

TYPE OF CANCER: Adult Cancer Patients
(Myelodysplastic Syndrome, Acute Myelogenous Leukemia, Solid Tumors)

TYPE OF TRIAL: Phase I

TRIAL SPONSOR: Celgene

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STUDY SUMMARY

A Phase I, Open-Label, Multi-Center, Parallel Group Study to Assess the Pharmacokinetics and Safety of Subcutaneous Azacitidine in Adult Cancer Patients With and Without Impaired Renal Function

TREATMENT OVERVIEW

- Patients who choose to go on study will be randomized to receive Azacitidine subcutaneously at different dose levels for either 1 day or 5 consecutive days

PRE-TREATMENT ASSESSMENTS

- Demographics
- Medical and cancer history
- Physical examination
- Vital Signs
- Height, weight, and BSA
- ECOG performance score
- 12-lead ECG
- Prior and concomitant medication
- Hematology
- Serum Chemistry
- Pregnancy test (if applicable)
- Calculated creatinine clearance

ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL

INCLUSION CRITERIA

1. Diagnosis of one of the following:
 - MDS according to the French-American-British (FAB) classification system:
 - refractory anemia [RA],
 - RA with ringed sideroblasts [RARS],
 - RA with excess blasts [RAEB],
 - RAEB in transformation [RAEB-T], or

- chronic myelomonocytic leukemia [CMML]; or
 - acute myelogenous leukemia [AML] in remission; or
 - malignant solid tumor (histologically or cytologically confirmed);
- 2. Solid tumor patients must have metastatic (except hepatic) or inoperable solid tumors for which no standard treatment exists, or have progressed or recurred following prior therapy. Patients must not be eligible for therapy of higher curative potential (where an alternative therapy has been shown to prolong survival in an analogous population). Measurable or evaluable disease is preferred but not required;
- 3. Patients with a history of treated brain metastases should be clinically stable for ≥ 4 weeks prior to signing the informed consent form and off glucocorticoid therapy for CNS edema for at least 4 weeks;
- 4. Be capable of giving informed consent, have signed the informed consent form, and be willing to comply with scheduled visits, dose administration, laboratory tests, and other study procedures;
- 5. Be ≥ 18 years of age;
- 6. Have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2;
- 7. Have a life expectancy ≥ 3 months;
- 8. Have stable renal function for at least 2 months prior to the first day of treatment (Day 1);
- 9. Have average calculated creatinine clearance of:
 - >80 mL/min/1.73m² for Cohorts 1, 2, 3, and 4,
 - < 30 mL/min/1.73m² for Cohort 5 - Severe renal impairment,
 - 50-80 mL/min/1.73m² for Cohort 6 - Mild renal impairment,
 - 30 to < 50 mL/min/1.73m² for Cohort 7 - Moderate renal impairment;
- 10. Have organ and marrow function at the screening and pre-dose visits as defined by:
 - Hemoglobin ≥ 8 g/dL,
 - Absolute neutrophil count $\geq 1.0 \times 10^3/\mu\text{L}$,
 - Platelets $\geq 50 \times 10^3/\mu\text{L}$,
 - Total bilirubin ≤ 1.5 times the upper limit of normal (ULN),
 - AST ≤ 2 times the ULN, and
 - ALT ≤ 2 times the ULN;
- 11. Have a 12-lead electrocardiogram (ECG) that is not clinically significant, as determined by the Investigator, at screening;
- 12. Have serum bicarbonate or serum CO₂:
 - ≥ 20 mEq/L for patients with normal renal function (Cohorts 1, 2, 3 and 4),
 - ≥ 16 mEq/L for patients with impaired renal function (Cohorts 5, 6 and 7);
- 13. Women of childbearing potential may participate, providing they meet the following conditions:

- Have a negative serum pregnancy test (β -HCG) obtained at screening, and a negative urine pregnancy test obtained prior to dosing on Day 1,
 - Agree to use at least 2 effective contraceptive methods throughout the study;
14. Males with a female partner of childbearing potential must agree to use at least 2 effective contraceptive methods throughout the study;
 15. Be a nonsmoker or must not have smoked for at least 30 days before the screening visit and agree to abstain from smoking during study participation.

EXCLUSION CRITERIA

1. Women who are pregnant or nursing;
2. Had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to the first day of treatment (Day 1);
3. Have been treated with an investigational agent within 4 weeks prior the first day of treatment (Day 1);
4. Have ongoing clinically significant adverse event(s) due to chemotherapy, radiotherapy or investigational agents administered more than 4 weeks prior to the first day of treatment (Day 1) as determined by the Investigator;
5. Have known or suspected hypersensitivity to azacitidine or mannitol;
6. Have an uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or social situations that would limit compliance with study requirements, as determined by the Investigator;
7. Have low blood pressure (supine blood pressure <90/60 mmHg);
8. Have psychiatric illness or alcohol / chemical abuse which would prevent granting of informed consent;
9. Have human immunodeficiency virus (HIV) or active hepatitis virus B or C;
10. Have advanced malignant hepatic tumors;
11. Have end-stage renal disease requiring dialysis.