

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

J. Lancet¹, J Karp², L Cripe³, G Roboz⁴, M Suster⁵, C Berman⁵, N Tan⁵, RE Hawtin⁵, JA Fox⁵, GC Michelson⁵

¹Moffitt Cancer Center, Tampa FL; ²Sidney Kimmel Cancer Center, Baltimore MD; ³Indiana University Cancer Center, Indianapolis IN;

⁴Cornell University/ New York Presbyterian Hospital, NY NY; ⁵Sunesis Pharmaceuticals, Inc., South San Francisco CA

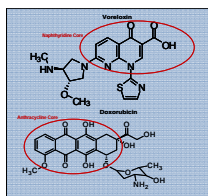


ABSTRACT – UPDATED

Background: Voreloxin is a first-in-class, replication-dependent, site-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 2007). In nonclinical 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; 4) explore pharmacodynamic markers of patient response; 5) evaluate ex vivo voreloxin sensitivity in bone marrow aspirates (BMA). **Methods:** Open label Phase 1b/2 study with dose escalation of voreloxin given on days 1 and 4 in combination with two schedules of cytarabine. Schedule A- cytarabine at 400 mg/m²/day continuous IV infusion (CIV) X 5 days; Schedule B- cytarabine at 1 gm²/IV daily bolus X 5 days. Voreloxin starting dose was 10 mg/m² for Schedule A and 70 mg/m² for Schedule B. Dose-limiting toxicities (DLTs) and PK were assessed during cycle 1. Pre- and post-dose PBMC were obtained to evaluate modulation of DNA damage response markers as possible indicators of patient response. Baseline BMA were evaluated for ex vivo sensitivity to voreloxin and cytarabine using the CellTiter-Glo[®] proliferation assay (assay conducted at Oncotech). Clinical response was determined by IWG criteria. Patients could receive up to 2 courses of induction, and patients achieving CR or CRp could receive up to 2 additional courses as consolidation. At MTD, additional cohorts of patients will be enrolled at both Schedules into Phase 2 arms (dose expansion) to assess response and safety in a first relapse population. **Results:** To date, 45 patients have been treated (39 patients Schedule A, dose escalation; 3 patients Schedule A dose expansion; 3 patients Schedule B, dose escalation). Preliminary data is available for 38 patients Schedule A, dose escalation only. MTD for this schedule is 80 mg/m². Safety: 2 DLTs were observed in 7 patients treated at 90 mg/m² (1 grade 3 diarrhea and bowel obstruction and 1 grade 3 oral mucositis lasting ≥ 7 days). Predominant grade 3/4 non-hematologic AEs ≥ 5% incidence (cumulative incidence): were infections (pneumonia, sepsis, etc. (38%). The most common reason for early study termination was disease progression. Voreloxin pharmacokinetics were dose proportional from 10 – 50 mg/m²; between 50 – 90 mg/m² exposure appeared to plateau. CRs and CRps were observed at voreloxin doses ≥ 20 mg/m², including patients with multiply relapsed or primary refractory disease. Predose BMA were available from 7 of 9 CR/CRp patients for use in the ex vivo activity assay. Most patients were Extreme Drug Resistant (EDR) to cytarabine (5 of 7); only 1 patient was EDR to voreloxin. These data suggest that voreloxin is the primary contributor to the majority of complete remissions observed to date. **Conclusions:** Voreloxin given in combination with continuous infusion cytarabine is well-tolerated, with encouraging signs of activity in patients with relapsed/refractory AML. An MTD of 80 mg/m² was established for Schedule A. Enrollment to the Phase 2 portion of Schedule A and to the Phase 1b dose escalation for Schedule B is ongoing. Ex vivo activity assay results suggest that voreloxin is the primary contributor to the majority of complete remissions.

VORELOXIN MECHANISM OF ACTION

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



Voreloxin: Novel topoisomerase II inhibitor and DNA intercalator

- Active in anthracycline-resistant settings
 - Not a P-glycoprotein substrate
 - Unaffected by p53, p63 or p73 status
 - Not a CYP450 inhibitor or inducer
- Low potential for drug-drug interaction
- Lower potential for cardiotoxicity than anthracyclines
 - Anthracyclines generate substantial Reactive Oxygen Species (implicated in cardiotoxicity), unlike voreloxin

STUDY OBJECTIVES AND TRIAL DESIGN

Study Design	Phase 1b dose-escalation with Phase 2 expansion at MTD Voreloxin combined with two cytarabine treatment regimens
Populations	Dose escalation: relapsed or refractory AML ≤ 3 prior regimens for AML Expansion at MTD: first relapse AML with duration of CR ≥ 3 months
Voreloxin Regimen	D1, D4
Cytarabine Regimens	Schedule A: 400 mg/m ² /d CIV for 5 days Schedule B: 1 gm ² /d 2 hour IV infusion for 5 days
Objectives	Safety, pharmacokinetics and anti-leukemic activity

STUDY STATUS

Schedule A: Dose Escalation	Completed. MTD of voreloxin is 80 mg/m ² D1,D4 with CIV cytarabine (400 mg/m ² /d X 5 d)
Schedule A: Dose Expansion	Currently Enrolling
Schedule B: Dose Escalation	Cohort 1 open: 70 mg/m ² voreloxin D1,D4 with 2 hr IV infusion cytarabine (1 gm ² /d X 5d)
Schedule B: Dose Expansion	Open pending Schedule B MTD determination

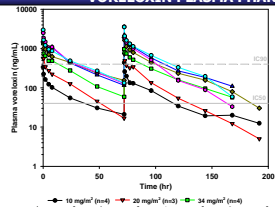
DEMOGRAPHICS - SCHEDULE A (CIV CYTARABINE)

Number of patients	38
Age (range)	61 (30-75) yrs
Gender (f pts)	27M 11F
Median Prior Regimens (Range)	2 (1-4)
Cytogenetics (%)	
Favorable	3
Intermediate	55
Unfavorable	32
Unknown	11
Disease Status (%)	
1 st relapse	24
2 nd relapse	16
1 st refractory	40
Refractory relapse	11
Frontline	5
Unknown	5

SAFETY SCHEDULE A: VORELOXIN WITH CIV CYTARABINE

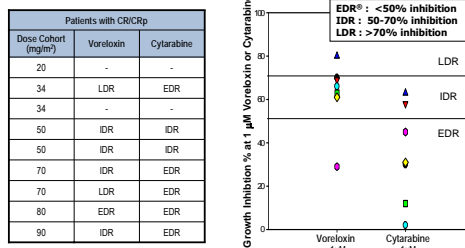
Adverse Event	# of Patients (%); n=37
Febrile Neutropenia	17 (46%)
Hypokalemia	6 (16%)
Stomatitis/Mucosal Inflammation	4 (11%)
Hyperglycemia	4 (11%)
Hypophosphatemia	3 (8%)
Hypotension	3 (8%)
Pneumonia	3 (8%)
Acute Renal Failure	2 (5%)
C. Difficile Colitis	2 (5%)
Diarrhea	2 (5%)
Hypocalcemia	2 (5%)
Hypoxia	2 (5%)
Sepsis	2 (5%)

VORELOXIN PLASMA PHARMACOKINETICS



Voreloxin plasma exposure (AUC) increased with dose from 10 – 50 mg/m². Above 50 mg/m², exposure appeared to plateau. Voreloxin levels above in vitro IC50 and IC90 were sustained at 80 mg/m² MTD for 163 hr (6.8 d) and 58 hr (2.4 d), respectively.

PHARMACODYNAMICS: CR/CRP PATIENT EX VIVO RESPONSE TO VORELOXIN AND CYTARABINE



E, I, L, DR: extra, intermediate and low drug resistant. Baseline BMA were evaluated in a 5 day CellTiter-Glo proliferation assay with continuous exposure to either voreloxin or cytarabine. EDR samples were inhibited < 50%; IDR samples were inhibited by 50-70%, and LDR samples were inhibited by >70%. EDR correlates with clinical drug resistance in solid tumors (www.aacrjournals.org). The relationship is not established in AML.

- Predose BMA were available for 7 of 9 CR patients; only 1 of 7 samples were EDR to voreloxin; 5 of 7 samples were EDR to cytarabine. These data suggest that voreloxin is the primary contributor to the complete remissions.
- Analysis of PBMC from treated patients indicates preliminary correlation between induction of DNA damage response markers (pDNA-PK and pChk2) and clinical response. Data analysis continues.

PRELIMINARY RESPONSES SCHEDULE A

Cohort	Voreloxin (mg/m ²)	N	DLTs	Complete Remissions
1	10	4	0	0
2	20	3	0	1 CR (BMT)
3	34	4	0	2 CR (1 BMT)
4	50	6	0	1 CR, 1 CRp
5	70	7	1 (sepsis death)	1 CR, 1 CRp
6	80 MTD	7	1 (esophagitis)	1 CR
7	90	7	2 DLTs in 1 patient (photosensitivity, bowel obstruction) 1 G3 mucositis > 7 days	1 CR 2 awaiting marrow recovery

Median days to ANC >1000 = 35
Median days to platelet count >100,000 = 34
30-day all-cause mortality = 8 of 38 treated patients (21%) for whom data are available

CHARACTERISTICS OF RESPONDERS SCHEDULE A

Vor. Dose (mg/m ²)	Disease Status (f Prior Tx)	Response, Duration Prior Tx	Cyto. (Age/Gender)	CR Duration
20	Relapsed (2)	CR 1 yr 7 + 3 CR 2 yr 7 + 3	Int.(52F)	CR 9+ mo. BMT
34	Relapsed (1)	CR 1 yr 7 flavo., Ara-C, mbo.	Int.(68M)	CR 8+ mo.
34	Trans. MDS	PD decline	Unfav.(63M)	CR 4 mo. Relapsed after BMT
50	Relapsed (1)	CR 1 yr flud., Ara-C, mbo.	Int.(71M)	CRp 4+ mo.
50	Refractory (3)	CR 1.5 yr mbo./Ara-C CR 2.0 yr Ara-C PD PRI-104 vaccine	Int.(70M)	CR 5+ mo.
70	Relapsed (2)	CR 1.3 yr 7+3/etoposide CR 2.5 yr flud., Ara-C, mbo.	Unfav.(61M)	CRp 4+ mo.
70	Relapsed (1)	CR 2 yr HU, clonazepam	Int.(71M)	CR 4+ mo.
80	Refractory (2)	PD decline/decadron PD 7 + 3	Int.(56M)	CR 3+ mo.
90	Refractory (2)	Daclabine, 7+3 and 5+2	Int.(47M)	CR 1+ mo.

CONCLUSIONS AND FUTURE DIRECTIONS

Schedule A: voreloxin (D1,D4) in combination with CIV cytarabine (400 mg/m² qd x 5)

- Demonstrated preliminary activity with 9 complete remissions (CR/CRp) observed
 - Therapeutic activity observed with voreloxin dosing range of 20 – 90 mg/m²
 - Voreloxin MTD of 80 mg/m² established
 - Generally well tolerated with an acceptable safety profile in this heavily pretreated patient population
 - Voreloxin plasma exposure (AUC) increased with dose from 10 – 50 mg/m² and an apparent plateau of exposure above 50 mg/m²
 - Voreloxin levels above in vitro IC50 and IC90 were sustained at 80 mg/m² MTD for 163 hr (6.8 d) and 58 hr (2.4 d), respectively
 - Ex vivo data suggest that voreloxin activity is the primary contributor to anti-leukemic activity
 - Phase 2 expanded cohort is now enrolling with first relapse AML patients
- Schedule B:** voreloxin (D1,D4) in combination with bolus (2 hr infusion) cytarabine (1 gm² qd x 5)
- Cohort 1 (70 mg/m² voreloxin) of the Phase 1b dose-escalation is enrolled and will be followed as standard practice for safety assessment prior to dose escalation