University of Wisconsin
Paul P. Carbone
Comprehensive Cancer Center

HO 09902 FAST FACT SHEET

HO 09902- "An Open Label, Dose-Escalation, Phase 1 Study of MLN9708, A Second-Generation Proteasome Inhibitor, in Adult Subjects with Lymphoma"

Principal Investigator: Julie Chang, M.D.
Study Sponsor: Millennium Inc.

Background: MLN9708 is a proteasome inhibitor that has had activity in lymphoma animal models. It is felt that MLN9708 is a more potent proteasome inhibitor than VELCADE (bortezomib), another proteasome inhibitor which has established activity in lymphomas. This patient population has few good treatment options available once disease has transformed or relapsed.

Objectives: The primary objective of this study is to determine the maximum tolerated dose (MTD), safety profile, & recommended phase 2 dose of MLN9708 administered by IV in lymphoma patients. This study will also characterize the pharmacokinetics & pharmacodynamics of MLN9708 in blood & urine. This study will assess any disease response. Exploratory objectives include assessing potential relationship between polymorphic variations in genes encoding CYPS and drug transporters and the systemic exposure and clinical effects of MLN9708; assess relationship of candidate biomarkers of tumor responsiveness to therapy & MLN9708 anti-tumor activity using archived tumor specimens; and assess potential relationships between MLN9708 treatment and electrocardiogram parameters.

Treatment Plan: This is an open-label, multicenter, phase 1, dose-escalation study of MLN9708. MLN9708 will be given via IV bolus on days 1, 8, & 15 of 28 day treatment cycles. A modified accelerated titration design will be used to determine the MTD of MLN9708. If one patient experiences a DLT, or any 2 patients exhibit MLN9708 related grade 2 or greater toxicity, or dose level 1mg/m2 has been evaluated, dose escalation will then follow a conservative 3+3 design. Once the MTD is established, a total of 16 patients at the MTD will be evaluated to more fully characterize the safety, tolerability, PK, and pharmacodynamics of MLN9708 & evaluate disease response.

Eligibility:

Must be male or female patient 18 years or older.
Must have ECOG PS of 0-2
Must have a confirmed diagnosis of lymphoma that is relapsed and/or refractory after at least 2 prior chemotherapeutic regimens and for which no curative option exists. Subjects with Waldenstrom's macroglobulinemia are not eligible for enrollment in this study. Subjects with Hodgkin lymphoma are considered eligible for this study.
Must have radiographically or clinically measurable disease as defined by the IWG criteria (see protocol)
Must have suitable venous access for the study-required blood sampling for PK and pharmacodynamic evaluations.

Female patients must be -postmenopausal for at least 1 yr before the scrn. visit, OR -surgically sterile, OR -if they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug, or agree to completely abstain from heterosexual intercourse.
Male patients must: -agree to practice effective barrier contraception during the entire study treatment period and through 30 days after the last dose of study drug, OR -agree to completely abstain from heterosexual intercourse
Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
Must have clinical lab values as specified below within 3 days before the first dose of study drug: ANC 1250/mm3; Platelet > 100,000/ mm3; T. Bili < 1.5 x ULN; ALT or AST must be < 2.5 x ULN. AST and ALT may be elevated up to 5 x ULN if their elevation can be reasonably ascribed to the presence of disease in the liver. Creat. Clearance or calculated creatinine clearance > 30mL/minute
Must not have neuropathy > gr. 2 on clinical examination
Female patients must not be lactating or must not have a positive serum preg. test during the scrning period
Must not have autologous stem cell transplant within 6 months before Day 1 of Cycle 1 or prior allogeneic stem cell transplant at any time.
Must not have had major surgery within 14 days before the first dose of study drug
Must not have infection requiring systemic antibiotic therapy or other serious infection within 14 days before the first dose of study treatment.
Must not have life-threatening illness unrelated to cancer
Must not have diarrhea > gr. 1 based on NCI CTC categorization
Must not have systemic antineoplastic therapy within 21 days preceding first dose of study treatment, or rituximab therapy within 2 months preceding first dose of study treatment (unless there was evidence of PD since their last dose of rituximab).
Must not have had radiotherapy within 21 days before the first dose of study treatment
Must not have systemic treatment with: -strong inhibitors of CYP1A2 (fluvoxamine, enoxacin), -strong inhibitors of CYP3A (clarithromycin, telithromycin, intraconazole, voriconazole, ketoconazole, nefazodone) or -strong CYP3A4 inducers (rifampin, riapentine, rifabutin, carbamazepine, phenytoin, Phenobarbital) within 14 days before the first dose MLN9708
Must not have ongoing therapy with corticosteroids
Must not have clinically uncontrolled CNS involvement. Patients who have a history of CNS involvement, but no evidence of active CNS disease are not excluded.
Must not have evidence of current uncontrolled cardiovascular conditions, including cardiac

arrhythmias, congestive heart failure (CHF), angina, or myocardial infarction within the past 6 months
Must not have QTc > 470 milliseconds (msec) on a 12 lead ECG obtained during the screening period. If a machine reading is above this value, the ECG should be reviewed by a qualified reader and confirmed on a subsequent ECG. Look at C1 D1 QTC also.
Must not have known HIV positive
Must not have known hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection
Must not have any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
Must not have treatment with any investigational products within 28 days before the first dose of study treatment
Must not have known allergy to boron or excipients in the formulation

Potential Toxicities: The likely side effects of MLN9708 based on animal studies include:

- Gastrointestinal effects such as feeling nauseous, vomiting, diarrhea, dehydration, electrolyte imbalance (blood chemical imbalance), and blockage in bowel function;
- Low platelet count;
- Lowering of lymphoid cells (a type of immune cells) that may be associated with reactivation of the herpes virus infection such as herpes zoster (shingles) that can sometimes cause local pain that may last after recovery from the skin rash and does not go away for some time.
- Effects on nervous system that may cause painful feelings or numbness or tingling in hands and feet. The nerves that control things like heart rate, gut movement, and urinary bladder may be affected.

There also may be side effects that are not known. There is a risk of death from this investigational treatment.

Study Contact: Phase I Program, UW Paul P. Carbone Comprehensive Cancer Center
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