A Phase I/II Study of GMI-1271, a Novel E-selectin Antagonist, in Combination with Induction Chemotherapy in Relapsed/Refractory and Previously Untreated Elderly Patients with Acute Myeloid Leukemia; Results to Date

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ABC level: 4

Background

Treatment of patients with acute myeloid leukemia (AML) remains a significant challenge. Poor outcomes result from low response rates and short duration of remission when achieved. Although intensive chemotherapy remains the cornerstone of treatment, novel agents are needed to improve clinical outcomes.

Methods

A Phase I/II open-label trial evaluating GMI-1271 co-administered with chemotherapy was conducted. Eligible patients (≥18 years) with untreated or chemically relapsed/refractory AML (Phase 1) or previously untreated AML (Phase 2) were eligible. GMI-1271 was administered on days 1 and 8 of each chemotherapy cycle. Patients were stratified into safety/tolerability and PK/PD groups.

Results

Pharmacokinetics

Pharmacokinetic (PK) analysis showed dose-proportional kinetics and elimination 1-2.5 h after administration. Clearance of GMI-1271 was in a typical 65-year-old subject was 1.82 h. Overall, clearance of GMI-1271 decreased about 2% per year with age, possibly as a function of changes in creatinine clearance. PK profiles (shown below) were consistent with previously healthy volunteer trials.

Clinical Outcomes

Since baseline to Day 1 at the end of 4 days of GMI-1271 given concurrently with MDS chemotherapy was highly significant (p<0.0001), no dose responses were seen.

Conclusions

We report the Phase I/II Phase 2 Clinical Assessment of novel e-selectin antagonist GMI-1271 in combination with induction chemotherapy in heavily pretreated, high-risk patients with relapsed/refractory AML pilot Phase 2 assessment of the same in older patients with newly diagnosed AML. Safety

The combination of GMI-1271 with induction chemotherapy (MEC or 7+3) has been well tolerated with no Dose Limiting Toxicities seen in Phase 1 dose escalation (R) or in Phase 2 Safety Run-in (Am B).

PK/PD

GMI-1271 plasma levels were above levels associated with anti-leukemic activity in animal models of AML Reduction in all leukemic cell burden and minimal disease after the combination of the three doses in Phase 3

Clinical Outcomes

CR rate was 45% for those with R/R disease (combined Phase 1/Phase 2); no observable dose response in Phase 1

Median follow up for Phase 1 is 163 days; median OS and DSS have not been reached

CR rate was 73% for older adults (≥80 years) with newly diagnosed AML, with no deaths in the first 60 days

Current Status

20 subjects have enrolled (of 47 planned) in Arm A; 14 subjects (of 25 planned) in Arm B

Summary

Complete response rate appears higher than expected given the high risk patient population and disease features in these patients. Remission duration has been sufficient to allow patients to proceed to hematopoietic cell transplant (N=7 to date).

Planing is underway for randomized controlled trials.