A novel regimen for relapsed/refractory adult acute myeloid leukemia using a *KMT2A* partial tandem duplication targeted therapy: results of phase 1 study NCI 8485

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APPENDIX 1

Eligibility Criteria

1) Patients must be age ≥18 and <60 with relapsed or refractory acute myeloid leukemia (AML).
2) Patients with secondary AML or therapy related disease (t-AML) are eligible. Patients who received decitabine or 5-azacytidine as prior treatment for myelodysplastic syndrome or AML are eligible. Patients who previously received high dose cytarabine (≥1gm/m^2/dose) are eligible.
3) If the patient has co-morbid medical illness, life expectancy attributed to this must be greater than 6 months.
4) ECOG performance status ≤2
5) Patients must have adequate organ function as defined below:
    a. Total bilirubin <2.0mg/dL
    b. AST(SGOT)/ALT(SGPT) <2.5x institutional upper limit of normal
    c. Creatinine <2.0mg/dL
    d. New York Heart Association (NYHA) Congestive Heart Failure (CHF) Class II or better
6) The effects of decitabine, vorinostat, and cytarabine on the developing human fetus at therapeutic doses are unknown. For this reason, 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. If the patient does not agree, the patient is not eligible. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
7) Ability to understand and willingness to sign the written informed consent.
8) Patients with known HIV infection without a history of AIDS and with sufficiently high CD4 cells (>400/mm^3) and low HIV viral loads (<30,000 copies/ml plasma) not requiring anti-HIV therapy are eligible.
9) Patients must have recovered from the toxicity of prior therapy to less than Grade 2.
10) Patients who 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 (to less than grade 2) due to agents administered more than 4 weeks earlier.
11) Patients may not have taken valproic acid, or any other histone deacetylase inhibitor, for at least 2 weeks prior to study enrollment.
12) Patient receiving any other investigational agents or patients that have received other investigational agents within 14 days of enrollment.
13) Patients with active central nervous system disease or with granulocytic sarcoma as sole site of disease.
14) Patients with history of medically serious allergic reactions attributed to decitabine, vorinostat, or cytarabine or compounds of similar chemical or biologic composition that are not easily managed.
15) Patients with the following will be excluded: uncontrolled intercurrent illness including but not limited to, symptomatic congestive heart failure, unstable angina pectoris, serious cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements, myocardial infarction within 6 months prior to enrollment, New

York Heart Association (NYHA) Class III or IV heart failure, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Patients with medical comorbidities that will preclude safety evaluation of the combination should not be enrolled.

16) Patients with serious medical or psychiatric illness likely to interfere with participation in this clinical study.
17) Pregnant women or women who are breastfeeding are not eligible because decitabine, vorinostat and cytarabine are agents 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 decitabine, vorinostat and cytarabine, breastfeeding should be discontinued. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
18) Patients with advance malignant solid tumors are excluded. Patients with active additional hematologic malignancies are excluded.
19) Patients with a history of neurologic toxicity with cytarabine or vorinostat are excluded.
20) As infection is a common feature of AML, patients with active infection are permitted to enroll provided that the infection is under control. Patients with uncontrolled infection shall not be enrolled until infection is treated and brought under control.
21) Patients who are unable to swallow pills are excluded.
22) Patients requiring warfarin are excluded.