A Phase I Study of Vosaroxin Plus Azacitidine for Patients with Myelodysplastic Syndrome

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INTRODUCTION

Although hypomethylating agents (HMAs) are the mainstay of treatment for myelodysplastic syndromes (MDS), these agents provide remission in a minority of patients and are not curative.

The combination of vosaroxin and azacitidine was found to be synergistic in primary myeloblasts (CD34+CD45dim) by flow cytometry. Non-responders to additional patient samples is ongoing.

STUDY DESIGN

Patient characteristics

Summary of Patient Outcomes

Summary of Best Responses

Primary objectives: To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of vosaroxin when given in combination with azacitidine in patients with MDS.

Secondary objectives: To determine best response (including hematologic improvement) in ≥1 cycles, best overall response, and time to response in patients treated with vosaroxin plus azacitidine according to Modified IWG criteria; to describe the tolerability of vosaroxin plus azacitidine; and to describe the safety and tolerability of vosaroxin plus azacitidine plasma concentrations with multiple-dose regimens. Vosaroxin is an orally available pharmacologic agent that targets DNA methylation and has been shown to have activity in hematologic malignancies.

Exploratory objectives: To prospectively collect all existing blood and bone marrow specimens in a manner that preserves blast identity, to determine the safety and tolerability of vosaroxin plus azacitidine plasma concentrations with multiple-dose regimens. Vosaroxin is an orally available pharmacologic agent that targets DNA methylation and has been shown to have activity in hematologic malignancies.

Patient Characteristics

- Abbreviations: RCMD, Refractory cytopenia with multilineage dysplasia; RAEB-1, Refractory anemia with excess blasts-1; RAEB-2, Refractory anemia with excess blasts-2; CMML, Chronic myelomonocytic leukemia; IPSS, International Prognostic Scoring System; N/A, Not applicable; N/E, Not evaluable

Evaluation of Dose Escalation and Dose Limiting Toxicity

Figure 1: Dose Escalation and Dose Limiting Toxicity

- The MTD of vosaroxin in MDS patients was 34 mg/m²/day when given on 3 of 7 days, with a head dose of 75 mg/m²/day on days 1–7.

Table 1: Evaluation of Dose Escalation and Dose Limiting Toxicity

- The major non-hematologic toxicities of febrile neutropenia, infection, and mucositis were expected to be more frequent in the dose-escalation population and patients with higher disease burden.

The combination of vosaroxin and azacitidine showed promising activity with responses rates comparable or better than those generally observed with HMAs treated with vosaroxin. The results of this study confirm the tolerability and activity of the combination of vosaroxin and azacitidine from primary patient samples is ongoing.

Table 2: Summary of Best Responses

Table 3: Summary of Grade 3 or Greater Toxicities

Figure 2: Summary of Grade 3 or Greater Toxicities

Table 4: Summary of Patient Outcomes

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Figures 1–3: Illustrations from the study showing the dose escalation and dose limiting toxicity in patients treated with vosaroxin plus azacitidine.

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