Protocol Title: Phase I / Randomized Phase II Study of MLN0128 (TAK-228) vs. Pazopanib in Patients with Locally Advanced / Unresectable and / or Metastatic Sarcoma

Target Population:
- High Grade Sarcoma
- Recurrent or Metastatic Synovial Sarcoma
- Uterine Corpus Leiomyosarcoma
- Recurrent or Metastatic Malignant Peripheral Nerve Sheath Tumor
- Recurrent or Metastatic Undifferentiated Pleomorphic Sarcoma

Summary:
- Phase I / II: To determine the safety and maximum tolerable dose of Sapanisertib (MLN0128 [TAK-228]) within this patient population.
- Phase II: To determine the differences in progression-free survival (PFS) in patients with Sarcoma who receive MLN0128 (TAK-228) as compared to Pazopanib.

Key Inclusion Criteria:
- Patients must have slides available for submission to central pathology review because this review is mandatory prior to registration to confirm eligibility and proper cohort assignment.
  - **HISTOLOGIC COHORT 1:**
    - Undifferentiated Pleomorphic Sarcoma (includes: Malignant Fibrous Histiocytoma, Myxofibrosarcoma, High Grade Sarcoma Not Otherwise Specified [NOS])
  - **HISTOLOGIC COHORT 2:**
    - Leiomyosarcoma (either Uterine or Extra-uterine)
  - **HISTOLOGIC COHORT 3:**
    - Other (either Malignant Peripheral Nerve Sheath Tumor or Synovial Sarcoma)
- Patients must have histopathologically confirmed Sarcoma of 1 of the subtypes listed, by central review.
- Locally Advanced or Metastatic Disease.
- Measurable Disease.
- Progression on at least 1 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.
- Prior treatment with Pazopanib or any PI3K, mTOR, Protein Kinase B (AKT), or dual PI3K/mTOR Complex (CREB Regulated Transcription Coactivator [TORC]1 / TORC2) Inhibitors will be prohibited.
- Chronic concomitant treatment with PPIs must discontinue use 7 Days prior to registration on the study.
- Chronic concomitant treatment with:
  - Strong CYP3A4 Inhibitors must discontinue use 14 Days prior to registration
  - Strong CYP3A4 Inducers must discontinue use 14 Days prior to registration

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For additional information: [https://clinicaltrials.gov/ct2/show/NCT02601209](https://clinicaltrials.gov/ct2/show/NCT02601209)