University of Wisconsin
Paul P. Carbone
Comprehensive Cancer Center

CO 08901 FAST FACT SHEET

CO 08901-"A Phase I Dose Escalation Study of Oral SB939 when administered Thrice Weekly (every other day) for 3 weeks in a 4-week cycle in Patients with Advanced Malignancies"

Principal Investigator: George Wilding, M.D.
Study Sponsor: S*BIO

Background: SB939 is a small molecule (dialkyl benzimidazole) competitive inhibitor of histone deacetylase (HDAC). It effectively inhibits acetylation of histones and various other target proteins in a variety of human tumor cell lines at the same concentrations as it inhibits proliferation and promotes apoptosis. Lymphomas and tumors of hematological origin show the highest sensitivity. The antitumor activity of orally administered SB939 has been demonstrated in several xenograft mouse models of solid and hematological malignancies including colorectal cancer, ovarian cancer, prostate cancer, AML and B cell lymphoma.

There are no findings from pharmacodynamic, pharmacokinetic and metabolism, and toxicology studies of SB939 that would preclude its development in human patients with relapsed or refractory cancers, provided adequate precautions are taken, consistent with those for other HDAC inhibitors that are currently in clinical trials and approved for marketing. The proposed starting dose for initiation of Phase I clinical studies in patients with advanced cancers is 10 mg/day. Phase I clinical studies will assess two schedules: (1) Dosing every other day three times weekly for 3 consecutive weeks, followed by 1 week off-dosing, with cycles repeated every 4 weeks and (2) Dosing on Days 1-5 and Days 15-19 (5 consecutive days followed by 9 days off-dosing) in a 4 week cycle. This Phase I study will assess the first of the two schedules listed above.

Objectives: The purpose of this study is to assess the safety & tolerability of SB939 when administered orally every other day 3 times a week for 3 weeks in 4 week cycles in patients with advanced malignancies. In addition, this study will determine the maximum tolerated dose (MTD), recommended phase II dose, dose limiting toxicities (DLTs), and pharmacokinetic (PK) profile of SB939 as well as assess the histone acetylation in PBMC & other biomarkers. Finally the anti-tumor activity of SB939 will be documented.

Treatment Plan: This is a multi-center, open-label, dose escalation study with 2 arms (Arm A and Arm B). Arm A will assess the safety and tolerability of escalating doses of SB939 in cohorts of patients with advanced solid tumors. Arm B will assess the safety and tolerability of escalating doses in cohorts of patients with advanced hematologic malignancies. The starting dose of SB939 will be 10mg three times a week (every other day) for 3 weeks of a 4 week cycle. Cohorts will consist of 3 to 6 subjects depending on dose limiting toxicities seen. Level of dose escalation will be determined after discussion between the investigator and the sponsor but will not increase more than 50%. Enrollment of Arm B will not start until the enrollment of the second cohort in Arm A has been opened. All subjects will have pharmacokinetic and pharmacodynamic assessments on study days 1, 8, and 15 of cycle 1. In addition, optional tumor biopsies (solid tumor subjects) will be obtained from all consenting subjects at baseline and cycle 1 day 15. Please note, the UWCCC will not be participating in the pharmacogenetic sub-study. When the MTD is reached, 3 additional subjects (in Arm A & B) will be added to confirm tolerability and PK/PD relationships.

Eligibility:

Arm A, Solid tumor patients inclusion criteria:

Must have pathologically-confirmed, locally advanced or metastatic solid tumors that are refractory to standard therapy or for which conventional therapy is not reliably effective
Must have evidence of unidimensionally measurable disease by radiographic assessments (CT or MRI)
Must be age ≥18 years
Must have ECOG performance status (PS) 0-2
Must have life expectancy ≥3 months
Patients must have adequate organ system function
Must not be pregnant or breastfeeding. Female patients must be surgically sterile or postmenopausal or must agree to use effective contraception during the period of treatment. All female patients with reproductive potential must have a negative pregnancy test (serum) within 14 days prior to enrollment
Male patients must be surgically sterile or must agree to use effective contraception during the period of treatment. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate
Must not have clinically significant co-morbidities, such as cardiac or pulmonary disease, active CNS disease, and active infection
Must not have known HIV infection
Must have ability to cooperate with treatment and follow-up
Must have ability to understand and willingness to sign informed consent prior to initiation of any study procedures

Arm B, Hematologic malignancy patients inclusion criteria:

Must have hematologic malignancy, including refractory or relapsing leukemia, high-risk MDS, MM, indolent or aggressive NHL, or Hodgkin's disease, that has failed, relapsed, or is not eligible for standard effective therapy or a peripheral blood stem cell transplant
Must be age ≥18 years
Must have ECOG performance status (PS) 0-2
Must have life expectancy ≥3 months
Patients must have adequate non-hematologic organ system function
Must not be pregnant or breastfeeding. Female patients must be surgically sterile or postmenopausal or must agree to use effective contraception during the period of treatment. All female patients with reproductive potential must have a negative pregnancy test (serum) within 14 days prior to enrollment.
Male patients must be surgically sterile or must agree to use effective contraception during the period of treatment. The definition of effective contraception will be based on the judgment of the principal investigator or a designated associate
Must not have clinically significant co-morbidities, such as cardiac or pulmonary disease, active CNS disease, and active infection
Must not have known HIV infection
Must have ability to cooperate with treatment and follow-up
Must have ability to understand and willingness to sign informed consent prior to initiation of any study procedures

Exclusion Criteria

Must be recovered from the reversible effects of previous chemotherapy, radiotherapy, or immunotherapy prior to enrollment
Must not have had any of the following in the past 12 months: myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, clinically symptomatic and uncontrolled cardiovascular disease, ongoing cardiac dysrhythmias of NCI CTC Grade ≥2, atrial fibrillation of any grade. Prolongation of the QTc interval to >450 msec for males or >470 msec for females at baseline
Must not have received any of the following within the specified time frame prior to administration of study drug: any investigational agent or enrolled in any clinical trials within 4 weeks; previous therapy for malignancy within 21 days, including any chemotherapy, immunotherapy, biological or hormonal therapy (6 weeks for nitrosoureas or mitomycin C); major surgery within 4 weeks
Must not have had concomitant treatment with HDAC inhibitors such as valproic acid
Must not have had known brain metastasis or leptomeningeal disease
Must not have had manifestation of malabsorption due to prior surgery, GI disease, or for an unknown reason. Patients may have had major GI surgery but must not have residual symptomatic manifestations of malabsorption
Must not have had any acute or chronic medical or psychiatric condition, or a laboratory abnormality that may increase the risks associated with study participation/study drug administration or may interfere with the interpretation of study results

Potential Toxicities:
This is the first time SB939 will be tested in humans. Expected toxicities based on animal studies include neutropenia, thrombocytopenia, and shrinking of male reproductive organs with decreased sperm counts (which was reversible after stopping the drug).

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