**Voreloxin in Combination with Cytarabine Demonstrates Preliminary Clinical Responses in a Phase 1b/2 Study In Relapsed/Refractory Acute Myeloid Leukemia**

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**ABSTRACT – UPDATED**

**Background:** Voreloxin is a first-in-class, replication-dependent, cell-selective DNA damaging agent that causes apoptosis by DNA intercalation and inhibition of topoisomerase II. A previous Phase 1 study of single-agent voreloxin demonstrated acceptable safety and strong signs of clinical activity in patients with relapsed/refractory AML (ASH 2017). In traditional models, the combination of voreloxin and cytarabine demonstrated enhanced activity (ASH 2006). Preliminary results of an ongoing Phase 1b study of combination voreloxin plus cytarabine in relapsed/refractory AML patients are reported. Objectives: 1) establish safety, tolerability and MTD of escalating doses of voreloxin in combination with cytarabine; 2) characterize voreloxin PK in combination with cytarabine; 3) assess clinical activity by IWG criteria; 4) explore pharmacodynamic markers of patient response; 5) evaluate voreloxin sensitivities in bone marrow aspirates (BMA). Methods: Open label Phase 1b study with dose escalation of voreloxin given on days 1 and 4 in 4+1 combination with two schedules of cytarabine: Schedule A: cytarabine at 400 mg/m2/day for 5 days; 70 mg/m2 X 5 days. Schedule B: voreloxin 1 g/m2 2 hr IV infused for 5 days. Objectives: Study design, Populations, Voreloxin Regimen, Cytarabine Regimens, Objectives, Study Schedule and Dose Escalation, Schedule A: Exclusion criteria, Population, safety, Pharmacokinetics, Clinical Activity, Pharmacodynamics, Conclusions and Future Directions.

**STUDY OBJECTIVES AND TRIAL DESIGN**

**Study Design:** Phase 1b dose-escalation with Phase 2 expansion at MTD. Voreloxin combined with two cytotoxic treatment regimens.

**Populations:**

- **Phase 1b: dose-escalation:**
  - 30 patients Schedule A dose-escalation.
  - 5 patients Schedule B dose-escalation.
  - MTD of voreloxin is 80 mg/m2

- **Phase 2 expansion:**
  - 163 patients including 38 patients with refractory relapsed AML.
  - 45 patients with refractory relapsed AML treated to date.

- **Schedules:**
  - **Schedule A:** voreloxin (D1,D4) in combination with CIV cytarabine (400 mg/m2 qd X 5)
  - **Schedule B:** voreloxin (D1,D4) in combination with bolus (2 hr infusion) cytarabine (1 g/m2 qd X 5)

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**SAFETY SCHEDULE A: VORELOXIN WITH CIV CYTARABINE**

**Non-Hematologic Grade 3 or 4 AEs**

- **Prior Tx**
  - 10 4 0 0

- **Vor. Dose**
  - 70 7 1 (sepsis death) 1 CR, 1 CRp

- **Open pending Schedule B MTD determination**

- **Favorable**
  - 1 CR

- **Refractory relapse**
  - 1 CR

- **Frontline**
  - 1 CRp

**PHARMACODYNAMICS – EX Vivo PATIENT EX VIVO RESPONSE TO VORELOXIN AND CYTARABINE**

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**CONCLUSIONS AND FUTURE DIRECTIONS**

Voreloxin plasma exposure (AUC) increased from 10 – 50 mg/m2 above 50 mg/m2, exposure appeared to plateau. Voreloxin levels above in vitro (60) and IC50 were sustained at 80 mg/m2 MTD for 163 hr (8.6 d) and 58 hr (2.4 d), respectively.

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**CHARACTERISTICS OF RESPONDERS SCHEDULE A**

**Voreloxin Plasma Pharmacokinetics**

**Voreloxin Plasma PK Parameters**

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- **Characteristics of responders Schedule A**

Voreloxin has a Validated Mechanism of Action With Distinct Advantages Over Anthracyclines

**VORELOXIN MECHANISM OF ACTION**

Voreloxin has a Validated Mechanism of Action With Distinct Advantages Over Anthracyclines

1. Voreloxin: Novel topoisomerase II inhibitor and DNA intercalator
   - Active in anthracycline-resistant settings
   - Not a p53/p63/p73-responsive agent
   - Low potential for drug-drug interaction

2. Naphthyridine Core
   - Active in anthracycline-resistant settings
   - Low potential for drug-drug interaction
   - Anthrapyridine genotoxic DNA adducts
   - Reactive Oxygen Species (implicated in cardiotoxicity), unlike voreloxin

3. Voreloxin is the primary contributor to the majority of complete remissions.

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5. Voreloxin Pharmacokinetics: CIV Patient vs Voreloxin and Cytarabine

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Cytarabine plasma exposure (AUC) increased from 10 – 50 mg/m2 above 50 mg/m2, exposure appeared to plateau. Voreloxin levels above in vitro (60) and IC50 were sustained at 80 mg/m2 MTD for 163 hr (8.6 d) and 58 hr (2.4 d), respectively.

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