University of Wisconsin
Paul P. Carbone
Comprehensive Cancer Center

CO 08914 FAST FACT SHEET

CO 08914: Phase I Study of PXD101 in Combination with 5-Azacitidine (5-Aza) for Advanced Hematologic Malignancies

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Study Sponsor: NCI

Background: It's believed that combining PXD101 with the DNA hypomethylating agent 5-Aza will lead to an additive or synergistic effect on transcriptional de-repression and upregulation of specific target genes. In the dose escalation part of the study we plan to establish the MTD of PXD101 when given with a fixed dose of 5-Aza. Once the MTD is established, this cohort will be expanded to enroll additional patients that will be randomized to either the 5-Aza (control arm) or the combination (PXD101+ 5-Aza) in the first cycle only, and will have tumor samples collected for pharmacodynamic assays. The randomized portion of the study will enable the establishment of a proof of concept principle for any additive or synergistic effects of the combination on re-expression of specific target genes. This may serve as a platform for the design of future randomized Phase II studies to investigate the efficacy of the combination in a relatively homogenous patient population.

Objectives: The primary objective of this study is to determine the maximum tolerated dose (MTD) of PXD101 when it is given in combination with azacitidine. This study will also look at if any synergistic effects of the combination of the two drugs exist on pharmacodynamic parameters (including apoptosis and re-expression of specific target genes). Lastly, this study will assess any evidence of clinical activity of this combination in patients with advanced hematologic malignancies.

Treatment Plan: This is a multi-center, open-label, Phase I study with a Dose Escalation and Dose expansion portion. This is a traditional design to determine the primary objectives of the study: safety & tolerability, synergistic effects, and clinical efficacy that will allow further exploration at the MTD between a control arm and the radomized arm.

Correlative studies will be obtained on the randomized portion of the study only. Bone marrow (aspirates only) will be collected at baseline, day 4 or 5 (post therapy), and after 1 cycle of therapy. The baseline and post course 1 samples are considered standard of care, however a portion of them will be used for research purposes. Course 1 Day 4 (or 5) bone marrow aspirates and biopsies will be for research ONLY (not standard of care) and these will only be done on subjects enrolled onto the randomized portion of the study.

Eligibility:

Must have histologically confirmed diagnosis of one of the following: ▪ Relapsed or refractory acute myeloid leukemia (AML)--must also have evidence of dysplasia on bone marrow histology. ▪ Secondary AML including AML arising from antecedent hematologic diseases such as myelodysplastic or myeloproliferative disorders or therapy related AML - must have evidence of dysplasia on bone marrow histology ▪ Elderly patients over the age of 60, previously untreated who are not candidates for or who are unwilling to undergo induction therapy for AML - must also have evidence of AML associated with dysplasia on bone marrow histology ▪ Myelodysplastic syndromes (MDS) including chronic myelomonocytic leukemia (CMMOL). ▪ Patients with MDS must have intermediate or high risk IPSS scores (≥ 0.5) to be eligible (see Appendix B). ▪ MDS patients with low risk IPSS scores must have one or more of the following criteria to be eligible: ▪ Hg < 10 g/dL and/or red cell transfusion dependence ▪ Platelets < 50,000/uL ▪ ANC < 1,000/uL The disease must be refractory to standard therapy or one for which no standard therapy exists.
Three is no limitation to the number of prior regimens received. At least 2 weeks must have elapsed since prior chemotherapy or radiation (6 weeks for mitomycin c and nitrosoureas, 4 weeks if prior therapy was with an investigational agent) with the exception of hydroxyurea which may be administered up to 24 hours prior to starting therapy. Patients must have recovered from clinically significant toxic effects of prior therapy.
Must be ≥ 18 years old. Because no dosing or adverse event data are currently available on the use of PXD101 in combination with 5-azacytidine patients < 18 years of age, children are excluded from this study, but will be eligible for future pediatric phase 1 combination trials.
Must have CALGB performace status ≤ 2 (Karnofsky ≥ 60%, see Appendix A).
Must have organ and marrow function within the limits defined below: ▪ total bilirubin ≤ 2.0 mg/dL (unless due to Gilbert's syndrome) ▪ ALT (SGPT) ≤ 3X institutional upper limit of normal (unless due to disease) ▪ creatinine ≤ 2 mg/dL
The effects of PXD101 on the developing human fetus are unknown. For this reason and because HDAC inhibitors as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Discussed w/ pt.on _____(date) & they agree w/ compliance of elig. criteria. Y_____ N_____ N/A_____
Must have ability to understand and the willingness to sign a written informed consent document.
Must not have had chemotherapy or radiotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier.
Must not be receiving other investigational agents.

Patients with known active CNS involvement with disease should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation or neurologic and other adverse events.
Must not have history of allergic reactions attributed to compounds of similar chemical or biologic composition to PXD101 or 5-azacytidine.
Must not have history of allergic reactions to mannitol.
Must not have history of dose limiting toxicity on prior treatment with 5 azacytidine.
Must not have taken valproic acid another histone deacetylase inhibitor for at least 2 weeks prior to enrollment
Must not have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symtomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
Pregnant women are excluded from this study because PXD101 is an HDAC inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with PXD101, breastfeeding should be discontinued if the mother is treated with PXD101. These potential risks may apply to other agents used in this study.
Must not be HIV positive on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with PXD101. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.
Patients with a marked baseline prolongation of QT/QTc interval, for example, repeated deomnstration of a QTc interval > 500 msec; Long QT Syndrome; or patients with a required use of concomitant medication on PXD101 infusion days that my cause Torsade de Pointes (See Appendix C below for list), should be excluded from this study. Drugs that may cause Torsade de Pointes: Disopyramide, Dofetilide, Ibutilide, Procainamide, Quinidine, Sotalol, Bepridil, Amiodarone, Arsenic Trioxide, Cisapride, Calcium-channel Blockers: lidoflazine (not marketed in the United States), Antinfective agents (clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxin), antiemetic agents (domperidone, droperidol), antipsychotic agents (chlopromazine, haloperidol, mesoridazine, thioridazine, pimozide, methadone)
Must not have uncontrolled cardiovascular disease including unstable angina pectoris, severe uncontrolled hypertension, uncontrolled congestive heart failure related to primary cardiac disease, uncontrolled cardiac arrhythmiz, uncontrolled ischemic or severe valvular heart disease, or a myocardial infarction within 6 months prior to the trial entry.

Potential Common Toxicities:
PXD101: fatigue, malaise (tiredness, loss of strength), nausea
Azacitadine: low white blood cell count, low platelets, fatigue, injection site reaction, constipation, rash, nausea

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