and after exposure to MLN0128 (TAK-228) were performed (Figure 6). Unlike single agent and combined mTORC1 (rapamycin) and IGF1R (A12) inhibition, dual mTORC1/mTORC2 (MLN0128 (TAK-228)) causes complete blockade of the PI3K/AKT/mTOR pathway as noted by complete inhibition of pAKT, pS6K, pS6 and p4EBP1.

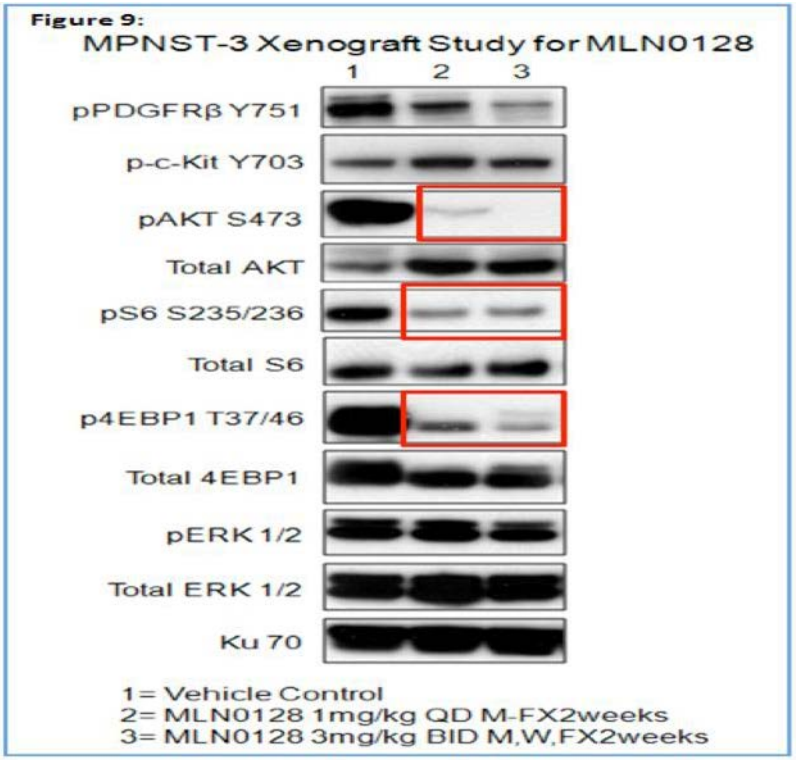


In addition, as indicated by the presence of cleaved PARP, exposure of the sarcoma cell lines to MLN0128 (TAK-228) causes cellular disassembly and apoptosis (Figure 7).



Efficacy of MLN0128 (TAK-228) has also been confirmed in xenograft models (Figure 8). With lysates confirming total blockage of the PI3K/AKT/mTOR pathway as found in the sarcoma cell lines (Figure 9). Taken together, all of these data strongly support the clinical application of MLN0128 (TAK-228) across sarcoma subtypes.





1.4 Clinical Data

MLN0128 (TAK-228) (Millennium/Takeda) is a selective and highly potent ATP competitor of both mTORC1 and mTORC2 [21].MLN0128 (TAK-228) is currently in clinical development. At the time of writing this protocol, MLN0128 (TAK-228) was being tested in two phase I studies as a single agent, one in solid tumors and the other in multiple myeloma and Waldenstroms macroglobulinemia, and in one Phase I study in combination with paclitaxel +/- trastuzumab (Investigator's Brochure, Edition 7). As of December 2013, 248 patients have received MLN0128 (TAK-228) on these three trials. The single agent experience with the Phase I Solid Tumor and the Phase I hematology trials are listed (Table 1).

Phase I Solid Tumors	QD schedule	2mg (3pts), 4mg (7pts), 6mg (13pts), 7mg (8pts)	MTD – 6mg	RP2D 5mg
	QW schedule	7mg (3 pts.), 10mg (3 pts.), 15mg (3 pts.), 20 mg (3 pts.), 30 mg (3 pts.), 40 mg (15 pts.)	MTD – 40mg	RP2D 30mg
	QD x 3d QW	6mg (3 pts.), 9mg (8 pts.), 12mg (6 pts.), 16 mg (12 pts.), 20 mg (4pts),	MTD – 16mg	
	QD x 5d QW	7mg (6 pts.), 10mg (13 pts.), 13mg (3 pts.)	MTD – 10mg	

	Expansion QD schedule	5mg (16 pts.)		
	Expansion QW schedule	40 mg (27 pts.), 30 mg (7 pts.)		
Phase I MM and WM (Heme)	QD schedule	2mg (5pts), 4mg (7pts), 6mg (6pts), 7mg (8pts)		
	QD x 3d QW	9mg (6pts), 12mg (7pts)		

Safety:

As of 09 December 2014, a total of 335 patients had received ≥ 1 dose of study drug across studies. A total of 18 deaths that occurred within 30 days of the last study drug dose had been reported to the clinical database as of the data cutoff; of these events, 1 (cardiac arrest; Study INK128-001) was considered related to TAK-228. At least 1 treatment-emergent SAE, regardless of causality, had been reported in 125/335 patients (37%). Across the studies and regardless of causality or dosing regimen, the most common TEAEs included nausea, fatigue, hyperglycemia, vomiting, diarrhea, stomatitis, and decreased appetite.

To date, MLN0128 (TAK-228) appears well tolerated with the report of most toxicities as reversible grade 1 and 2. In the solid tumor phase I study, 41% of patients experienced treatment-emergent serious adverse events (TESAE). The most common was mucosal inflammation (4%), asthenia, and pneumonia (3% each), and abdominal pain, stomatitis, and renal failure (2% each). 98% of 142 treated patients had a treatment-emergent adverse event (TEAE). Hyperglycemia was recorded in 65% of patients, nausea in 63% of patients and vomiting in 54% of patients. Most TEAEs were grade 1 or 2 and easily manageable with supportive care. Grade 3 or greater TEAE were recorded in 6% of patients with the most frequent (regardless of causality) were hyperglycemia 6%, asthenia 8%, anemia 7%, and hypophosphatemia and lymphopenia 6%.

Due to the cardiac death on study INK128-001, study C31002, a phase 1 single-arm study to evaluate the effect of a single dose of 40 mg TAK-228 on the QT/QTc interval was initiated in patients with advanced solid tumors. After completing the per-protocol PK/ECG/cardiac contractility monitoring, the patients continued TAK-228 30 mg QW with continued cardiac monitoring. The study results showed that treatment with TAK-228 was not associated with clinically meaningful effects on the overall elecrocardiographic safety profile, and that ECHO/MUGA at screening was not required.

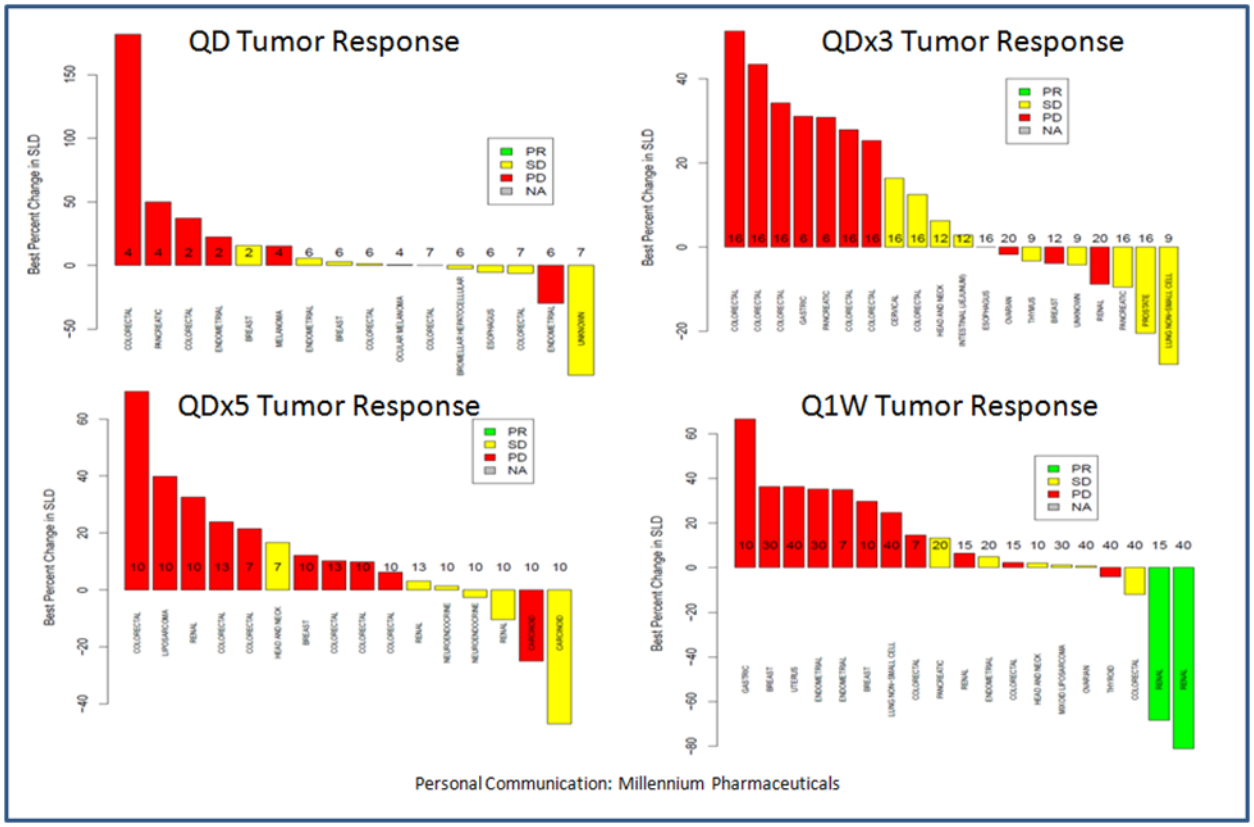
Pharmacokinetics: MLN0128 (TAK-228) has been tested as a single agent in several doses and schedules as outlined above. It appears to exhibit fast absorption [Tmax] 1-4 hours after dosing, dose linear pharmacokinetics with a mean plasma half-life (t1/2) of approximately 8 hours, an apparent total body clearance of approximately of 20L/hr., and does not appear to accumulate in plasma when dosed as frequently as once daily. MLN0128 (TAK-228) exposures also increase linearly with dose and the pharmacokinetics are consistent across the various dose levels.

Both daily and weekly dosing schedules are being considered for Phase II trials. However, the weekly dosing schedule is now believed to be superior (see below).

Reporting on clinical responses is not yet available through the IB. Millennium Pharmaceutical has provided a graphic of best responses on their Phase I solid tumor trial. To our knowledge, only one patient with sarcoma has been treated with MLN0128 (TAK-228). This was a patient with liposarcoma who progressed on the 10mg QDx5 dose and schedule. Of all of the patients

treated, only two patients with Renal Cell Carcinoma have achieved a partial response. Both of these patients were on the Q week dosing schedule at 15 and 40mg, respectively. Millennium Pharmaceuticals believes that these data underscore that MLN0128 (TAK-228) should be used in a weekly dosing schedule. Preclinical data suggests that higher/intermittent dosing of MLN0128 (TAK-228) may be superior in sarcoma than daily dosing (Figure A). As of November, 2014, MLN0128 (TAK-228) capsule was reconfigured to contain a milled active pharmaceutical ingredient (API). The milled API may result in faster absorption with possibly higher maximum concentration (Cmax), which could result in a different safety profile compared to the current unmilled API. For this reason, a Phase Ib component is included in this protocol utilizing a Qweek dosing and a standard 3+3 design. The Phase I component will be used to confirm safety of the new formulation prior to entering into the randomized Phase II portion of the trial. Please see Sections 7 and 8 for treatment plan and dose modification details.

Figure A



The new capsule API requires administration in fasting conditions. MLN0128 (TAK-228) milled API should be administered once weekly. It is recommended that each dose is given orally with 8 ounces (240 mL) of water. MLN0128 (TAK-228) should be administered on an empty stomach. The patients should be instructed to refrain from eating and drinking (except for water and prescribed medications) for 2 hours before and 1 hour after each dose.

Development of a Milled Formulation of TAK-228

In order to allow more predictable absorption of TAK-228 after oral administration and to allow scale-up manufacturing of TAK-228 capsules, Millenium/Takeda developed a new milled formulation of the agent. The physical milling step during the granulation process controls particle size distribution of TAK-228. In order to observe whether this milling step altered the safety and PK profile of TAK-228, the company performed in vivo studies with PK analysis of

milled TAK-228. These studies indicated that the milled formulation may result in faster absorption with possibly higher maximum concentration (Cmax), which could result in a different safety profile, compared to the previous unmilled API capsules.

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

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

The significant difference in tolerability observed in the comparison of the MTDs between unmilled and milled TAK-228 when administered QD may be possibly explained due to the effect of food on the safety/tolerability of unmilled TAK-228 in study IND128-001. The GastroPlus™ simulation performed under fasting conditions on the trial demonstrated that unmilled and milled TAK-228 administration result in comparable exposures to TAK-228; whereas in the fed state, milled TAK-228 resulted in higher C_{max} (1.5- to 2-fold higher) and earlier T_{max} than unmilled TAK-228 with comparable AUCs. Consequently, a dose of 3 mg QD was chosen as the RP2D of milled TAK-228 dose in empty stomach conditions.

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

TAK-228-1004, a phase I, open label study to evaluate the safety, tolerability, and pharmacokinetics of TAK-228 in combination with paclitaxel in adult patients with advanced non-hematological malignancies-), with the new milled API was used to determine the recommended phase 2 dose (RP2D) for TAK-228 QD×3days per week in combination with paclitaxel. The RP2D of milled TAK-228, given 3 consecutive days weekly, in combination with weekly paclitaxel at 80 mg/m2, was 6 mg.

1.5 Pazopanib

In a key multicenter, placebo-controlled Phase 3 trial, pazopanib at a dose of 800 mg daily demonstrated a significant benefit in progression-free survival for patients with metastatic soft tissue sarcomas that had progressed on at least one prior therapy[22]. Median PFS (with 95% confidence interval) was 4.6 months (3.7 – 4.8) versus 1.8 months for placebo (0.9-1.8); Hazard Ratio 0.31 (0.24 – 0.40)[22]. Overall survival was not significantly improved, with a median OS of 12.5 vs 10.7 months, HR 0.86, 95% CI 0.67 – 1.11. The trial was not powered to detect a 3-month difference of median OS. Of note, adipocytic STS was excluded, as were embryonal rhabdomyosarcoma, osteosarcoma, chondrosarcoma, Ewing's sarcoma, gastrointestinal stromal tumor, dermatofibrosarcoma protuberans, and inflammatory myofibroblastic sarcomas. Based on this trial, the FDA granted approval for pazopanib to treat non-adipogenic metastatic soft tissue sarcomas in the second-line setting.

Although median dose intensity on this trial was 96%, it is notable that 49% of patients required a dose interruption, and 39% required a dose reduction [22]. The most common adverse events were fatigue, diarrhea, nausea, weight loss, and hypertension. Venous thromboembolic events

occurred in 5% of the study population who received pazopanib. A drop in Left Ventricular Ejection Fraction occurred in a similar number of patients, the majority of which were asymptomatic. Dose reductions were mainly caused by hypertension, fatigue, diarrhea, hand/foot syndrome, and elevation of AST/ALT. Grade 3 fatigue occurred in 13% of patients; other Grade 3 toxicities were hypertension and gastrointestinal in nature.

1.6 Registration Quality of Life (QOL) Measurements

QOL measurements of fatigue and overall perception of QOL are routinely included in Alliance studies and will be assessed upon registration in this study. Evidence has arisen indicating that baseline single-item assessments of fatigue and overall QOL are strong prognostic indicators for survival in cancer patients, independent of performance status. This evidence was derived from two separate meta-analyses recently presented at ASCO, the first involving 23 NCCTG and Mayo Clinic Cancer Center oncology clinical trials, the second involving 43 clinical trials. Routine inclusion of these measures should be considered similar to that of including performance status, either as stratification or prognostic covariates. It will take approximately one minute to complete this measure [23].

1.7 Impact of this Trial

Pazopanib represents the first oral multikinase inhibitor that has a specific FDA-approved indication for the treatment of non-GIST soft tissue sarcomas. This trial aims to compare TORC1/TORC2 inhibition with MLN0128 (TAK-228) against this regimen with established efficacy. Should this trial demonstrate a significant benefit in PFS, it would suggest a pivotal Phase III trial would be warranted to assess its benefit over the current standard.

1.8 Rationale for Pazopanib Dosing Change

On August 4, 2017, the protocol was suspended due to the DSMB stopping rules as outlined in section 13.7.1.2 of the old protocol. Five of the first 12 patients on the control arma (pazopanib) experienced a grade 3 or higher adverse event. All of these events were carefully reviewed by the study team and were felt to be expected toxicities of the pazopanib. The study team felt that the starting dose of pazopanib was too high, accounting for these toxicities, and not reflective of the starting dose used in routine clincial practice. For this reason, the protocol was amended to allow for pazopanib to be initiated at 400mg qd, with plans to titrate to tolerable doses as outlined in section 7.2.

2.0 OBJECTIVES

2.1 Primary Phase I objective

To determine the safety and maximum tolerable dose of MLN0128 (TAK-228) within this patient population.

2.2 Primary Phase II objective

To determine the differences in progression-free survival (PFS) in patients with sarcoma who receive MLN0128 (TAK-228) as compared to pazopanib.

2.3 Secondary Phase I/II objectives

2.3.1 To evaluate adverse events.

2.3.2 To evaluate Overall Response Rate (ORR), Clinical Benefit Rate (CBR), and Duration of Response (DOR).

2.3.3 To evaluate Time to Progression (TTP) and Overall Survival (OS).

2.4 Exploratory Phase II objectives

2.4.1 To evaluate PFS and secondary endpoints within patients crossing over to MLN0128 (TAK-228), upon disease progression during treatment with pazopanib**.**

2.4.2 To evaluate the 4 month CBR observed within patients treated with MLN0128 (TAK-228) and grouped by histologically defined Cohorts.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

Prior to discussing protocol entry with prospective patients, site staff must go to the A091304 study page on the CTSU web site to check cohort status and accrual. Please note that Cohort 3 is limited to 25 patients and as of Update #05, this applies to Arms 5 and 6. If a patient is eligible (from local pathology review) for Cohort 3, and 18 or more patients have accrued to Cohort 3 (post-Update #05), contact the Alliance Registration Office at random01@mayo.edu or 507-284-4130 (during regular business hours 8:00-4:30 CT) to be sure that there is an available spot for the patient. If the Registration Office has confirmed that a spot is available, site staff may then proceed to consent and pre-register the patient.

3.1 On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient. No ischemic myocardial or cerebrovascular event, class III or IV heart failure, placement of pacemaker, or pulmonary embolism within six months of receiving first dose of MLN0128 (TAK-228).
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years.
- Patients who cannot swallow oral formulations of the agent(s).

In addition:

- Women and men of reproductive potential are advised to use 2 acceptable methods of birth control (one of which must include a condom as a barrier method of contraception) due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom). The methods should be continued for three months for females and 4 months for males after completing study drug. Men must agree not to donate sperm during the course of this study or within 4 months after receiving their last dose of study drug.
- Drugs that prolong the QTc interval should be avoided if possible. Pazopanib can prolong the QTc interval. Drugs that are generally accepted to have a risk of causing Torsades de Pointes should be discontinued or replaced with drugs that do not carry this risk, if at all possible. Patients who receive potential QTc-prolonging medications should be monitored closely.

3.2 Pre-Registration Eligibility Criteria (Step 0)

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following pages.

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

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

___ **3.2.1 Central pathology review submission**

Patients must have slides available for submission to central pathology review. This review is mandatory prior to registration to confirm eligibility and proper cohort assignment. See Section 6.2 for details on slide submission.

Sarcoma of the following histologic subtypes by local pathology review may be submitted for central pathology review**:

- HISTOLOGIC COHORT 1: Undifferentiated Pleomorphic Sarcoma (Includes: Malignant Fibrous Histiocytoma, Myxofibrosarcoma, High Grade Sarcoma NOS).
- HISTOLOGIC COHORT 2: Leiomyosarcoma (Either Uterine or Extra-Uterine).
- HISTOLOGIC COHORT 3: Other (Either Malignant Peripheral Nerve Sheath Tumor or Synovial Sarcoma). During the Phase II portion of the study, enrollment will be limited to maximum of 25 patients in this cohort. This applies to those assigned to Arms 5 and 6, as of Update #05.

** Note that the Phase I is limited to the histologic subtypes listed above. Since patients will be enrolling onto Dose cohorts during the Phase I, they will not enroll onto specific Histologic Cohorts, although the histologic subtype informed will be collected during patient enrollment.

3.3 Registration Eligibility Criteria (Step 1)

___ **3.3.1 Documentation of Disease:**

Histologic Documentation: Eligible patients must have histopathologically confirmed sarcoma of one of the subtypes listed in Section 3.2.1, by central review.

Locally advanced or metastatic disease. Locally advanced disease is defined as disease not amenable to local therapy such as surgery and/or radiation.

___ **3.3.2 Measurable disease** as defined in Section 11.0.

___ **3.3.3 Prior Treatment**

___ • Progression on at least one prior systemic chemotherapy for advanced, unresectable or metastatic disease. Prior adjuvant or neoadjuvant therapy is not included as prior systemic chemotherapy unless treatment occurred within the 6 months prior to study enrollment.

___ • There is no limit to the number of prior lines of treatment a patient has received.

___ • No treatment with biological therapy, immunotherapy, chemotherapy, investigational agent for malignancy, or radiation ≤ 28 days before study registration. No treatment with nitrosourea or mitomycin ≤ 42 days before study registration.

___ • No treatment with radiation therapy ≤ 28 days before study registration.

___ • Patients should have resolution of any toxic effects of prior therapy (except alopecia) to NCI CTCAE, Version 4.0, grade 1 or less.

___ • Prior treatment with pazopanib or any PI3K, mTOR, AKT, or dual PI3K/mTOR complex (TORC1/TORC2) inhibitors will be prohibited.

___ **3.3.4 Not pregnant and not nursing,** because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown and an agent that has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7 days prior to registration is required.

___ **3.3.5 Age ≥ 18 years**

___ **3.3.6 ECOG Performance Status ≤ 1**

___ **3.3.7 Patient history: patients who have any of the following are NOT eligible:**

___ • CNS: Symptomatic, untreated, or uncontrolled brain metastases present

___ • Heme: Active bleeding or bleeding diathesis

___ • GI:

- Abdominal fistula, GI perforation, or intra-abdominal abscess within 28 days prior to registration
- Acute GI bleed within 28 days of registration

___ • Diabetes Mellitus: Patients with diabetes mellitus with inadequate control, based on either a glycosylated hemoglobin (Hgb A1c) of >7.0 or fasting blood glucose above or equal to 130 mg/dL.

___ • Cardiac and Vascular Disorders:

- History of congenital long QT syndrome or torsades de pointes
- Any arrhythmia that is currently not rate-controlled (rate between 60 and 100)
- Prolongation of corrected QT interval via Friderica's formula (QTcF) >480 msec
- Ongoing unstable angina
- Symptomatic peripheral vascular disease
- Arterial thrombosis within 28 days of registration including TIA, CVA, MI.
- Patients with DVT or PE must be on a stable dose of anticoagulation for 14 days prior to registration
- Uncontrolled hypertension, defined as BP > 140/90
- MUGA with EF, 50% or echo with low EF
- Class III or IV CHF within 28 days of registration

___ **3.3.8 Concomitant Medications:**

• Chronic concomitant treatment with proton pump inhibitors must discontinue the drug for 7 days prior to registration on the study.

___ • Chronic concomitant treatment with strong inhibitors of CYP3A4 inhibitors must discontinue the drug for 14 days prior to registration on the study. See Section 7.3 for more information.

___ • Chronic concomitant treatment with strong CYP3A4 inducers is not allowed. Patients must discontinue the drug 14 days prior to the start of study treatment. See Section 7.4 for more information.

___ **3.3.9 Required Initial Laboratory Values:**

Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Platelet Count	≥ 100,000/mm^3
Creatinine	≤ 1.5 x upper limit of normal (ULN)
Total Bilirubin	≤ 1.5 x upper limit of normal (ULN)*
AST / ALT	≤ 3 x upper limit of normal (ULN)**
UPC	≤ 1***
TSH	WNL****

* Unless patient has Gilbert disease

** If liver metastases, ≤ 5 x upper limit of normal (ULN)

*** If UPC ≥ 1, then a 24-hour urine protein must be assessed. Eligible patients must have a 24-hour urine protein value < 1 g/L

**** Supplementation is acceptable to achieve a TSH WNL. In patients with abnormal TSH however if the Free T4 is normal and patient is clinically euthyroid, patient is eligible.

4.0 PATIENT REGISTRATION

4.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov mailto:>.

4.2 CTSU Site Registration Procedures

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

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Site Registration Documents

Site registration forms may be downloaded from the A091304 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol # A091304
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

4.2.2 Requirements for A091304 Site Registration

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

  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Radiological Physics Center (RPC)

monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility.

4.2.3 Submitting Regulatory Documents

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

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

When applicable original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

4.2.4 Checking Your Site's Registration Status

You can verify your site registration status on the members' section of the CTSU website

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

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Phase I Enrollment Requirements

4.3.1 Pre-Registration Requirements (Step 0)

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Slot reservation:** patient enrollment will be facilitated using the Slot-Reservation System in conjunction with the Registration system on Oncology Patient Enrollment Network (OPEN). Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to insure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to pre-register the patient. Once a patient is pre-registered, specimens should be submitted for central pathology review.
- **Central pathology review submission:** Patients who have 1) met pre-registration eligibility criteria, 2) been consented, and 3) have received a slot reservation confirmation, will be pre-registered using the OPEN registration system (see Section 4.5) in order to submit specimens for central pathology review. Once the patient is pre-registered, the sarcoma tissue slides from diagnostic biopsy should be sent to:

Dr. Fabrizio Remotti
Department of Pathology VC14-215
Columbia University Medical Center
630 W 168th St, New York, NY 10032

along with a completed "Central Pathology Review Form", per Section 6.2.2. Failure to submit this form with the specimens will delay turnaround time for central pathology review. The specimen will be centrally reviewed to confirm study eligibility. The tissue slides will not be returned.

4.3.2 Registration Requirements (Step 1)

- **Confirmation of eligibility by central pathology review:** Sites will be notified via e-mail within 5 business days of receipt, whether or not the patient is eligible based on the central pathology review. The results section of "Central Pathology Review Form" will be completed by the pathologist, scanned and sent via e-mail to the Responsible CRA listed on the form. The form will indicate whether or not the patient is eligible, and if a discrepancy was found in central vs. local pathology review. If the central review disagrees with local review, then the following may occur:
  - Complete discordance: the patient is ineligible for the trial. The treating physician should inform the patient and determine next steps.
  - Partial discordance: the patient is eligible as they have one of the histologic subtypes allowed on the trial. However, the subtype that they have is discordant between the local and central review. The patient should be informed of the discordance.

After receiving the results form via e-mail, ~~t~~the institution must forward the form to the Alliance Patient Registration office at random01@mayo.edu in order to register the patient. Once the form is forwarded to the Alliance Patient Registration Office and the Registration Eligibility Criteria have been met, the patient can be registered using the OPEN system per Section 4.5. Registration must occur within 21 days of specimen submission. The same patient ID number obtained at pre-registration from the OPEN system should be used to register the patient. Please contact Alliance Patient Registration office at random01@mayo.edu or 507-284-4130 if registration problems occur. **Dose Cohort assignment will be made at registration.** If the patient is ineligible you will need to contact the registration/randomization office to release the slot.

- Once a patient is enrolled on the phase I portion of the study and assigned a dose cohort, one representative from the institution must participate in a bi-weekly conference call. Institutions with a patient enrolled who do not participate in the bi-weekly conference call will be denied future registrations to this study. These calls will be used to review adverse events, discuss dose limiting toxicity, and address any questions that arise over the course of the Phase I. These calls can be attended by the Principal Investigator, a Co-Investigator or the Study Coordinator responsible for A091304 at that site.

4.4 Phase II Patient Enrollment Requirements

4.4.1 Pre-Registration Requirements (Step 0)

- **Cohort Status and Accrual:** Prior to discussing protocol entry with prospective patients, site staff must go to the A091304 study page on the CTSU web site to check cohort status and accrual. Please note that Histologic Cohort 3 is limited to 25 patients and for enrollment associated with Update #05 (Arms 5 and 6). Sites will be notified when the accrual goal has been met for Cohort 3. If the patient has been pre-registered when the accrual has goal has been met for Cohort 3 the patient will be allowed to

proceed to registration. If a patient has been consented but not pre-registgered when the accrual goal has been met for Cohort 3 the patient will not be allowed to register to the study.

- **Informed consent:** the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration.
- **Central pathology review submission:** Patients who meet the pre-registration eligibility criteria (and who have been consented) will be pre-registered using the OPEN registration system (see Section 4.5) in order to submit specimens for central pathology review. Once patient is consented and pre-registered, all representative H&E and IHC slides used locally for diagnosis (Include slides representative of stains for the sarcoma subtype involved) should be sent to:
  Dr. Fabrizio Remotti
  Department of Pathology VC14-215
  Columbia University Medical Center
  630 W 168th St, New York, NY 10032
  Tel: 212-342-0419

  along with a completed "Central Pathology Review Form", per Section 6.2.2. **Failure to submit this form with the specimens will delay turnaround time for central pathology review.** The specimen will be centrally reviewed to confirm study eligibility and histologic cohort assignment. The tissue slides may not be returned.
- **Protected Health Information**: H & E slides will be sent directly to the Department of Pathology of Columbia University Medical Center. These slides will be labeled with patient initials, study ID and collection date.

4.4.2 Patient Registration Requirements (Step 1)

- **Confirmation of eligibility by central pathology review:** Sites will be notified via e-mail within 5 business days of receipt, whether or not the patient is eligible based on the central pathology review. The results section of "Central Pathology Review Form" will be completed by the pathologist, scanned and sent via e-mail to the Responsible CRA listed on the form. The form will indicate whether or not the patient is eligible, and if a discrepancy was found in central vs. local pathology review. If the central review disagrees with local review, then the following may occur:
  - Complete discordance: the patient is ineligible for the trial. The treating physician should inform the patient and determine next steps.
  - Partial discordance: the patient is eligible as they have one of the histologic subtypes allowed on the trial. However, the subtype that they have is discordant between the local and central review. The patient should be informed of the discordance.

  After receiving the results form via e-mail~~,~~ the institution must forward the form to the Alliance Patient Registration office at random01@mayo.edu in order to register the patient. Once the form is forwarded to the Alliance Patient Registration Office and the Registration and Randomization Eligibility Criteria have been met, the patient can be registered using the OPEN system per Section 4.5. Registration must occur within 21 days of specimen submission. The same patient ID number obtained at pre-registration from the OPEN system should be used to register the patient. Please contact Alliance

Patient Registration office at random01@mayo.edu or 507-284-4130 if registration problems occur. **Please note**: If your patient was registered to the wrong histologic cohort due to a discrepancy between the local and central pathology read the patient will be allowed to register to histologic cohort 3 regardless of the number of patients registered to the cohort.

4.5 Patient Enrollment through OPEN

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

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data *and, upon enrollment, initializes the patient in the Rave database.}*. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

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

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

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

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

Phase I patient enrollment: For the phase I portion of the study, patient enrollment will be facilitated using the Slot-Reservation System in conjunction with the Registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to insure that a slot on the protocol is available to the patient. See Section 4.4.1 for more information.

4.6 Re-Registration at the Time of Progression (Step 2, if applicable) (Phase II only)

Note: Effective 12/21/2018, patients will no longer be able to crossover to MLN0128 (TAK-228)

Upon progression on pazopanib, patients may elect to crossover to MLN0128 (TAK-228). **Women of child-bearing potential must have a negative pregnancy test within 7 days prior to re-registration.**

Re-registration procedures: Only for patients originally assigned to Pazopanib:

- For a patient on pazopanib, once they are deemed by their local physician to have progressive disease as per section 11.4.3, they may cross-over to receive MLN0128 (TAK-228).
- Follow OPEN enrollment procedures as detailed in Section 4.5 to register patient to crossover

The OPEN system will provide the registering site with a printable confirmation of re-registration. Please print the confirmation for your records. Further instructional information is provided on the CTSU members' website OPEN tab, or within the OPEN URL. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923, or ctsucontact@westat.com.

Once the patient has been re-registered and crossed over to MLN0128 (TAK-228), the initial shipment of MLN0128 (TAK-228) will arrive within 7-10 days. Patients must cross over within 6 weeks of documented progression and need to have a CT scan within 28 days of starting MLN0128 to serve as a baseline.

4.7 Stratification Factors, Treatment Assignments and Grouping Factors

4.7.1 Phase I

Patients will be directly assigned to a "Dose Cohort" at registration for MLN0128 (TAK-228) treatment. The dose cohorts are defined as follows:

- Dose Level -1: 15 mg MLN0128 (TAK-228) weekly
- Dose Level 0: 20 mg MLN0128 (TAK-228) weekly
- Dose Level 1: 25 mg MLN0128 (TAK-228) weekly
- Dose Level 2: 30 mg MLN0128 (TAK-228) weekly

All patients will be characterized and grouped by histology as follows:

- Histologic Subtype 1: Undifferentiated Pleomorphic Sarcoma (Includes: Malignant Fibrous Histiocytoma, Myxofibrosarcoma, and High Grade Sarcoma NOS),
- Histologic Subtype 2: Leiomyosarcoma (Either: Uterine or Extra-Uterine), and
- Histologic Subtype 3: Other (Either: Malignant Peripheral Nerve Sheath Tumor or Synovial Sarcoma)].

4.7.2 Phase II

As of protocol Update #05, the balancing of treatment arms will re-start for patients enrolled to Arms 5 and 6.

Stratification factors used at the time of patient randomization will include the number of prior systemic anticancer therapies for this cancer (1-2, >2) and the sarcoma histologic subtype [Histologic Cohort 1: Undifferentiated Pleomorphic Sarcoma (Includes: Malignant Fibrous Histiocytoma, Myxofibrosarcoma, and High Grade Sarcoma NOS), Histologic Cohort 2: Leiomyosarcoma (Either: Uterine or Extra-Uterine), Histologic Cohort 3: Other (Either: Malignant Peripheral Nerve Sheath Tumor or Synovial Sarcoma)].

5.0 STUDY CALENDAR

Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- To be completed ≤ 16 DAYS before registration: All laboratory studies, history and physical.
- To be completed ≤ 28 DAYS before registration: Any scan which is utilized for tumor measurement per protocol.
- To be completed ≤ 42 DAYS before registration: Any baseline exams used for screening, or ultrasound of uninvolved organs which is not utilized for tumor measurement.

	Prior to Registration*	Days 1 and 15 of cycles 1 and 2, then Day 1 of cycles 3 and on*†	Post treatment follow up**	At PD, withdrawal, or removal***
Tests & Observations				
History and physical, weight, PS	X	X	X	
Height	X			
Pulse, Blood Pressure	X	X		
ECG Ψ	X	X		
Adverse Event Assessment Ω	X	X	X	
Patient Medication Diary Φ		X	X	
TTE/MUGA π	X			
Registration Fatigue/Uniscale Assessment #	X			
Laboratory Studies				
Complete Blood Count, Differential, Platelets	X	X		
Chemistry (Serum Creatinine, AST, ALT, Alk. Phos., Bili)	X	X		
Fasting glucose	X	X(1)		
Hemoglobin A1c		X(2)		
TSH	X	A		
Serum or Urine HCG	X(3)			
UPC ratio/urine protein	X	A		
Staging				
Central Pathology review for eligibility	X(4)			
CT/MRI chest/abd/pelvis	X (5)	B	B	X
Correlative studies: For patients who consent to participate				
Tissue sample	Archival tissue for banking, see Section 6.2			

* Labs completed prior to registration may be used for day 1 of cycle 1 tests if obtained ≤ 16 days prior to treatment. For subsequent cycles, labs, tests and observations may be obtained +/- 3

days from scheduled day of assessment. Radiographic windows are +/- 7 days from scheduled day of assessment.

** Physical examination, adverse event assessment, and medication diary are required 4 weeks (+/- 7 days) after the end of treatment.

*** Patients discontinuing less than 15 months post-registration for reasons other than progressive disease will have staging scans every 8 weeks (+/- 7 days) until they have reached 15 months post-registration or until documented progression, whichever occurs first. Thereafter, survival information is required every 6 months for 2 years post-registration. For patients who discontinue treatment for progressive disease, survival information is required every 6 months for 2 years post-registration. See also Section 12. For crossover patients after completion of open label MLN0128 (TAK-228), only survival information is required every 6 month for 2 years the date of randomization onto the study.

† Follow this column for crossover patients during therapy.

Ψ ECG at baseline then day 1 of every other cycle, starting with day 1 cycle 3, +/- 3 days. QTc should be calculated using Friderica formula (see Section 3.3.7).

Ω Solicited AEs are to be collected starting at baseline. Routine AEs are to be collected starting after registration. See Section 9.1 for expedited reporting of SAEs.

Φ Medication diary should be completed by the patient throughout treatment, and should be collected at day 1 of every cycle starting with day 1 cycle 2. Completion of the medication diary is mandatory effective with Update #05.

π Baseline echo or MUGA is recommended for patients at risk of cardiac dysfunction, at the discretion of the treating physician.

To be completed after pre-registration and prior to registration, see Appendix I.

1 Glucose needs to be fasting only in patients randomized to MLN0128 (TAK-228).

2 Glycosylated hemoglobin should be checked every 3 cycles in patients receiving MLN0128 (TAK-228) only, starting with day 1 cycle 3.

3 For women of childbearing potential (see Section 3.2). Must be done ≤ 7 days prior to registration, and must be repeated in crossover patients within 7 days of re-registration.

4 See Sections 4.4 and 6.2.

5 Baseline scans can include either: 1) a CT, spiral CT, or MRI, or 2) an FDG-PET scan and diagnostic CT performed with both IV and oral contrast, and the CT acquired with 5 mm or less slice thickness (per Section 11.0). Supporting documentation is to be submitted, per Section 6.1.1.

A Patients randomized in Phase II to receive pazopanib should have TSH and UPC every other cycle starting with day 1 cycle 3.

B Every 8 weeks (e.g. prior to Cycle 3 Day 1) for 1 year, then every 12 weeks until evidence of progression. Scans may be done within +/- 7 days of a scheduled time point. Patients initiating crossover will restart their scanning intervals as every 8 weeks from date of crossover for 6 assessments, followed by every 12 weeks thereafter. **Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline.**

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data collection and submission

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

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

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

A Schedule of Forms is available on the Alliance study webpage, within the Case Report Forms section. The Schedule of Forms is also available on the CTSU site within the study-specific Education and Promotion folder, and is named Time & Events.

6.1.1 Supporting documentation

This study requires supporting documentation for diagnosis and progression. Supporting documentation will include pathology report, radiology report, and clinic note. These must be de-identified and uploaded into iMedidata Rave at registration and progression. Additionally, the "Central Pathology Review Form" confirming eligibility and histologic subtype and histologic cohort assignment must be uploaded via iMedidata Rave on the Screening form.

Effective with Update #05 the Patient Medication Diaries will be required for all patients. The medication diaries will need to be updloaded into iMedidata Rave.

6.2 Specimen collection and submission

For all patients pre-registered to Phase I or Phase II component of Alliance A091304: Real-time histopathology review will be conducted in patients with sarcoma of the following subtypes**:

- HISTOLOGIC COHORT 1: Undifferentiated Pleomorphic Sarcoma (Malignant Fibrous Histiocytoma, Myxofibrosarcoma, High Grade Sarcoma NOS).
- HISTOLOGIC COHORT 2: Leiomyosarcoma (Uterine and Extra-Uterine).
- HISTOLOGIC COHORT 3: Other (Malignant Peripheral Nerve Sheath Tumor and Synovial Sarcoma). NOTE: During the Phase II portion of the study, enrollment will be limited to maximum of 25 patients in this cohort. This applies to those assigned to Arms 5 and 6, as of Update #05.

** Note that the Phase I is limited to the histologic subtypes listed above. Since patients will be enrolling onto Dose Cohorts during the Phase I, they will not enroll onto specific Histologic Cohorts, although the histologic subtype informed will be collected during patient enrollment.

	≤ 3 days from pre-registration	**Submit to:**
Mandatory for all patients pre-registered to A091304:		
All representative H&E and IHC slides used locally for diagnosis (Includinge slides representative of stains for the sarcoma subtype involved.)	X	Columbia (Dr. Remotti)
For patients pre-registered to A091304:**		
Archival FFPE tumor block OR 20 unstained tissue slides* (4-5 microns thickness, if site does not have 20 slides, please send as many as possible, up to 20)	X	OSU

* Slides are acceptable but tumor block is preferred.

**For patients who consent to biobanking for future research: All participating institutions must ask patients for their consent to store samples for future research, although patient participation is optional. Rationale and methods for the scientific components of banking are described in Section 14.0. For patients who consent to participate, a portion of the archival FFPE tumor block OR tissue slides will be stored for future research. Please see section 6.2.1 for BIOMS instructions.

6.2.1 Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers

(Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted H&E, IHC slides and tumor blocks must be labeled with the protocol number (A091304), Alliance patient number, patient's initials and date and type of specimen collected. If you are submitting unstained slides as block alternative, please make sure each each slide is labeled with the specimen surgical pathology number and block number either via your institution's standard method for labeling clinical slides or using a permanent marker. **Please DO NOT use sticky labels**.

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens to both Dr. Remotti's office and the Alliance biorepository at Ohio State University.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Shipment on Monday through Thursday by overnight service to assure receipt is encouraged. Do not ship specimens on Fridays or Saturdays.

All representative H&E and IHC slides used locally for diagnosis for pathology review including slides representative of stains for the sarcoma subtype involved should be sent to:

Dr. Fabrizio Remotti
Department of Pathology VC14-2015
Columbia University Medical Center
630 W 168th St, New York, NY 10032
Tel: 212-342-0419

Tumor blocks (or up to 20 unstained slides) should be sent to the following address:

Alliance Biorepository at Ohio State University
Department of Pathology
Polaris Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Tel: 614-293-7073 Fax: 614-293-7967

6.2.2 Collection and processing of tissue

When shipping blocks and /or FFPE slides, it is important to avoid extreme heat. If environmental conditions indicate, specimens may be shipped in containers containing cold packs. The diagnostic slides must be appropriately packed to prevent damage (e.g. slides should be placed in appropriate slide container) and placed in an individual plastic bag. It is also important that blocks are shipped in appropriately padded and secure containers to avoid physical damage. Do not wrap blocks or slides in tissue or paper toweling that is in direct contact with the paraffin.

The Alliance has instituted special considerations for the small percentage of institutions whose policy prohibits long-term storage of blocks, and the smaller percentage of institutions whose policies prohibit release of any block. For those instituations, please submit 20 unstainded slides (thickness of 4-5 microns) as block alternatives (if the istituton does not have 20 slides, please send as many as possible, up to 20).

The goal of the Alliance is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All slides/blocks may be returned with written request by the site.

A de-identified surgical pathology report should be sent with all specimens. Usually, this is generated by obscuring all PHI (names and dates) with white-out or a black magic marker, labeling each page of the report with the Alliance patient ID, and photocopying the report.

Central Pathology Review

Consistent and accurate histologic grading is important for this study. All **representative** H&E and IHC slides including slides representative of stains for the sarcoma subtype involved from the diagnostic biopsy must be submitted to Dr. Remotti. Please be aware that those slides will not be returned. If slides used locally for diagnosis can't not be released, please make a separate set of slides for this study. The submission should be taken from the highest grade area as identified by your local pathologist/investigator.

In addition to the pathology report, the institution must complete and submit the "Central Pathology Review Form" with slides to Dr. Remotti. Failure to submit this form with the specimens will delay turnaround time for central pathology review. The top portion of the form must be completed by typing and cannot be handwritten. For Alliance members, the form may be found on the A091304 study page on the Alliance website under the "Supplemental Materials" tab. For non-Alliance institutions, the form can be found under "Miscellaneous" documents section of the CTSU A091304 study page (www.ctsu.org).

Tissue Banking

A FFPE tumor block **OR** up to 20 unstained tissue slides (thickness of 4-5 microns) of the patient's locally advanced/unresectable and/or metastatic sarcoma of selected subtypes diagnosis should be retrieved from the surgical pathology department. Blocks which contain minimal amounts of tissue specimen or that are very thin should not be submitted unless the block is the only representative tissue for the case.

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin ≤ 10 days of registration. For questions regarding treatment, please see the study contacts page.

Administration ≤ +/- 1 day of schedule will not be considered a protocol violation. In addition, patients are permitted to have a new cycle of therapy delayed up to 7 days for major life events (e.g., serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

7.1 Phase I Description and Treatment Plan

The Phase I portion of this study will assess safety and tolerability of the new milled dosage of MLN0128 (TAK-228). Protocol therapy will consist of MLN0128 (TAK-228) administered weekly on days 1, 8, 15, and 22 over a 28 day cycle. MLN0128 (TAK-228) should be taken on an empty stomach. A patient medication diary will be used to assess adherence to therapy.

Patients may remain on treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

7.1.1 Phase I- Determination of Maximum Tolerated Dose (MTD)

Dose Levels

All patients on the phase I portion of the study will receive MLN0128 (TAK-228). This will be a dose-escalation scheme to determine the MTD of MLN0128 (TAK-228). Patients will be placed in one of the dose cohorts of MLN0128 (TAK-228) listed below, using a conventional 3+3 design. Only the first cycle will be used to determine dose limiting toxicity.

The dose of MLN0128 (TAK-228) will be dictated by the dose cohort to which a patient is assigned. Patients will be assigned to a new dose cohort only after it has been determined that the MTD has not been exceeded in the previous dose cohort (see section 13.2.2 for details).

Table 7.1.1 Phase I Dose Finding Plan

Dose Level	MLN0128 (TAK-228) weekly (Days 1, 8, 15, 22)
-1	15mg
*0	20 mg
1	25 mg
2	30 mg

* Starting dose level

- **Plan:** Three to 6 patients will be treated at each dose level and observed for a minimum of 28 days to assess adverse events in cycle 1 before new patients are treated. The MTD will be determined by DLTs seen in cycle 1 of therapy (please refer to section 13.2.2 for details regarding definition of the MTD and criteria for dose level escalation and de-escalation). Please note that if the DLTs are met at dose level 0, then dose level -1 will be initiated.
- **Intrapatient dose escalation:** Intra-patient escalation of dosing is allowed if it has been determined that the MTD has not been exceeded for the next dose level, and the patient has not required any dose modifications or delays as a result of adverse events. Intrapatient escalation will be managed during the toxicity calls, and is only allowed if approved by the Alliance study chair and executive officer.
- **Missed doses:** A dose may be made up as long as it is taken within 24 hours of the scheduled dose. For patients who have a missed dose in excess of 24 hours, they will be replaced for purposes of the dose finding plan. If they miss doses during cycle 2 and beyond, the patients will not be replaced during the phase I portion of this study.
- **Toxicity calls:** Phase I conference calls will be held every other week and are mandatory for all sites with a patient registered on the phase I portion of the study. These calls will be used to review adverse events, assess study enrollment and address any questions that arise over the course of the study. These calls will be attended by the study team (Study chair, statistician, executive officer, and protocol coordinator). Site staff attendance can be the Principal Investigator, a Co-

Investigator or the Study Coordinator responsible for A091304 at that site. In addition, a Dose Escalation conference call will be held immediately after a dose cohort has completed accrual and all patients have been treated for 28 days (1 cycle). All phase I Principal Investigators should participate in these calls.

7.1.2 Definitions of DLT

DLTs will be determined during cycle 1 of therapy. Adverse events will be graded per CTCAE, version 4.0.

For this protocol, DLT will be defined by the following adverse events at least possibly related to study therapy:

Grade 3 or higher non-hematologic adverse events, with the following exceptions:

- Alopecia is not expected but is not considered a DLT
- Nausea, vomiting and diarrhea
- Hypokalemia, Hypomagnesemia, Hypophosphatemia
- Hyperglycemia
- Rash
- Fatigue

Grade 4 hematologic adverse events, with the following exceptions:

- Grade 4 lymphopenia
- Grade 4 neutropenia will only be considered a DLT if it lasts longer than 7 days
- Grade 4 thrombocytopenia will only be considered a DLT if it lasts longer than 7 days or is associated with a ≥grade 3 bleeding event.

The maximum tolerated dose is the dose level where at most 1 out of 6 patients treated at that dose level report a DLT and the next higher dose level is such that 2 or more patients treated at that dose level reported a DLT.

7.2 Phase II Description and Treatment Plan

Patients with locally advanced/unresectable and/or metastatic sarcoma of selected subtypes will be randomized in a 1:1 fashion to receive either MLN0128 (TAK-228) at 30 mg weekly or pazopanib. Pazopanib will start at 400mg orally once daily and titrated to tolerance by the treating physician. At the day 15 visit of cycle 1 and 2, decisions will be made to escalate the pazopanib. For example, at Day 15 of Cycle 1, attempts will be made to escalate the patient to 600mg once daily based. The patient will be seen again on Day 1 of Cycle 2 for a toxicity check. On Day 15 of Cycle 2, reassessment will be made for dose escalation to 800mg. Escalations will be in a stepwise fashion of 200mg. If the treating physician decides not to escalate at these times, they can use their clinical judgement as to the timing of any escalation or the highest pazopanib dose that is clinically safe for the patient to receive. The pazopanib dose will not exceed 800 mg orally once daily.

Pazopanib should be taken without food at least two hours after and one hour before a meal. The tablets should be swallowed whole and must not be crushed or broken. The time of day the tablets are taken should be relatively constant. **For patients receiving a medically necessary H2-receptor antagonist,** pazopanib should be taken without food at least 2 hours before or at least 10 hours after a dose of the H2-receptor antagonist. Pazopanib should be administered at least 1 hour before or 2 hours after administration of short acting antacids.

In patients who are randomized to pazopanib, the patient may crossover to MLN0128 (TAK-228) at time of progression (see Section 4.7). If a patient does crossover, MLN0128 (TAK-228) must begin within 6 weeks of the last dose of pazopanib on study. If restaging imaging has not been done within 28 days before treatment with MLN0128 (TAK-228), it must be repeated.

At the time of crossover, pregnancy test must be repeated. Other lab tests and observations will be performed per study calendar in Section 5.0.

Patients will remain on treatment as long as there is no progression of disease, excessive toxicity requiring the patient to come off of treatment, or the patient withdraws from treatment.

ARMS 1, 5 and crossover (Arm 3):

Agent	Dose & Route	Frequency	Cycle Length (ReRx)
MLN0128 (TAK-228)	30 mg PO	Weekly	every 4 weeks

ARM 2 (patients enrolled prior to Update #05):

Agent	Dose & Route	Frequency	Cycle Length (ReRx)
Pazopanib	800 mg PO	Once daily	every 4 weeks

ARM 6 (patients enrolled after Update #05):

Agent	Dose & Route	Frequency	Cycle Length (ReRx)
Pazopanib	400 mg PO to start, with escalations as outlined in section 7.2	Once daily	every 4 weeks

7.3 CYP3A4 Inhibitors

Chronic concomitant treatment with strong inhibitors of CYP3A4 is not allowed on this trial. The following drugs are EXAMPLES of strong inhibitors of CYP3A4 and are not allowed during treatment with pazopanib.

- Indinavir
- Clarithromycin
- Ketoconazole

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to inhibit CYP3A4. Examples of resources that may be utilized include the product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA and/or IUPUI websites, or your local institution's pharmacist.

7.4 CYP3A4 Inducers

Chronic concomitant treatment with strong inducers of CYP3A4 is not allowed during on this trial. The following drugs are EXAMPLES of strong inducers of CYP3A4 and are not allowed during treatment with pazopanib.

- Rifampin
- Carbamazepine

Because lists of these agents are constantly changing, please consult and review any drugs for their potential to induce CYP3A4. Examples of resources that may be utilized include the

product information for the individual concomitant drug in question, medical reference texts such as the Physicians' Desk Reference, the FDA and/or IUPUI websites, or your local institution's pharmacist.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary therapy, concomitant medications, and supportive care

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment with hormones or other chemotherapeutic agents may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic in solid tumor protocols.

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

8.1.5 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

8.1.6 Palliative radiation therapy may **not** be administered. Irradiate a symptomatic lesion, or one that may produce disability (e.g., unstable femur) prior to study initiation, provided other measurable disease is present.

Patients who require radiation therapy during protocol treatment will be removed from protocol therapy due to disease progression.

8.1.7 Surgery: Patients who require surgery during protocol treatment may proceed as such, unless the surgery involves resection of sarcoma. Pazopanib should be held prior to and after surgery, for a maximum of 28 days. If the patient requires an interruption of > 28 days, then they will be removed from protocol therapy.

8.1.8 Pneumonitis: Patients with suspected pneumonitis should undergo full evaluation, which may include CT scan, PFTs, O2 saturation, bronchoscopy. Treatment may involve steroids, at the discretion of the treating physician.

8.1.9 Alliance Policy Concerning the Use of Growth Factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of

Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based, Clinical Practice Guideline. J Clin Oncol 24(19): 3187-3205, 2006.

Epoetin (EPO): Use of epoetin in this protocol is permitted at the discretion of the treating physician.

Filgrastim (G-CSF) and sargramostim (GM-CSF)

1. Filgrastim (G-CSF)/pegfilgrastim and sargramostim (GM-CSF) treatment for patients on protocols that do not specify their use is discouraged.
2. Filgrastim/pegfilgrastim and sargramostim may not be used:
   a. To avoid dose reductions, delays or to allow for dose escalations specified in the protocol.
   b. For the treatment of febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented.
   c. If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

8.1.10 Hyperglycemia:

Phase I

Most episodes of hyperglycemia occur within the first 60 days after initiation of treatment with TAK-228. Patients developing hyperglycemia during the study should have their glucose closely monitored, at a frequency that is at the discretion of the treating physician. With ≥Grade 2 hyperglycemia it is recommended to treat with oral hypoglycemic agents and/or insulin. The investigator should consult an endocrinologist, if needed. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution, due to the higher risk of inducing hypoglycemia in patients.

Phase II

Management of Hyperglycemia

On the basis of the clinical experience in TAK-228 trials, most episodes of hyperglycemia observed occurred within the first 60 days after initiation of treatment with TAK-228 and have been either Grade 1 or Grade 2, and have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since the institution of a standard regimen for early treatment of hyperglycemia.

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

It is recommended that patients with elevated fasting blood glucose be initially treated with a fast acting insulin sensitizer such as metformin at 500 mg orally QD, and titrate up to a maximum of 1000 mg orally BID as needed. Concurrent addition to metformin of DPP-4

inhibitors (eg, sitagliptin or vildagliptin) and/or insulin should also be considered. Oral sulfonylureas (eg, glipizide or glyburide) should be used with caution, due to the higher risk of inducing hypoglycemia in patients. The dose of oral hypoglycemic agents should be adjusted in patients with renal insufficiency. In addition, patients should be encouraged to follow a low carbohydrate diet once hyperglycemia is first observed.

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

In-Home Daily Fasting Glucose Monitoring

In addition to obtaining fasting glucose levels at the clinic visits as outlined in the study calendar (Section 5.0), all patients randomized to receive MLN0128/TAK-228 will be given a glucometer to monitor their daily FBG levels at home. The level should be collected daily, predose on dosing days, and at approximately the same time each day. The glucometer reimbursement form can be found under Supplemental Materials (on the Alliance web site) and under MISC (on the CTSTU web site).

On Cycle 1 Day 1, the patient will be provided an in-home glucometer. Patients should be trained on proper use of the glucometer and instructed to collect a daily FBG level every morning (predose on dosing days), starting on Cycle 1 Day 2. Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia.

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

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

8.2 Dose Modifications

8.2.1 General Rules

- If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed.
- Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.
- MLN0128 (TAK-228) or pazopanib will not be re-escalated once reduced.
- If dose reduction beyond dose level -2 for MLN0128 (TAK-228) is required or MLN0128 (TAK-228) or pazopanib is held for 4 weeks, MLN0128 (TAK-228) or pazopanib will be discontinued.
- Descriptors below utilize CTCAE version 4.03. AERs reporting may be required for some adverse events (See Section 9.0).
- Dose reductions for pazopanib are based on the criteria listed in section 8.2.5. Dose reductions for pazopanib will be made in 200mg increments. Patients cannot be dose reduced below 200mg of pazopanib, therefore three dose reductions are allowed for patients receiving 800mg of pazopanib, two dose reductions for patients receiving 600mg, and only one dose reduction for patients receiving 400mg. Patients must come off study if a dose reduction is required at 200mg.

8.2.2 Dose Modification Levels for Phase I

Please note that the MLN0128 (TAK-228) starting dose in the phase I portion of the protocol will be dictated by the dose level to which the patient is assigned.

Dose Level	Drug Name	Dose (weekly)	Dose (weekly)	Dose (weekly)	Dose (weekly)
0*	MLN0128 (TAK-228)	15mg	20. mg	25 mg	30 mg
-1	MLN0128 (TAK-228)	10mg	15 mg	20 mg	20 mg
-2	MLN0128 (TAK-228)	8mg	10 mg	15 mg	15 mg

*Dose level 0 refers to the starting dose in the dose cohort to which the patient has been assigned.

8.2.3 Dose Modification Levels for Phase II

Arms 1, 5, and Crossover (Arm 3)

Dose Level	Drug Name	Dose (weekly)
0*	MLN0128 (TAK-228)	30mg weekly
-1	MLN0128 (TAK-228)	20mg weekly
-2	MLN0128 (TAK-228)	15mg weekly

*Dose level 0 refers to the starting dose.

Arm 2 (patients enrolled prior to Update #05)

Dose Level	Drug Name	Dose (daily)
0*	Pazopanib	800mg once daily
-1	Pazopanib	600mg once daily
-2	Pazopanib	400mg once daily
-3	Pazopanib	200mg once daily

*Dose level 0 refers to the starting dose.

Arm 6 (patients enrolled after Update #05)

Dose Level	Drug Name	Dose (daily)
+2	Pazopanib	800mg once daily
+1	Pazopanib	600mg once daily
0*	Pazopanib	400mg once daily
-1	Pazopanib	200 mg once daily

*Dose level 0 refers to the starting dose.

8.2.4 MLN0128 (TAK-228)

Hematologic Toxicities

Grade ≥3 neutropenia, thrombocytopenia, or neutropenic fever: Delay MLN0128 (TAK-228) until ≤ grade 2, then resume with one dose level reduction of MLN0128 (TAK-228) for all subsequent doses.

Gastrointestinal Toxicities

- **Grade ≥ 3 diarrhea:** Delay MLN0128 (TAK-228) until diarrhea improves to ≤ grade 2, then resume MLN0128 (TAK-228) with one dose level reduction.
- **Grade ≥ 3 nausea or vomiting:** Delay MLN0128 (TAK-228) until nausea/vomiting improves to ≤ grade 2, then resume MLN0128 (TAK-228) at same dose
- **Grade 3 stomatitis:** Delay MLN0128 (TAK-228) until ≤ grade 1 then resume with one dose level reduced.
- **Grade 4 stomatitis:** Discontinue MLN0128 (TAK-228)

Skin Toxicity

- **Grade 3 or 4 Acneiform Rash:** Delay MLN0128 (TAK-228) until grade ≤ 2, then restart at one dose level decreased

- **Grade 3 Maculopapular Rash:** Delay MLN0128 (TAK-228) until grade ≤ 2, then restart at one dose level decreased

Pulmonary Toxicity

- **Grade 2 or 3 pneumonitis:** Delay MLN0128 (TAK-228) until ≤ grade 1, then resume MLN0128 (TAK-228) at one dose level decreased. For recurrent grade 3 pneumonitis, discontinue TAK-228.
- **Grade 4 pneumonitis:** Discontinue MLN0128 (TAK-228)

Renal Toxicity

- **Grade 2 increased creatinine:** Delay MLN0128 (TAK-228) until grade ≤ 1, then resume with one dose level decreased
- **Grade 3 and 4 increased creatinine:** Discontinue MLN0128 (TAK-228)

Metabolism

- **Grade 3 Hyperglycemia:** Delay MLN0128 (TAK-228) until grade ≤ 2, then resume at same dose
- **Grade 4 Hyperglycemia:** Discontinue MLN0128 (TAK-228)

Cardiac Toxicity

- **For grade 3 ECG QTc interval prolonged,** delay MLN0128 (TAK-228) until grade ≤ 1, then resume MLN0128 (TAK-228) with one dose level reduction
- **For grade 4 ECG QTc interval prolonged,** discontinue MLN0128 (TAK-228)

General Disorders

- **Grade 3 Edema:** Delay MLN0128 (TAK-228) until ≤ grade 2, then resume at one dose level decreased

Other Non-hematologic Toxicities

For other clinically significant grade 3/4 non-hematologic toxicities likely related to MLN0128 (TAK-228), delay MLN0128 (TAK-228). Resume MLN0128 (TAK-228) at 1 dose level reduced when the toxicity resolves to a clinically acceptable level (grade 1/2).

8.2.5 Pazopanib

Hematologic toxicity

- **For grade 3 ANC on Day 1 of a cycle:** Delay pazopanib until ≤ grade 2, then resume pazopanib at the previous dose level.
- **For grade 4 ANC on Day 1 of a cycle:** Delay pazopanib until ≤ grade 2, then resume pazopanib with one dose level reduction.
- **For grade 3 or 4 ANC decreased during a cycle** omit pazopanib until ANC improves to ≤ grade 2, then resume pazopanib with one dose level reduction.
- **Febrile neutropenia:** Delay pazopanib until toxicity resolves and ANC ≤ grade 2, then resume pazopanib with one dose level reduction.
- **For grade 3 or 4 thrombocytopenia:** Delay pazopanib until platelets ≤ grade 1, then resume pazopanib with one dose level reduction.

Hepatic Toxicity

- **For grade 2 ALT, AST, or bilirubin,** continue pazopanib, but monitor weekly until ALT, AST, and bilirubin return to ≤ grade 1.
- **For grade 3 or 4 ALT, AST, or Bilirubin,** delay pazopanib. Restart treatment with one dose level reduction of pazopanib when AST, ALT and bilirubin improve to ≤ grade 1.
- **For grade ≥ 2 ALT/AST AND concurrent grade ≥ 2 bilirubin,** discontinue pazopanib.
- **For ≥ grade 3 hepatic failure,** discontinue pazopanib.
- **For any AST/ALT elevation occurring in a patient receiving simvastatin,** discontinue simvastatin and follow the appropriate dose modification for pazopanib.

Proteinuria

- **For UPC Ratio ≥ 2.0 and < 3.0 or urine protein ≥ 2.0 g/24 hours and < 3.0,** hold pazopanib until proteinuria resolves to UPC < 2.0 or urine protein < 2.0 g/24 hours, then resume pazopanib at current dose level.
- **For UPC Ratio ≥ 3.0 and < 4.0 or urine protein ≥ 3.0 g/24 hours and < 4.0,** hold pazopanib until proteinuria resolves to UPC < 2.0 or urine protein <2.0 g/24 hours. Once resolved, resume pazopanib with one dose level reduced.
- **For UPC Ratio ≥ 4.0 or Nephrotic Syndrome:** Discontinue pazopanib.

Nephrotoxicity

- **For grade 2 creatinine increased,** delay pazopanib until toxicity resolves to ≤ grade 1, then resume pazopanib with one dose level reduction.
- **For grade 3 or 4 creatinine increased,** discontinue pazopanib.

Cardiac Toxicity

- **For grade 3 ECG QTc interval prolonged,** delay pazopanib until grade ≤ 1, then resume pazopanib with one dose level reduction
- **For grade 4 ECG QTc interval prolonged,** discontinue pazopanib

Thrombosis

- **For grade 2 or 3 venous thrombosis requiring anticoagulation,** delay pazopanib. If the planned duration of full dose anticoagulation is ≤ 2 weeks, omit pazopanib until anticoagulation is completed, then resume pazopanib at same dose. If the planned duration of full dose anticoagulation is > 2 weeks, pazopanib may be restarted at same dose during anticoagulation if all of the following are met:
    - The patient must have an in-range INR (usually between 2 and 3) on a stable dose of warfarin or be on a stable dose of LMWH prior to restarting pazopanib.
    - The patient must not have any pathological condition that carries a high risk of bleeding.
    - The patient must not have had any hemorrhagic events while on study.
- **For recurrent/worsening venous thromboembolic events** after resumption of pazopanib, discontinue pazopanib.
- **For grade 4 venous thromboembolic events,** discontinue pazopanib.

- **For arterial thromboembolic events (any grade)** including cerebrovascular ischemia, cardiac ischemia/infarction, peripheral or visceral arterial ischemia, discontinue pazopanib.

Hypertension

- **For persistent Grade 3 hypertension (Systolic ≥ 160 Diastolic ≥ 100):** Hold pazopanib until grade ≤ 2, then resume pazopanib at1 dose level reduction. HOWEVER, if the patient requires hospitalization for management of symptomatic systolic BP > 180 or diastolic BP > 110, permanently discontinue pazopanib.
- **Grade 4 Hypertension (life-threatening consequences of hypertension):** Permanently discontinue pazopanib.

  NOTE: Stopping or reducing the dose of pazopanib is expected to cause a decrease in BP. The treating physician should monitor for hypotension and adjust the number and dose of antihypertensive medication(s) accordingly.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

For signs and symptoms suggestive of RPLS, delay pazopanib. If RPLS is confirmed by MRI, discontinue pazopanib. If RPLS is ruled out via MRI, the decision to resume pazopanib should be based on symptoms: for grade ≥ 2 RPLS considered ≥ possibly related to pazopanib, discontinue pazopanib.

Hemorrhage

- **For grade 2 CNS or pulmonary hemorrhage,** discontinue pazopanib.
- **For non-CNS, non-pulmonary grade 2 bleeding**, delay pazopanib until resolved to ≤ grade 1, then resume at 1 dose level reduced.
- **For any grade 3 or 4 hemorrhage,** discontinue pazopanib.

Fistula, perforations, bowel obstruction or wound dehiscence

- **For any grade perforation** of any organ, GI leak, or any fistula, discontinue pazopanib.
- **For any grade bowel obstruction requiring medical intervention,** delay pazopanib until obstruction resolves completely, then resume pazopanib at the previous dose. For obstruction requiring surgery delay pazopanib until full recovery from surgery, then resume pazopanib at the previous dose. Also see Section 8.1.7
- **For wound dehiscence** requiring medical or surgical intervention discontinue pazopanib.

Thyroid Dysfunction

For grade 3 or 4 hyper-or hypothyroidism, discontinue pazopanib.

Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura

For any grade of hemolytic uremic syndrome (thrombotic microangiopathy) or thrombotic thrombocytopenic purpura, discontinue pazopanib.

Other Non-Hematologic Grade 3 or 4 Toxicity

For other grade 3 or 4 non-hematologic toxicity not described above, (excluding nausea, vomiting, and diarrhea; unless refractory to anti-emetics and/or anti-diarrheals) and considered at least possibly related to treatment, delay pazopanib treatment until toxicity improves to ≤ grade 1, then resume treatment with one dose level reduction.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. **However, CTCAE v5.0 must be used for serious AE reporting through CTEP-AERS as of April 1, 2018.** The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

9.1 Routine adverse event reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 5.0. For this trial, "Adverse Events: Baseline" and "Adverse Events: Solicited" will be used for routine AE reporting in Rave.

Solicited Adverse Events: The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment.

CTCAE v4.0 Term	CTCAE v4.0 System Organ Class (SOC)
Rash maculo-papular	Skin and subcutaneous tissue disorders
Hyperglycemia	Metabolism and nutrition disorders
Anorexia	Metabolism and nutrition disorders
Diarrhea	Gastrointestinal disorders
Mucositis oral	Gastrointestinal disorders
Fatigue	General Disorders and Administration Site Conditions
Neutrophil count decreased	Blood and Lymphatic System Disorders
Platelet count decreased	Blood and Lymphatic System Disorders
Electrocardiogram QT corrected interval prolonged	Cardiac Disorders
Hypertension	Vascular Disorders

9.2 CTCAE Routine Study Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

***Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible	a	a	a, b	a, b	a, b
Probable	a	a	a, b	a, b	a, b
Definite	a	a	a, b	a, b	a, b

a) Adverse Events: Other CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Adverse Events: Late CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date and applies to Grade 3-5 events considered at least possibly related to study treatment.

9.3 Expedited Adverse event reporting (CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Investigational Drug Branch (IDB), the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All reactions determined to be "reportable" in an expedited manner must be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS).

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

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

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

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

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

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

outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

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

Hospitalization	• Grade 1 Timeframes	• Grade 2 Timeframes	• Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour; 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS ≤ 24 hours of learning of the event followed by a complete CTEP-AERS report ≤ 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted ≤ 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusion to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Alliance A091304 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.
- Grade 3/4 hematosuppression and hospitalization resulting from such do not require CTEP-AERS, but should be submitted as part of study results. All other grade 3, 4, or 5 adverse events that precipitate hospitalization or prolong an existing hospitalization must be reported via CTEP-AERS.
- The AML/MDS Secondary Reporting form is no longer available on the CTEP website. In lieu of this form, AML/MDS events are now to be reported.
- Treatment expected adverse events include those listed in the package insert and in the CAEPR for pazopanib. Note that the ASAEL column of the CAEPR has been replaced with the Specific Protocol Exceptions to Expedited Reporting (SPEER) column. The SPEER includes "expected" severity grades in addition to event terms. Events listed in the SPEER only require expedited reporting if the severity grade is above the grade noted in SPEER.
- CTEP-AERS reports should be submitted electronically.
- When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and submitted, along with any additional medical information (form is available on the CTEP website at http://ctep.cancer.gov/). The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.
- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.
- Pregnancy loss is defined in CTCAE as "Death in utero." Any Pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.
- A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

9.4 CAEPRs

9.4.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pazopanib (GW786034, NSC 737754)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2383 patients. Below is the CAEPR for Pazopanib (GW786034)

NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.8, January 31, 2019[1]

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Hemolytic uremic syndrome[2]	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Cardiac disorders - Other (Torsades de Pointes)	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction	
	Sinus bradycardia		
ENDOCRINE DISORDERS			
	Hypothyroidism		
EYE DISORDERS			
		Eye disorders - Other (eye hemorrhage, retinal hemorrhage)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		
		Gastrointestinal fistula[3]	***Gastrointestinal fistula[3] (Gr 2)***
		Gastrointestinal hemorrhage[4]	
		Gastrointestinal perforation[5]	***Gastrointestinal perforation[5] (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
		Infection[6]	
INVESTIGATIONS			
	Activated partial thromboplastin time prolonged		
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 4)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 3)***
Blood bilirubin increased			***Blood bilirubin increased (Gr 3)***
	Creatinine increased		***Creatinine increased (Gr 2)***
		Ejection fraction decreased	
		Electrocardiogram QT corrected interval prolonged	
Lymphocyte count decreased			***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
White blood cell decreased			***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 3)***
	Hypercalcemia		
Hyperglycemia			***Hyperglycemia (Gr 2)***
	Hyperkalemia		***Hyperkalemia (Gr 2)***
	Hypermagnesemia		
	Hypernatremia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		***Hypocalcemia (Gr 3)***
	Hypoglycemia		***Hypoglycemia (Gr 2)***
	Hypokalemia		
	Hypomagnesemia		
Hyponatremia			***Hyponatremia (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		

Adverse Events with Possible Relationship to Pazopanib (GW786034) (CTCAE 5.0 Term) [n= 2383]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
	Tumor pain		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
		Intracranial hemorrhage	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Hematuria	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	***Urinary fistula (Gr 2)***
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
		Reproductive system and breast disorders - Other (female genital tract fistula)	***Reproductive system and breast disorders - Other (female genital tract fistula) (Gr 2)***
		Uterine fistula	***Uterine fistula (Gr 2)***
		Vaginal fistula	***Vaginal fistula (Gr 2)***
		Vaginal hemorrhage	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Respiratory hemorrhage[7]		***Respiratory hemorrhage[7] (Gr 2)***
		Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[8]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		***Alopecia (Gr 2)***
Hair color changes			***Hair color changes (Gr 2)***
	Palmar-plantar erythrodysesthesia syndrome		
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism[9]	
Hypertension			***Hypertension (Gr 3)***
		Thromboembolic event[9]	

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

[2]Thrombotic microangiopathy (TMA) which includes both Hemolytic uremic syndrome (HUS) and Thrombotic thrombocytopenic purpura (TTP) has been reported in clinical trials of GW786034.

[3]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Enterovesical fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[4]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[6]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[7]Respiratory hemorrhage includes Bronchopulmonary hemorrhage, Epistaxis, Laryngeal hemorrhage, Mediastinal hemorrhage, Pharyngeal hemorrhage, and Pleural hemorrhage under the RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS SOC.

[8]Interstitial lung disease may include, Adult respiratory distress syndrome, Pneumonitis, Pulmonary fibrosis, Respiratory, thoracic and mediastinal disorders - Other (Acute respiratory distress syndrome), Respiratory, thoracic and mediastinal disorders - Other (Aveolitis), Respiratory, thoracic and mediastinal disorders - Other (Bronchiolitis obliterans), Respiratory, thoracic and mediastinal disorders - Other (Interstitial fibrosis), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Interstitial pneumonitis), Respiratory, thoracic and mediastinal disorders - Other (Organizing pneumonia), Respiratory, thoracic and mediastinal disorders - Other (Pulmonary infiltrates), Respiratory, thoracic and mediastinal disorders - Other (Toxic pneumonitis).

[9]These events can result in life-threatening pulmonary, cardiac, cerebral, and other complications.

Adverse events reported on pazopanib (GW786034) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that pazopanib (GW786034) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (sinus arrest); Cardiac disorders - Other (supraventricular extrasystoles); Cardiac disorders - Other (Takotsubo [Broken Heart Syndrome]); Chest pain - cardiac; Pericardial effusion; Supraventricular tachycardia
ENDOCRINE DISORDERS - Adrenal insufficiency
EYE DISORDERS - Blurred vision; Dry eye; Eye disorders - Other (asthenopia); Eye disorders - Other (foreign body sensation in eyes); Eye pain; Floaters; Glaucoma; Photophobia; Retinal tear
GASTROINTESTINAL DISORDERS - Abdominal distension; Dry mouth; Duodenal obstruction; Dysphagia; Esophagitis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (hyperactive bowel); Gastrointestinal disorders - Other (pneumatosis intestinalis); Gastrointestinal pain; Oral pain; Pancreatitis; Periodontal disease; Proctitis; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Malaise; Non-cardiac chest pain; Pain
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising
INVESTIGATIONS - Blood lactate dehydrogenase increased; Cardiac troponin T increased; Cholesterol high; GGT increased; INR increased; Investigations - Other (blood TSH increased); Lipase increased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Hypertriglyceridemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Chest wall pain; Generalized muscle weakness; Head soft tissue necrosis; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain
NERVOUS SYSTEM DISORDERS - Extrapyramidal disorder; Ischemia cerebrovascular; Memory impairment; Paresthesia; Peripheral sensory neuropathy; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Reproductive system and breast disorders - Other (vaginal necrosis); Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Laryngeal edema; Oropharyngeal pain; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumothorax; Postnasal drip; Sore throat; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Pruritus; Purpura; Skin hyperpigmentation; Skin ulceration
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Vasculitis

Note: Pazopanib (GW786034) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.4.2 Comprehensive Adverse Events and Potential Risk list (CAEPR) For MLN0128 (TAK-228) (INK128, NSC 768435)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 311 patients.* Below is the CAEPR for MLN0128 (TAK228).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, April 26, 2016[1]

Adverse Events with Possible Relationship to MLN0128 (TAK228) (CTCAE 4.0 Term) [n= 311]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac arrest	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
Mucositis oral			***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	General disorders and administration site conditions - Other (mucosal inflammation)		***General disorders and administration site conditions - Other (mucosal inflammation) (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Urinary tract infection		***Urinary tract infection (Gr 2)***
INVESTIGATIONS			
	Creatinine increased		***Creatinine increased (Gr 2)***
		Electrocardiogram QT corrected interval prolonged	
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 2)***
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		

Adverse Events with Possible Relationship to MLN0128 (TAK228) (CTCAE 4.0 Term) [n= 311]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Back pain		***Back pain (Gr 2)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
PSYCHIATRIC DISORDERS			
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
	Respiratory, thoracic and mediastinal disorders - Other (oropharyngeal pain)		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Pruritus			***Pruritus (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***

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

Adverse events reported on MLN0128 (TAK228) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MLN0128 (TAK228) caused the adverse event:

CARDIAC DISORDERS - Heart failure; Pericardial effusion; Sinus tachycardia
EYE DISORDERS - Blurred vision; Eye disorders - Other (visual acuity reduced); Eye pain; Photophobia
GASTROINTESTINAL DISORDERS - Dyspepsia; Dysphagia; Esophagitis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (intestinal obstruction); Oral pain; Pancreatitis; Small intestinal obstruction; Small intestinal perforation; Toothache
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Gait disturbance; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Gallbladder obstruction
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Kidney infection; Lung infection; Sepsis; Skin infection; Upper respiratory infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Tracheal obstruction

INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cholesterol high; Lymphocyte count decreased; Neutrophil count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Metabolism and nutrition disorders - Other (vitamin D deficiency)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Flank pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Nervous system disorders - Other (carotid artery occlusion); Tremor
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Personality change
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Urinary tract pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Nasal congestion; Pleural effusion; Pneumothorax; Postnasal drip; Productive cough
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Rash acneiform; Urticaria
VASCULAR DISORDERS - Flushing; Hypotension; Thromboembolic event

Note: MLN0128 (TAK228) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.0 DRUG INFORMATION

10.1 Pazopanib (Commercial; IND Exempt)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for oral administration as:

Tablets: 200 mg

Preparation, Storage and Stability

Refer to package insert for complete dispensing instructions. Store tablets at room temperature between 20ºC and 25ºC (68ºF and 77ºF); excursions permitted between 15ºC and 30ºC (59ºF and 86ºF).

Administration

Refer to the treatment section for specific administration instructions. The manufacturer recommends pazopanib be administered on an empty stomach, 1 hour before or 2 hours after a meal. Do not crush tablet (rate of absorption may be increased; may affect systemic exposure).

Drug Interactions

Cytochrome P450 Effect: Pazopanib is metabolized principally by CYP3A4 with minor contributions from CYP1A2 and CYP3A4. Therefore, inhibitors and inducers of CYP3A4 may alter the metabolism of pazopanib.

CYP3A4 Inhibitors and Inducers: Coadministration of pazopanib with strong inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, clarithromycin) increases pazopanib concentrations and should be avoided. Grapefruit juice should be avoided as it inhibits CYP3A4 activity and may also increase plasma concentrations of pazopanib. CYP3A4 inducers such as rifampin may decrease plasma pazopanib concentrations. Pazopanib should not be used if chronic use of strong CYP3A4 inducers cannot be avoided.

Transporter Inhibitors: In vitro studies suggested that pazopanib is a substrate of P-glycoprotein and breast cancer resistance protein (BCRP). Therefore, absorption and subsequent elimination of pazopanib may be influence by products that affect P-glycoprotein and BCRP. Concomitant treatment with strong inhibitors of P-glycoprotein and BCRP should be avoided.

CYP Substrates: Results from drug-drug interaction trials conducted in cancer patients suggest that pazopanib is a weak inhibitor of CYP3A4, CYP2C8, and CYP2D6 in vivo, but had no effect on CYP1A2, CYP2C9, or CYP2C19. Concomitant use of pazopanib with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended. Coadministration may result in inhibition of the metabolism of these products and create the potential for serious adverse events.

Concomitant use of pazopanib and simvastatin increases the incidence of ALT elevations. If a patient receiving concomitant simvastatin develops ALT elevations, follow dosing guidelines for pazopanib or consider discontinuing simvastatin. Insufficient data are available to assess the risk of concomitant administration of alternative statins and pazopanib.

Concomitant administration of pazopanib with esomeprazole, a proton pump inhibitor, decreased the exposure of pazopanib by approximately 40% (AUC and Cmax). Concomitant use of pazopanib with drugs that raise gastric pH should be avoided. If such drugs are needed, short acting antacids should be considered in place of proton pump inhibitors and H2 receptor

antagonists. Separate antacid and pazopanib dosing by several hours to avoid a reduction in pazopanib exposure.

Pazopanib should be used with caution in patients with a history of QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interal, and those with relevant pre-existing cardiac disease. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes (e.g. calcium, magnesium, potassium) within the normal range should be performed.

Pharmacokinetics

Absorption and Bioavailability: Pazopanib is absorbed orally with median time to achieve peak concentration of 2 to 4 hours after the dose. Median absolute bioavailability is 21%. Systemic exposure to pazopanib is increased when administered with food. Administration with a high-fat or low-fat meal results in an approximately 2-fold increase in AUC and Cmax. Pazopanib should be administered at least one hour before or 2 hours after a meal.

Plasma protein binding: 99%

Half-life elimination: 30.9 hours after administration of a single 800 mg dose

Time to peak, plasma: 2-4 hours

Excretion: Primarily via feces with renal elimination accounting for < 4% of the administered dose

Metabolism: In vitro studies demonstrate pazopanib is metabolized by CYP3A4 with a minor contribution from CYP1A2 and CYP2C8.

Adverse Events

Consult the package insert for the most current and complete information. **Important Safety Information including Boxed WARNING: Severe and fatal hepatotoxicity, manifested as increases in serum transaminases (ALT, AST) and bilirubin, has been observed in clinical trials. Monitor hepatic function and interrupt, reduce or discontinue dosing as recommended.**

Common known potential toxicities, > 10%:

Cardiovascular: Hypertension, bradycardia, peripheral edema
Central nervous system: Fatigue, headache, dizziness
Dermatologic: Hair discoloration, skin rash, alopecia, palmar-plantar erythrodysesthesia, skin depigmentation
Endocrine & metabolic: Hyperglycemia, hypophosphatemia, hyponatremia, increased thyroid-stimulating hormone (TSH), hypomagnesemia, hypoglycemia, hyperkalemia
Gastrointestinal: Diarrhea, nausea, weight loss, anorexia, vomiting, dysgeusia, increased serum lipase, abdominal pain, mucositis, stomatitis
Hematologic: Leukopenia, lymphocytopenia, thrombocytopenia, neutropenia
Hepatic: Increased serum AST, increased serum ALT, increased serum bilirubin, decreased serum albumin, increased serum alkaline phosphatase
Neuromuscular & skeletal: Musculoskeletal pain, myalgia, weakness
Respiratory: Dyspnea, cough
Miscellaneous: Tumor pain

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Chest pain, left ventricular systolic dysfunction, venous thrombosis, ischemic heart disease or myocardial infarction, prolonged QT interval on ECG, facial edema, transient ischemic attacks
Central nervous system: Insomnia, voice disorder, chills

Dermatologic: Xeroderma, nail disease
Endocrine & metabolic: Hypothyroidism
Gastrointestinal: Dyspepsia, oral hemorrhage, rectal hemorrhage
Hematologic: Febrile neutropenia, pancytopenia, lymphopenia, anemia
Opthalmic: Blurred vision
Renal: Proteinuria, hematuria
Respiratory: Epistaxis, pneumothorax, hemoptysis, pulmonary embolism

Rare, less than 1% (limited to important or life-threatening):

Cardiac disease, cerebral hemorrhage, cerebrovascular accident, congestive heart failure, gastrointestinal fistula, gastrointestinal perforation (including fistulas), hemolytic-uremic syndrome, hepatotoxicity, hypertensive crisis, intracranial hemorrhage, nephrotic syndrome, pancreatitis, reversible posterior leukoencephalopathy syndrome (RPLS), thrombotic thrombocytopenic purpura, torsade de pointes

Nursing Guidelines

- Pazopanib should be taken without food (1 hour before or 2 hours after a meal). Should be taken whole with water and not broken or crushed. If a dose is missed, do not take if it is less than 12 hours until the next dose.
- There are numerous drug to drug interactions between pazopanib and other agents metabolized through the P450 system. Assess patient's concomitant medications, including OTC and herbal products.
- Hypertension is a commonly reported side effect. Monitor blood pressure closely per study guidelines. Administer antihypertensives as ordered by MD.
- Inform patient of possible changes in hair color.
- Gastrointestinal side effects are common (diarrhea, nausea, vomiting, loss of appetite). Treat symptomatically and assess for effectiveness.
- Due to the similarity in nature of this agent to other VEGF inhibitors (bevacizumab, VEGF-trap, etc.) monitor for signs of bleeding, thrombosis and PE. Instruct patient to report any calf tenderness, shortness of breath, chest pain or bleeding immediately.
- Cytopenias are common. Monitor CBC w/diff and instruct patient to report any unusual bruising or bleeding and/or signs of infection to study team.
- Monitor LFT's. Patients who have AST/ALT levels > 3x ULN and concurrent bilirubin >2X ULN should permanently discontinue pazopanib. Patients with AST/ALT levels as above and mild hyperbilirubinemia (with suspected or known Gibert's syndrome) should be monitored weekly while continuing pazopanib.
- Cardiac side effects (CHF, MI, chest pain, etc). while rare can be serious and life threatening. Instruct patient to report any cardiac symptoms to study team immediately.
- RPLS, CVA, and TIA are uncommon, but are life threatening. Instruct patient to report any neurological symptoms to the study team immediately.

10.2 MLN0128 (TAK-228) (Supplied) (INK128, NSC #768435, IND 121931); IND holder: CTEP

Investigators ordering and/or dispensing supplied agents at any time for study treatment must be currently registered with PMB, DCTD, NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents.

Procurement

MLN0128 (TAK-228) is an investigational agent supplied by the National Cancer Institute (NCI). Millennium Pharmaceuticals, Inc. will supply MLN0128 (TAK-228) to the CTEP/DCTD/NCI and will be distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI.

Drug Ordering: NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

Agent Inventory Records - The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Oral Drug Accountability Record Form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

Classification: mTOR inhibitor, TORC1/2

CAS Registry Number: 1224844

Molecular Formula: $C_{15}H_{15}N_7O$ **M.W.:** 309.3

Approximate Solubility

MLN0128 exhibits a pH-dependant aqueous solubility: at physiological pH the solubility is approximately 0.1 mg/mL and at or below pH 3 the solubility is greater than 15 mg/mL.

Mode of Action:

MLN0128 is a non-rapamycin analog mTOR (mechanistic target of rapamycin) kinase inhibitor. The mTOR kinase regulates cell growth, translational control, angiogenesis, and cell survival by integrating nutrient and hormonal signals. The mTOR complex (TORC) is an intracellular point of convergence for a number of cellular signaling pathways. ML0128 is a potent and selective adenosine tri-phosphate (ATP)-competitive inhibitor of mTOR complex 1 and 2 (TORC1/2).

Description:

MLN0128 drug substance is a white to off-white, crystalline powder.

How Supplied:

MLN0128 is supplied by Millennium Pharmaceuticals, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as size 2 hard gelatin capsules in the

following strength: 5 mg (gray opaque color). The composition of the drug product consists of a blend of MLN0128 drug substance, microcrystalline cellulose, and magnesium stearate. **Milled** formulations will have a white label with a large watermark of the strength on the label.

MLN0128 capsules are packaged in 30-count, 60-cc high-density polyethylene (HDPE), white, opaque, round, tamper- and child-resistant bottles.

Storage:

Capsules are to be stored in the original package between 15°C to 30°C.

Route of Administration:

MLN0128 (TAK-228) should be taken on an empty stomach at least 2 hours after food and do not eat or drink (except water) for at least one hour after taking MLN0128 (TAK-228). Do not chew, open or manipulate the capsule in any way prior to swallowing. Each dose should be taken with 8 ounces (240 mL) of water.

Potential Drug Interactions:

Multiple human metabolizing enzymes are involved in the Phase I metabolism of MLN0128. When normalized for human liver content, the CYP isoforms CYP3A4, CYP2C9, and CYP2C19 appear to contribute to MLN0128 metabolism. MLN0128 displayed low potential (IC_{50} > 25 μM) for inhibition of the major human CYP isoforms.

Other pathways:

MLN0128 (TAK-228) did not inhibit P-glycoprotein but does inhibit breast cancer resistance protein (BCRP) and organic cation transporter 1 and 2.

Pharmacokinetics

Absorption: MLN0128 (TAK-228) is rapidly absorbed with a Tmax of 1 to 4 hour post dosing. Preliminary assessment of doses versus exposure relationship suggests MLN0128 (TAK-228) exposures increase linearly with dose. Studies in rats suggest that feeding state did not affect the absorption and pharmacokinetic profile of MLN0128 (TAK-228).

Distribution: Total body clearance is approximately 20 L/hour and does not appear to accumulate in plasma when dosed as frequently as once daily. MLN0128 (TAK-228) exposures also increase linearly with dose. MLN0128 (TAK-228) has the propensity to cross the blood-brain-barrier. MLN0128 (TAK-228) is 70.5% bound to human plasma proteins.

Metabolism: Hepatic to M1 metabolite (inactive) via Cytochrome P450 CYP2C9 (35.1%), CYP2C19 (28%) and CYP3A4 (27.8%)

Half-life elimination: Approximately 8 hours

Excretion: Biliary excretion of MLN0128 (TAK-228) and M1 each represented less than 1% of the total MLN0128 (TAK-228) dose after administration of a single IV dose of 0.5 mg/kg MLN0128 (TAK-228) to rats. Urinary excretion of MLN0128 (TAK-228) and M1 represented less than 1% and 21%, respectively, of the total MLN0128 (TAK-228) dose.

Patient Care Implications:

Women of childbearing potential should use effective methods of contraception during and through 3 months after the last dose of MLN0128.

Men should use effective methods of contraception and not donate sperm during and through 4 months after the last dose of MLN0128.

Adverse Events

Refer to MLN0128 (TAK-228) CAEPR in Section 9.4.2.

Nursing Guidelines

- Hyperglycemia is common. Monitor glucose levels as outlined in protocol. Patients who are diabetic will need to be monitored closely. Patients who are not diabetic may require daily home glucose monitoring. Instruct patients on this technique and instruct patients to report high blood sugars to study team.
- GI side effects include nausea, vomiting, diarrhea, constipation and abdominal pain. Treat symptomatically and monitor for effectiveness.
- Anemia and lymphopenia have been seen. Monitor CBC w/diff and report low blood counts to provider.
- Monitor electrolyte panel, as patients may experience low phosphorus, magnesium, and potassium levels.
- Patients may experience taste alterations, dry mouth, and stomatitis. Treat symptomatically and monitor for effectiveness.
- Warn patients they may experience flu-like symptoms, including pyrexia, asthenia, headache, back pain.
- Instruct patients to report any rash or itching to study team.

11.0 MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1)[28]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline.

11.1 Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated every 8 weeks for 6 assessments followed by every 12 weeks thereafter. Patients initiating crossover will restart their scanning intervals as every 8 weeks from date of crossover and for 6 assessments, followed by every 12 weeks thereafter.

11.2 Definitions of Measurable and Non-Measurable Disease

11.2.1 Measurable Disease

A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

Tumor lesions in a previously irradiated area are considered measurable disease under the following conditions: They are at least 1.0 cm in diameter and have grown by at least 0.5 cm (or 25%, whichever represents the smaller value) from the measured post-radiation nadir.

11.2.2 Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm). Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable as well.

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

11.3 Guidelines for Evaluation of Measurable Disease

11.3.1 Measurement Methods:

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

11.3.2 Acceptable Modalities for Measurable Disease:

- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

  As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.
- **PET-CT:** If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- **Chest X-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.
- **Physical Examination:** For superficial non-nodal lesions, physical examination is acceptable, but imaging is preferable, if both can be done. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **FDG-PET:** FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-

PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
   1) If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
   2) If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
   3) If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

11.3.3 Measurement at Follow-up Evaluation:

- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

11.4 Measurement of Treatment/Intervention Effect

11.4.1 Target Lesions & Target Lymph Nodes

- Measurable lesions (as defined in Section 11.2.1) up to a maximum of 5, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal (as defined in 11.2.1), where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

  Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.
- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- **Baseline Sum of Dimensions (BSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as

reference to further characterize any objective tumor response in the measurable dimension of the disease.

- **Post-Baseline Sum of the Dimensions (PBSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- **The minimum sum of the dimensions (MSD)** is the minimum of the BSD and the PBSD.

11.4.2 Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 11.2.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 11.4.3.3.

11.4.3 Response Criteria

11.4.3.1 All target lesions and target lymph nodes followed by CT/MRI/PET-CT/Chest X-ray/physical examination must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

11.4.3.2 Evaluation of Target Lesions

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to < 1.0 cm.
- **Partial Response (PR):** At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.4.1).
- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.

c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

11.4.3.3 Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesions or non-target lymph nodes.
- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
  c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

11.4.4 Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease:

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD

Target Lesions & Target Lymph Nodes	Non-Target Lesions & Non-Target Lymph Nodes	New Sites of Disease	Overall Objective Status
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

* See Section 11.4.3.1

11.4.5 Symptomatic Deterioration: Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11.5 Definitions of analysis variables

Formal definitions of variables used in analyses can be found in the Statistical Considerations section of the protocol.

12.0 END OF TREATMENT/INTERVENTION

12.1 Duration of Treatment

12.1.1 CR, PR, or SD: Patients who are in CR, PR or SD will continue on therapy until progression of disease, excessive toxicity requiring the patient to come off of treatment, or the patient withdraws from treatment. After treatment is discontinued, patients will be followed per the study calendar in Section 5.0. Patients receiving pazopanib may re-register and receive MLN0128 (TAK-228) following PD (see section 12.1.2). All follow-up and tests continue, as if the patient was initially randomized to receive MLN0128 (TAK-228).

12.1.2 Disease Progressio:

Upon Progression on Pazopanib: Patients may re-register and receive MLN0128 (TAK-228). All follow-up and tests continue, as if the patient was initially randomized to receive MLN0128 (TAK-228).

Upon progression on MLN0128 (TAK-228) Remove from protocol therapy any patient with disease progression. Document details, including tumor measurements, on data forms.

After disease progression, patients should be followed for survival per the study calendar (Section 5.0).

12.1.3 Discontinuation of study agent: If the patient discontinues their initial treatment assignment to either pazopanib or MLN0128 (TAK-228) for reasons other than disease progression or withdrawal of consent, and within 15 months of randomization, will continue following the Study Calendar (Section 5.0) for disease assessments.

12.2 Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Study participants who are registered to the trial but never receive study intervention (for a reason other than because they were deemed ineligible) must still complete follow-up requirements as specified below. Baseline, on-study, endpoint (e.g., relapse or progression), off treatment, and survival data submission required.

The organization holding the IND will also be notified if a patient is found to be ineligible upon audit or after the patient has already received several cycles of therapy.

12.3 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

13.0 STATISTICAL CONSIDERATIONS AND METHODOLOGY

13.1 Study Design

This study has two components, specifically 1) phase I dose seeking and 2) an unblinded randomized phase II study for patients having locally advanced/unresectable or metastatic sarcoma having failed prior treatments. All patients will be pre-registered to undergo a central pathology review to confirm eligibility and to properly assign patients to their respective histologically defined cohort.

Update # 05 (Dose Modification for Pazopanib Arm): On August 4th, 2017, this trial was suspended due to AE assocated with the pazopanib arm and based on the requirements of the DSMB Toxicity Stopping Rule. Data was reviewed, together with available treatment and AE data. The DSMB was notified of the situation. Upon a review of updated data and discussion with CTEP and the Alliance A091304 Study Team, Alliance Group Statistician, Alliance Experimental Therapeutics & Rare Tumor Committee Chair, the decision was made to continue the trial with a dosing scheme clower representing clinical practice. The impact on the study design was discussed and considered not only the expected rate of the control arm (pazopanib), but also the evaluability of 25 patients currently enrolled (13-MLN0128 arm; 12-pazopanib). The consensus reached was to replace those 25 patients already enrolled and for the determination of the Primary Endpoint, while summarizing and including/excluding the data from those patients in the appropriate Secondary Endpoints. The study design would not change, in consideration of the hazard ratio to detect, as well as the PFS rate assumed for the control arm (pazopanib). To these ends, at the time of the analysis and for all sections that follow, we will reference such patients in this section as the following:

- Analysis Group 1: Patients enrolled to the phase II component, up through August 4th, 2017.
- Analysis Group 2: Patients enrolled to the phase II component, after August 4th, 2017

13.1.1 Phase I

The primary goal of the phase I component is to evaluate the maximum tolerable dose (MTD) of MLN0128 (TAK-228). There will be no restriction on patient enrollment based on histologically defined cohorts. Patients enrolled onto the phase I component and treated at the maximum tolerable dose will not be allowed to enroll onto the phase II component, due to the randomization aspect of the phase II component which could potentially assign the patient to receive the opposite treatment (control arm, pazopanib) and result in non-concurrent randomization of patients and impact efficacy analysis.

13.1.2 Phase II

The primary goal of the phase II component is to evaluate differences in the progression-free survival (PFS) of patients treated with either pazopanib (control arm) or MLN0128 (TAK-228) (experimental arm). The expected PFS rate within the control arm (pazopanib) is 4.6 months[24]. Only patients enrolled after determining the MTD will be allowed to enroll onto this component of the study. In order to achieve meaningful numbers in a few specific subtypes for which there is strong preclinical and clinical rationale, we have limited enrollment to the following histologically defined cohorts:

- HISTOLOGIC COHORT 1: Undifferentiated Pleomorphic Sarcomas (UPS) including Malignant Fibrous Histiocytoma, Myxofibrosarcoma, High Grade Sarcoma NOS
- HISTOLOGIC COHORT 2: Leiomyosarcomas (Uterine and Extra-Uterine)

- HISTOLOGIC COHORT 3: Other Sarcomas [Malignant Peripheral Nerve Sheath Tumor (MPNST)].

During the Phase II, patients will undergo a central pathology review to confirm eligibility as well as to properly assign patients to their respective histologically defined cohort. Histologic Cohort 3 will be restricted to enrolling 25 patients in the Phase II component of the study and for Arms 5 and 6 due to the re-start of enrollment (Update #05).

Patients will be randomized in 1:1 scheme and using the stratification factors specified within this protocol (Section 4.8). Patients randomized to the pazopanib arm will have the opportunity to receive MLN0128 (TAK-228) upon disease progression.

13.2 Statistical Design and Analysis for the Primary Endpoint (Phase I)

13.2.1 Primary Endpoint

The primary endpoint is to determine the MTD of single agent MLN0128 (TAK-228), using the standard "cohorts of 3" or "3+3" design. Patients will be considered evaluable upon completion of Cycle 1 of treatment and adverse assessment.

13.2.2 MTD Definition and Determination

Three patients will be treated at each dose level and observed for a minimum of 28 days (i.e. one full cycle) before new patients are treated. Doses will not be escalated in any individual patient.

MTD Definition: MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity (DLT) in at least one-third of patients (at least 2 of a maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% [1 - (1-0.25)6].

Refer to Section 7 for definition of dose-limiting toxicity (DLT). The following steps will be used to determine the MTD. Doses may not be escalated within a patient.

- Step 1: The first cohort of three patients will be treated at the starting dose level 0.
- Step 2: Each patient is observed for at least 28 days from the start of treatment and to assess toxicity.

- If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower dose level.
- If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥2 of 6), the MTD will have been exceeded, and further accrual will cease to this cohort and the phase II component will be considered to activate, following discussions with Disease Committee Leadership, CTEP, and the Study Team. If dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level (ie, return to Step 1 and repeat this process).
- After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

- Evaluability: If a patient fails to complete the initial course of therapy (defined as drug administration and weeks observation) for reasons other than dose-limiting toxicity defined adverse events, the patient will be regarded as uninformative in regard to the primary study goal and an additional patient will be treated at the current dose level; however, all toxicity information will be utilized in the analysis.

13.2.3 Operating Characteristics:

The following table gives the probability of dose escalation at a single dose level as a function of the true probability of DLT at that level using the Cohorts 3+3 design described in Section 13.2.2.

True Rate of DLT (%)	Probability of Dose Escalation
10	.91
20	.71
30	.49
40	.31
50	.17

13.3 Statistical Design and Analysis for the Primary Endpoint (Phase II)

13.3.1 Primary Endpoint

The primary endpoint of this study is progression-free survival. An event will be defined as either disease progression or death (in cases where patients have died without evidence of disease progression). Patients will be censored at their most recent disease assessment in cases where they are either lost to follow-up or remain alive without progressive disease. We will perform the analysis as ITT (intention to treat) where patients deemed ineligible due to histology will be excluded.

NOTE: Patients erolled to Analysis Group 2 (see Section 13.1) will be used in the determination of the Primary Endpoint.

13.3.2 Statistical Design

We consider a median PFS of at least 7 months for patients treated with MLN0128 (TAK-228) as clinically promising (Ha: PFS of MLN0128 (TAK-228) arm is superior to that of the pazopanib arm), relative to expected median PFS of 4.6 months associated with pazopanib (Ho: PFS for the MLN0128 (TAK-228) arm is at best, equivalent to that of the pazopanib arm). This corresponds to observing a hazard ratio of 0.66 (MLN0128 (TAK-228) arm : pazopanib arm). Our goal is to show superiority and we will therefore be performing a 1-sided statistical tests with an overall alpha level targeted for 0.15. To test these hypotheses, we will enroll a total of 98 patients and perform 2 statistical tests. Here, we will have one planned interim analysis with the possibility of stopping for "futility" only and then the final efficacy analysis. We will be using a Lan deMets spending function family for both alpha and beta, with O'Brien-Fleming stopping boundaries [25, 26]. We expect accrual to be 10 patients per month and require 15 months follow-up for all patients. The study design and calculations were performed using EaST v6.

13.3.3 Study Operating Characteristics

There is an 80% chance of detecting a HR (MLN0128 (TAK-228):pazopanib) less than 1.0 with an attained significance level of 0.15, under the assumptions of the design parameters described in Sections 13.3.2 and 13.3.4. Based on 50,000 simulations, the probability of stopping early due to futility under the alternative hypotheses (HR=0.66) is 8.2% and the probability of rejecting for futility under the null hypotheses (HR=1) is 49.9%.

13.3.4 Analysis Plan

There will be two analyses performed for the primary endpoint.

- Futility Analysis: At the time we have reached 47 PFS events (53% of the 89 events required for the final efficacy analysis), we will conduct an interim analysis for "futility" (non-binding) only. If the p-value associated with a stratified Log-Rank test statistic is greater than 0.49989 (corresponding to a HR of 0.9992), we will stop the study due to evidence that MLN0128 (TAK-228) is no better than pazopanib and in terms of improving PFS. More specifically, the decision is based P, the cumulative probability from a Chi-square distribution (1 degree of freedom, assuming 1-sided test) of being less than the calculated stratified Log-Rank test statistic. If P is greater than 0.049989, we will stop the study for futility.
- Efficacy Analysis & Final Decision Rule: At the time we have reached 89 PFS events, we will perform the "efficacy" analysis. If the p-value associated with a stratified Log-Rank test statistic is less than 0.15, we will conclude that MLN0128 (TAK-228) has improved the median PFS from 4.6 months (with pazopanib) to 7 months.

13.4 Sample Size, Accrual Time, and Study Duration (Phase I and II)

It is expected that we will enroll 10 patients, per month, based on accrual to A091102. Specifically, A091102 enrolled an 8-9 patients per month when similar cohorts were actively enrolling. This study will further be open to enrollment, NCTN-wide, which was not the case for much of the accrual period for A091102.

13.4.1 Phase I

A maximum of three dose levels will be evaluated. Assuming that each dose level requires 6 patients, plus an extra patient at each dose level to account for patients deemed as non-evaluable (excluding the patients who are screen failures by histology in the pre-registration period), implies that we will require a maximum of 21 patients. Using a similar argument for the minimum number of patients (ie, 3 per dose level and only 2 levels) implies that we will require a minimum of 7 patients to fully evaluate the phase I component. We assume that it will take a maximum of 30 days after the last patient enrolled on the dose level, to confirm presence or absence of DLTs. Conservatively, we anticipate that the MTD could be identified within 9 months of study activation. We anticipate that 24 pre-registered patients (includes screen failures by histology in the pre-registration period plus patients deemed non-evaluable who were registered) will yield 7-21 patients who proceed to the phase I component of the study.

13.4.2 Phase II

Accrual will be limited to a maximum of 25 patients for Histologic Cohort 3 and to improve the opportunity to have meaningful conclusions for Histologic Cohort specific sub-analyses. The study design requires 98 patients; however, we will enroll to a maximum of 103 patients to account for patients who are deemed ineligible after registration and randomization (i.e.

inclusive of the addition 5% for patients deemed non-evaluable by eligibility criteria 3.3.1 and 3.3.2).

This study will include a pre-registration step to perform a central pathology review and to determine patient eligibility and proper classification of a histologically defined cohort. Based on current screen failure rates, we anticipate that there will be 114 pre-registered patients (includes 10% screen failures by histology in the pre-registration period), yielding the required 103 randomized patients.

Protocol Update #05: We will replace the initial 25 patients randomized onto the phase II portion prior to August 4th, 2017 (ie, Analysis Group 1) and will not change the original estimates of the number of pre-registered paitents (114) and randomized patients (103).

Protocol Update #07: The total number of pre-registered patients to Analysis Group 2 is increased to 140 (versus 114), after observing an unexpectedly high screen failure rate due to eligibility reasons beyond improper histology. This increase does not impact the sample size required for the study design.

Protocol Update #08: The total number of pre-registered patients to Analysis Group 2 is increased to 170 (versus 140), after observing a 2nd increase in the observed failure rate due to eligibility reasons beyond improper histology. This increase does not impact the sample size required for the study design.

13.4.3 Overall Maximum Accrual and Duration

As of Update #05, final and expected enrollment numbers appear in the table below.

Enrollment by Phase, as of the
Temporary Suspension on 8/4/2017 & Protocol Update #08

	Phase I	Phase II Through 8/4/2017 (Analysis Group 1)	Phase II After 8/4/2017 (Analysis Group 2)
Status on 8/4/2017	Closed	Closed	To complete
Pre-registrations	12	34	170[a,b]
Registrations/Randomizations	9	25[c]	103
Maximum Number of Pre-registrations, by Phase	12	204[b]	
MaximumNumber of Registrations/Randomizations, by Phase	9	128	
Total Number of Study Pre-registrations	216[b]		
Total Number of Study Registrations/Randomizations	137		

a) For Cohort 3 (Phase II, only) : We anticipate pre-registering a maximum of 25 cases to Analysis Group 2, with the expection that 10-15% may not be able to proceed

due to improper histology, as well as a few pre-registered patients being allowed to complete enrollment (i.e., randomization).

b) Update #08: increased from 140 to 170 patients (pre-registered Analysis Group 2), 174 to 204 patients (pre-registrations by Phase), and 186 to 216 (total number of study pre-registrations).

c) 12 were randomized to MLN0128;12 to pazaopanib.

As of Update #05 (Dose Modification Impacting Study Population & Re-activation of Phase II for Analysis Group 2), the phase I component had been permanently closed to enrollent and 25 patients enrolled to the phase II component (now called Analysis Group 2) will be excluded from the evaluation of the primary endpoint. Ten (10) months will be required to pre-register 114 patients, yielding the 103 patients randoimized to the trial. Fifteen (15) months of follow-up are required, beyond the randomization of the last patient. Therefore, we estimate that upon re-activation of the phase II component, the results can be reported within a total of 2.6 years (i.e. 1 year for pre-registration, an additional 15 months for maturity/cleaning, and 6 months for analysis and publication). This acknowledges that the re-activation of Alliance A091401 may briefly impact enrollment onto this trial. Enrollment was rapid on A091401 and approximately 50-60 patients are required within the overlapping histologic cohorts.

As of Update #08 (Re-activation, expanding total number of pre-registered patients): We expect to add an additional 1-2 months to the pre-enrollment phase for the increase in the number of pre-registrations. That is, we expect the reporting of the final study results to occur 1-2 months within the activation of this update (3.1 years after the original activation of Analysis Cohort 2).

13.5 Primary Endpoint Completion Time Estimation (For clinicaltrials.gov reporting)

At study activation, this study will have been registered within the "ClincialTrials.gov" web site. The Primary and Secondary Endpoints (ie, "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov.

As of Update #08 (Expansion of total number of pre-registered cases required for Analysis Group 2): For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3.1 years after the phase II component of this study reactivates to accrual and to fulfill the analysis of the primary endpoint within Analysis Group 2. The definition of "Primary Endpoint Completion Date" (PECD) for this study is the time the last patient registered onto the phase II component has been followed for at least 15 months.

13.6 Supplementary Analysis Plans (Phase I and II)

NOTE: All eligible patients having initiated treatment will be considered evaluable for these endpoints and according to their initial treatment assignments. Patients participating in the phase I portion of the trial will be analyzed separately from those enrolled to the phase II component. Unless otherwise specified, all patients randomized to the MLN0128 arms (ie, 1 and 5) will be combined; whereas, patients treated on the initial pazopanib arm (Arm 2) will be analyzed separately from those initiating treatment at the reduced dose (ie, Arm 6).

13.6.1 Adverse Events:

Patients will be evaluated for adverse events using the NCI Common Toxicity Criteria for Adverse Events version 4.0. All patients having at least one post-baseline assessment of adverse events are included in this analysis. Adverse events will be summarized by Dose Cohorts and treatment arm. Summary statistics (e.g., mean, median, standard deviation) and frequency tables will be used to describe the distributions of adverse events. Rates of

adverse events occurring in the MLN0128 (TAK-228) arm will be compared to the pazopanib arm with chi-squared tests (or suitable alternative) used for comparisons where applicable. Adverse event analyses will separate events associated with the original treatment assignments from those having occurred after crossing over to receive MLN0128 (TAK-228) at disease progression.

13.6.2 Tumor Response

The frequencies and rates of tumor response categories (CR, PR, SD, and PD, and too early/not evaluated) will be summarized by Dose Cohort and treatment arm, and Fisher's Exact test or applicable statistical tests will be used to compare the association of objective response rate (ORR, a tumor response of either CR or PR) and treatment.

13.6.3 Duration of Response

This will be defined as the time between each patient's best tumor response and progression (or date of last disease assessment for patients who die without progression or are lost to follow-up) will be analyzed using Kaplan-Meier methodology [27]. This endpoint will be summarized by Dose Cohort for the phase I component.

13.6.4 Clinical Benefit Rate (CBR)

CBR is defined the number of patients having either CR, PR, or stable disease for at least 6 months after starting treatment. Analyses will be similar to that performed for tumor response. This endpoint will be summarized by Dose Cohort for the phase I component.

13.6.5 Time-to-Progression (TTP) & Survival (OS)

TTP is defined as the time between randomization and disease progression. Patients will be censored at the date of their most recent disease assessment if they have died without evidence of progressive disease or are lost to follow up. OS is defined at the time between randomization and death due to any cause (or last contact for surviving patients and those lost to follow-up). Kaplan-Meier methodology will be used to estimate the distribution of TTP and OS. This endpoint will be summarized by Dose Cohort for the phase I component.

13.6.6 Exploratory Endpoints

13.6.6.1 Cross-Over Patients (Phase II, Only)

We anticipate a total of 42 of the 56 (75%) patients treated on the pazopanib arm (Arm 6) will cross over to receive MLN0128 (TAK-228) (Arm 3) at the time of disease progression. PFS and secondary endpoints will be evaluated in patients who cross over from pazopanib to MLN0128 (TAK-228) at the time of disease progression (with the exception of comparing PFS across two arms). The date used for the calculations of duration of response, TTP, PFS, and OS will be the date the patient initiated MLN0128 (TAK-228) (versus re-registration date). We note these analyses will be exploratory in nature. We may additionally include patients enrolled to pazopanib and part of Analysis Group 1, as it is specific to crossover treatment, only.

13.6.6.2 Cohort-Specific Evaluation of 4-month CBR (Phase II, Analysis Group 2 Only)

Due to the historical incidence of the subtypes defined for this study, we expect that Histologic Cohort 1 (Undifferentiated Pleomorphic Sarcoma) and Histologic Cohort 2 (Leiomyosarcoma) will comprise 75-80% of patients enrolled onto the trial providing an opportunity to perform a meaningful cohort-specific analysis of CBR. To facilitate this

exploratory analysis, we will limit Histologic Cohort 3 (i.e., Malignant Peripheral Nerve Sheath Tumors and Synovial Sarcomas) to maximum of 25 patients, leaving 88 patients to be enrolled to the other two histologic cohorts. This endpoint is powered for comparison across the two arms; therefore, we will restrict the patient population to Analysis Group 2. Specifically, there will be 22 patients within each of Histologic Cohorts 1 and 2 who have been randomized to receive MLN0128 (TAK-228). We expect a 12 week PFS rate of 40% which translates to a 4-month PFS rate of approximately 30%. A 29% CBR was observed in our recent study (A091103: Phase II Study of the Angiopoitein-1 and -2 Peptibody AMG 386 for the Treatment of Angiosarcoma. We would consider MLN0128 (TAK-228) has having an early signal of improving CBR in a histologic cohort if we achieve a CBR of at least 45%. A minimum of 20 patients yields 82% power using a 1-sided test and at 0.15 level of significance to detect a 4 month CBR of 45% if the true 4 month CBR is at most 25%, within a histologic cohort. We further note that Histologic Cohort 3 is comprised of very rare sarcoma subtypes (estimated numbers <500 cases diagnosed in the United States each year) and were included due to the strength of the preclinical data and outcomes will be exploratory and hypothesis generating/confirming. Only 12-13 patients from Histologic Cohort 3 randomized to receive MLN0128 (TAK-228), yielding 70% at 0.15 level of significance under the same assumptions specified for Histologic Cohorts 1 and 2. Nonetheless, the results of these exploratory analyses may lead to discussions with leadership and CTEP as to the value of expanding enrollment to best address other endpoints within any of the Histologic Cohorts.

13.6.6.3 Tissue Specimens for Banking (Phase I & Phase II) – Please see Section 14.0.

13.7 Study Monitoring

During the Phase I component, toxicity monitoring calls will be held every other week (see Section 7.1.1). The principle investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Alliance Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the Alliance Statistical Office.

13.7.1 Adverse Event Stopping Rule

13.7.1.1 Phase I

Given the nature of the study design and close monitoring of adverse events for determining the MTD, an adverse event stopping rule will not be defined in this section for this portion of the study.

13.7.1.2 Phase II

The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below. In such cases, the study team will consult with the Alliance DSMB and applicable entities (eg, CTEP/NCI) in terms of proceeding with the study.

Initial Arm Assignment: As of Update #05 and applicable to Arms 5 and 6 - Accrual will be temporarily suspended to this study if at any time we observe events considered at least

possibly related to study treatment (i.e. an adverse event with attribute specified as "possible", "probable", or "definite") on a study arm that satisfy either of the following:

- an excessive death rate, defined as 1% or higher mortality attributed to study drug, or
- if 3 or more patients in the first 15 patients in the experimental arm (or 30% when accrual is greater than 15 patients in the arm) experience a grade 3 or higher adverse event.
- if 3 or more patients in the first 15 patients in the control arm (or 30% when accrual is greater than 15 patients in the arm) experience a grade 3 or higher adverse event fron an unanticipated toxicty. Please refer to the most up to date version of the toxicity profile table of "anticipated" toxicities in section 9.4.1.

We note that we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

Crossover Treatment:

In patients receiving MLN0128 (TAK-228) after crossover from pazopanib on the phase II component of the study: Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible", "probable", or "definite") on a study arm that satisfy either of the following:

- an excessive death rate, defined as 1% or higher mortality attributed to study drug, or
- if 3 or more patients in the first 15 patients in the arm (or 30% when accrual is greater than 15 patients in the arm) treated patients experience a grade 3 or higher adverse event.

We will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

13.7.2 Accrual Monitoring Stopping Rule

Phase I

Given the expected accrual rate is around 2 patients per month, it is expected that the study will take around .75 year to fully accrue. We plan to monitor the accrual continually and if we only end up accruing 3 patients by the start of 3rd quarter, we will consider stopping the trial for slow accrual.

Phase II (Analysis Group 2 only, as of Update #05)

Given the expected accrual rate is around 10 patients per month, it is expected that the study will take around 10 months to pre-register a sufficient number of patients to randomize a total of 103 patients to Analysis Group 2. We plan to monitor the accrual continually and if we only end up accruing 12 patients by the start of 3rd quarter, we will consider stopping the trial for slow accrual.

13.8 Study Reporting

This study will be monitored by the Alliance Data Safety Monitoring Board (DSMB), an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

This study will be monitored by the Clinical Data Update System (CDUS) version 2.0. A full (i.e. Complete) report containing cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reporting time points are: January 31, April 30, July 31, and October 31.

This study will be monitored by the Food and Drug Administration due to the Investigational New Drug (IND) status of the agent. An IND report will be produced and submitted to the Regulatory Affairs Coordinator within 60 days of the anniversary date that the IND went into effect.

Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" web site. The Primary and Secondary Endpoints (ie, "Outcome Measures") along with other required information for this study will be reported on ClinicalTrials.gov. See Section 13.4 for further details.

13.9 Descriptive Factors

- Dose Cohorts (Phase I Component, Only): Level 0 vs Level -1 vs Level -2.
- Study Component: Phase I vs Phase II
- Histologic Cohort (Phase I & Phase II Components): 1 vs 2 vs 3

13.10 Inclusion of Women and Minorities

This study will be available to all eligible patients, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses. Expected sizes of racial by gender subsets for patients randomized to this study are shown in the following table.

Accrual Targets (as of Protocol Update #05)					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	3	4	0	0	7
Asian	3	1	0	0	4
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	4	4	0	0	8
White	51	57	5	5	118
More Than One Race	0	0	0	0	0
Total	61	66	5	5	137

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

14.0 CORRELATIVE AND COMPANION STUDIES

Tumor samples collected for banking will be used for future studies. This tissue collection **must be offered to all patients** enrolled on Alliance A091304 (although patients may opt to not participate). This tissue collection does not require separate IRB approval.

14.1 Tissue Specimens for Banking

For this study, we will store tissue specimens for which we do not have a defined plan at this time. See section 6.2 for details of tissue submission. This tissue will only be stored for patients who opt in for participation. A potential utility of these specimens would be the following:

14.1.1 Background

Emerging preclinical data, as outlined in Section 1.3 have supported the notion that PI3K/Akt/mTOR signaling axis is upregulated in multiple sarcoma subtypes. MLN-0128 is a potent inhibitor of both TORC1 and TORC2, with potent antitumor activity in preclinical models of sarcoma as well as breast adenocarcinoma, multiple myeloma, and renal cell carcinoma. More work is required to understand whether the baseline activity of this signaling pathway will correlate with benefit to inhibition of this pathway. This could be explored by IHC analysis of baseline paraffin-embedded tissue specimens of various sarcoma subtypes.

14.1.2 Objectives

1) The potential to explore the baseline activity of the PI3K/Akt/mTOR signaling pathway in undifferentiated pleomorphic sarcomas, leiomyosarcomas, and other sarcomas.

2) The potential to explore the relationship between baseline activity of the PI3K/Akt/mTOR pathway and clinical benefit with MLN-0128 and/or pazopanib.

14.1.3 Methods

Activity of the PI3K/Akt/mTOR pathway could be analyzed via immunohistochemistry performed on unstained slides obtained at baseline for the following targets, which include but are not limited to: PTEN, phosphorylated (p)-Akt-Ser473, p-Akt-Thr308, TORC1, TORC2, Rictor, Raptor, p-rS6, and p-4EBP1.

IHC would be semiquantified into categories (e.g. 0, 1+, 2+, 3+) and correlations with clinical outcomes such as response rate, PFS, and OS. Standard statistical methods appropriate for categorical data analysis, logistic regression, Kaplan-Meier methodology, and Cox Proportional Hazards models will be used. A formal statistical analysis plan will be developed based on the final list of scientifically relevant correlatives and approved prior to sample processing, by the appropriate entities.

As of Update #05, consideration will be given to the appropriate study population associated with the timing of the re-actiavation of the study to the phase II component of the trial and due to the change in dose scheme for the pazopanib arm. Any compairisons should include concurrently enrolled patients associated with the primary endpoint of the trial; however, a subset of analyses may include all patients depending on arm assignment. These details will be agreed upon and at the time of designing the formal Statistical Analysis Plan for analyses associated with biospecimens.

15.0 General Regulatory Considerations and Credentialing

There are no credentialing requirements for A091304.

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APPENDIX I REGISTRATION FATIGUE/UNISCALE ASSESSMENTS

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

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

APPENDIX II MEDICATION DIARIES

PATIENT MEDICATION DIARY –MLN0128 (TAK-228)

Today's date _____ **Agent:**MLN0128 (TAK-228)

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each week-period while you take MLN0128 (TAK-228)**.**
2. MLN0128 (TAK-228) should be taken on an empty stomach at least 2 hours after food and do not eat or drink (except water) for at least one hour after taking MLN0128 (TAK-228). The capsules should be swallowed whole and must not be crushed or broken. Drink at least 20 ounces of fluids per day to avoid dehydration.
3. Record the date, day of weekly dose, the number of capsules you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
5. If you miss a dose of MLN0128 (TAK-228), you should take it as soon as you remember, as long as it falls within 24 hours of the time you normally take your dose.
6. Please return this form to your physician when you go for your next appointment.

Week	Date	# of capsules taken	Comments
1			
2			
3			
4			

Physician's Office will complete this section:

How many days this cycle were 0 tablets taken? _____
How many days this cycle was only 1 tablet taken?_____
How many days this cycle were 2 tablets taken?_____
How many days this cycle were 3 tablets taken?_____
How many days this cycle were 4 tablets taken?_____
How many days this cycle were 5 tablets taken?_____
How many days this cycle were 6 tablets taken?_____
How many days this cycle were > 6 tablets taken?_____

1. Total number of capsules taken this month (each size)
   _____
2. Physician/Nurse/Data Manager's Signature
   _____

Patient's signature

_____

PATIENT MEDICATION DIARY – Pazopanib

Today's date _____ **Agent: Pazopanib**

Patient Name_____ (*initials acceptable)* **Patient Study ID** _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 4 week-period while you take **pazopanib.**
2. **Pazopanib should be taken orally without food at least 1 hour before OR 2 hours after a meal. The tablets should be swallowed whole and must not be crushed or broken.**
3. Record the date, the number of tablets you took, and when you took them. Record doses as soon as you take them; do not batch entries together at a later time.
4. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials. Example: ~~10:30 am~~ SB 9:30 am
5. If you miss a dose of pazopanib, you should take it as soon as you remember, but only if there are 12 or more hours remaining before the next dose. If the dose is due in less than 12 hours, skip the missed dose and take the next dose as scheduled.
6. If vomiting occurs after taking pazopanib, do not take a replacement dose on that day. Resume drug the next day.
7. Please return this form to your physician when you go for your next appointment.

Day	Date	Time of daily doses (am/pm)		# of tablets taken	Comments
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					

Day	Date	Time of daily doses (am/pm)		# of capsules taken	Comments
21					
22					
23					
24					
25					
26					
27					
28					
Only If Needed					
29					
30					
31					
32					
33					
34					
35					

Physician's Office will complete this section:

How many days this cycle were 0 tablets taken?_____
How many days this cycle was only 1 tablet taken?_____
How many days this cycle were 2 tablets taken?_____
How many days this cycle were 3 tablets taken?_____
How many days this cycle were 4 tablets taken?_____
How many days this cycle were > 4 tablets taken?_____

For Cycles 1 and 2, only: Was escalation attempted during cycle (yes vs no)? _____
If yes, provide date (mm/dd/yyyy) _____

3. Total number of tablets taken this month _____

4. Physician/Nurse/Data Manager's Signature
_____

Patient's signature
_____

APPENDIX III CRADA

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). -Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

APPENDIX IV: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

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

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

MLN0128 (TAK-228) interacts with a certain specific enzyme in your liver.

- The enzyme in question is CYP3A4 and MLN0128 (TAK-228) is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.

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

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

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

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

MLN0128 (TAK-228) must be used very carefully with other medicines that use certain liver enzymes. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP3A4.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.

Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD You are enrolled on a clinical trial using the experimental study drug MLN0128 (TAK-228). This clinical trial is sponsored by the NCI. MLN0128 (TAK-228) may interact with drugs that are processed by your liver. Because of this, it is very important to: ➢Tell your doctors if you stop taking any medicines or if you start taking any new medicines. ➢Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial. ➢Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	**MLN0128 (TAK-228)** interacts with a specific liver enzyme called CYP3A4**,** and must be used very carefully with other medicines that interact with this enzyme. ➢Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP3A4 ➢Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor. ➢Your study doctor's name is _____ and can be contacted at _____.