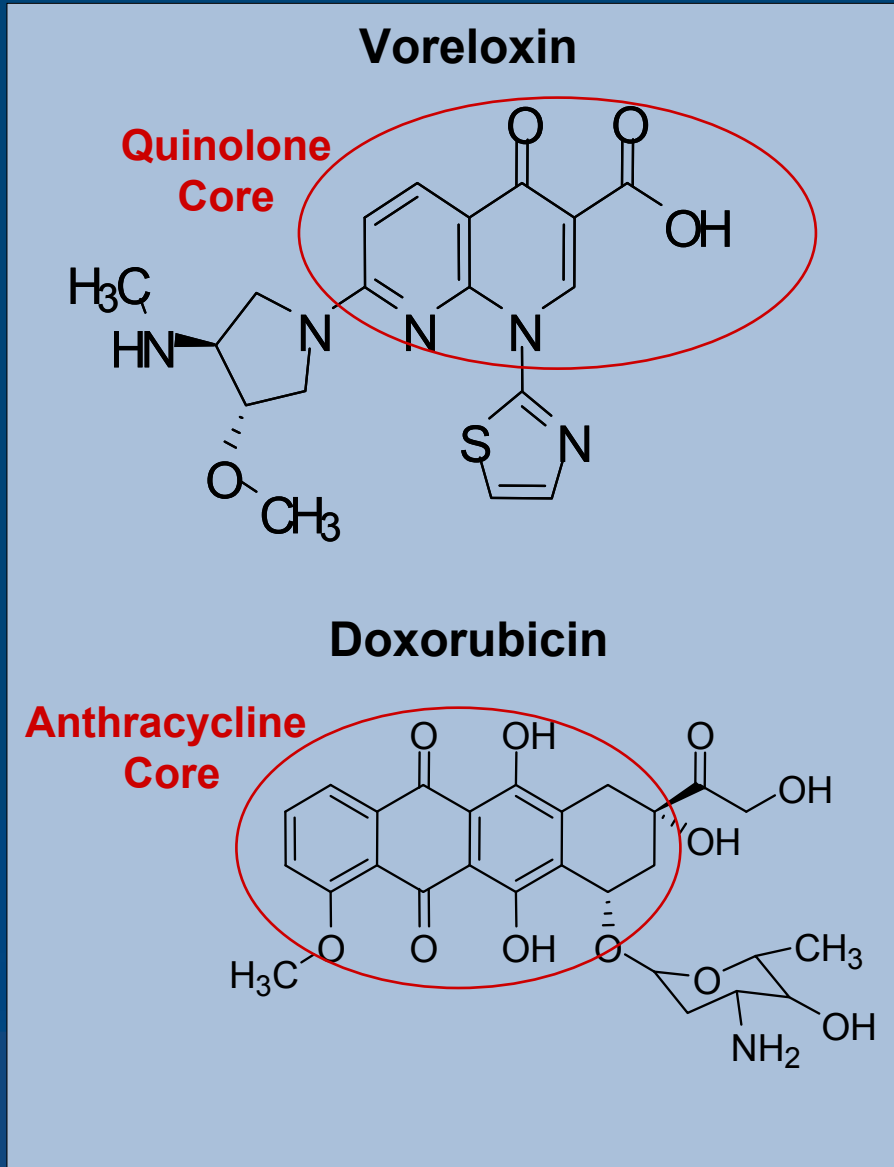


Phase 1b/2 Pharmacokinetic/Pharmacodynamic Study of Combination Voreloxin and Cytarabine in Relapsed or Refractory AML Patients

J. Lancet¹, G Roboz², L Cripe³, F. Ravandi⁴, A. List¹, A Conroy⁵, RE Hawtin⁵, T Chen⁵, K Mahadocon⁵, JA Fox⁵, GC Michelson⁵, J Karp⁶

¹Moffitt Cancer Center, Tampa FL; ²Cornell University/ New York Presbyterian Hospital, NY NY; ³Indiana University Cancer Center, Indianapolis IN; ⁴MD Anderson Cancer Center, Houston, TX, ⁵Sunesis Pharmaceuticals, Inc., South San Francisco CA; ⁶Sidney Kimmel Cancer Center, Baltimore MD

Voreloxin Anticancer Quinolone Derivative: A Next Generation Topo II Inhibitor



- Voreloxin intercalates DNA and inhibits topoisomerase II
 - Causes site-selective DNA damage and apoptosis
 - DNA damage analogous to quinolone antibacterials
 - Broad therapeutic index
 - Evades common drug resistance pathways of P-gp and p53
 - Active in anthracycline-resistant settings
 - Low potential for cardio/organ toxicity
 - Low risk of CYP450-mediated drug-drug interaction

Voreloxin: Phase 1 Single Agent Experience

- Voreloxin was well tolerated in patients with advanced leukemias
- MTD was 72 mg/m² weekly on days 1, 8, 15 and 40 mg/m² twice weekly on days 1, 4, 8, 11
- DLT was oral mucositis
- Predictable and dose-linear pharmacokinetics
- Complete Remissions (6) as well as reductions in bone marrow leukemic blasts were observed in relapsed and/or refractory AML

Study Design

Phase 1b Relapsed or Refractory AML

Voreloxin D1, 4 by ≤ 10 min IV infusion
10 mg/m² – 90 mg/m²
with
Cytarabine Daily x 5:
400 mg/m²/d CIV
OR
1 g/m²/d 2 hr IV infusion (Bolus)
N=57

Expansion Phase 2 Populations

Primary Refractory
Failed 1 – 3 standard inductions
N = 29+ (open)

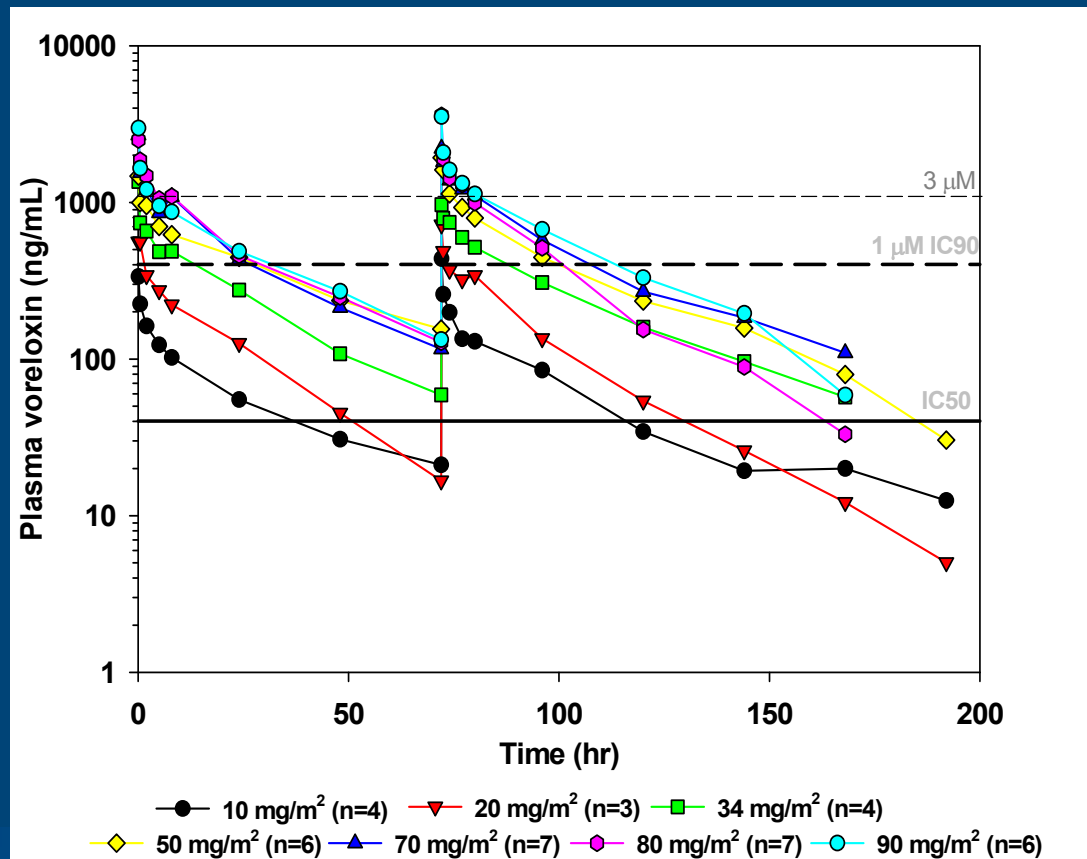
First Relapse
CR1 ≤ 12 months N = 27
CR1 > 12 months < 2 yr N = 10

- 80 mg/m² voreloxin D1, 4 with CIV cytarabine
- 90 mg/m² voreloxin D1, 4 with Bolus cytarabine

Voreloxin: Phase 1b Experience in Combination with Cytarabine

- Safety profile of voreloxin in combination with cytarabine similar to single agent (N=57 treated)
- DLTs with CIV cytarabine and bolus cytarabine were upper GI mucositis (N = 4), sepsis (N=1) and bowel obstruction (N=1)
- Recommended Phase 2 voreloxin doses:
 - 80 mg/m² voreloxin days 1, 4 with CIV cytarabine
 - 90 mg/m² voreloxin days 1, 4 with Bolus cytarabine
- Voreloxin PK predictable and dose-linear pharmacokinetics was unaffected in combination with Bolus or CIV cytarabine
- Complete Remissions (CR + CRp) (N = 13) achieved with 20 mg/m² – 90 mg/m² voreloxin in combination with cytarabine

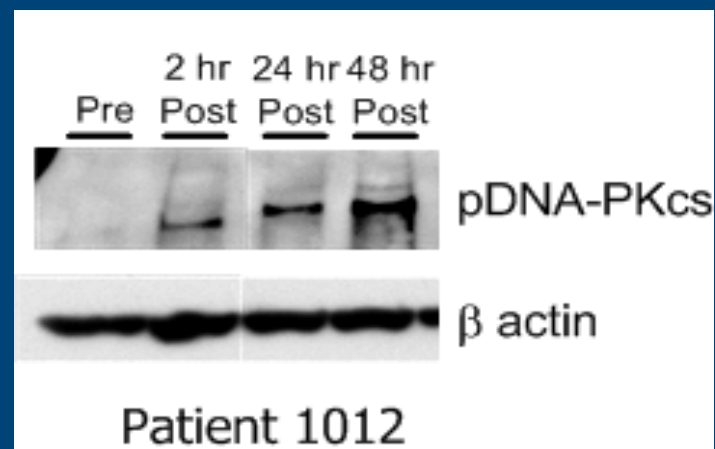
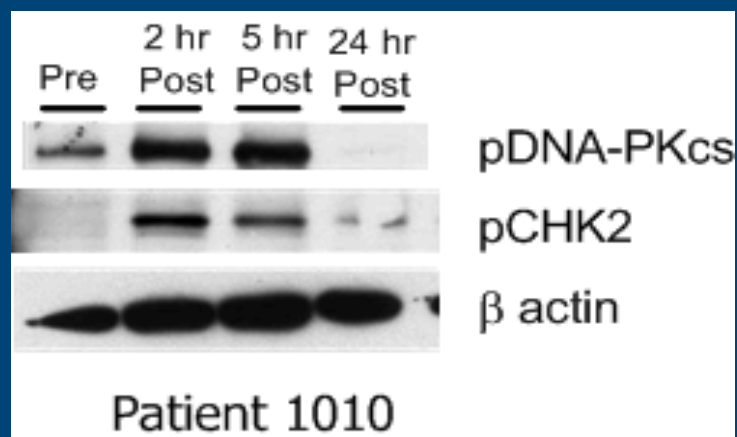
Prolonged Duration of Active Voreloxin Levels at Recommended Pivotal Dose



- Voreloxin plasma levels at active concentrations are sustained at recommended Phase 2 dose levels

Mechanism-Based Pharmacodynamic Activity in Treated Patients

DNA damage response (p-DNA-PKcs) and activation of homologous recombination repair (pCHK2)



Both patients achieved CR with 34 mg/m² voreloxin with CIV cytarabine

- DNA damage response observed in 15 of 23 (65%) patients assayed treated with ≥ 34 mg/m² voreloxin
 - No pharmacodynamic response at 10 – 20 mg/m² voreloxin
 - Analysis of relationship between anti-leukemic activity and DNA damage response is in progress

Phase 2 Demographics

| Population | Primary Refractory | First Relapse |
|----------------------|--------------------|---------------|
| N | 30 | 31 |
| Gender – Male | 63% | 71% |
| Median Age (range) | 57 (18,71) | 60 (34,72) |
| ECOG 0-1 | 87% | 94% |
| Cytogenetics by NCCN | | |
| Favorable | 3% | 3% |
| Intermediate | 52% | 64% |
| Unfavorable | 28% | 22% |
| Not available | 24% | 14% |

- Phase 1b or 2 patients receiving 80 – 90 mg/m² voreloxin with CIV or Bolus cytarabine

Toxicity Profile Of Voreloxin and Cytarabine in Combination

Voreloxin 70 – 90 mg/m² Non-Hematologic Grade 3 or Higher AEs > 10%

| | CIV Cytarabine N=38 | Bolus Cytarabine N=39 |
|---------------------------------|---------------------------|-----------------------------|
| Upper GI Mucositis ¹ | 18% | 13% |
| Lower GI Mucositis ¹ | 18% | 0% |
| Febrile Neutropenia | 45% | 28% |
| Sepsis/Bacteremia ¹ | 24% | 21% |
| Infections ¹ | 13% | 18% |
| Pneumonia ¹ | 16% | 5% |
| Hypokalemia | 29% | 8% |
| Hypophosphatemia | 13% | 0% |

¹ Aggregated preferred terms

Outcome in First Relapse and Primary Refractory Populations

Remission rate 31% with 7.8 month median overall survival

| | Outcome ^{1,2,3} | |
|---|--------------------------------|---------------------|
| First Relapse | 12 CR (33%) | |
| First Relapse > 12 months | N=9 | 5 CR, 2 CRi (1 CRp) |
| First Relapse CR1 6-12 months | N=17 | 3 CR, 1 PR to HST |
| First Relapse CR1 < 6 months | N=10 | 2 CR |
| Primary Refractory | 8 CR (29%) | |
| Time to ANC > 1,000 (range) | 32.5 (27 – 46) days | |
| Time to platelets > 100,000 (range) | 32 (21 – 41) days | |
| 30-day all-cause mortality | 1 (1%) ⁴ | |
| 60-day all-cause mortality | 5 (8%) ⁴ | |
| Preliminary Median Overall Survival (95% CI) | 7.8 months (4.7 – 10.2) | |

¹ Pooled Schedule A (N = 30) and B (N=36) patients who received 80 or 90 mg/m² voreloxin. Too early to evaluate patients excluded from efficacy analysis (N=2 as of 1DEC2009).

² Schedule B patients continue to enroll to Primary Refractory. ³ 18 confirmed CR/CRi patients with 1 CR, 1 CRp proceeding to HST with full heme recovery prior to confirmatory BMA. Majority of remissions were CR: 16 CR, 2 CRp, 2 CRi. For primary refractory: 7 CR, 1 CRp ⁴ 1 of 66 patients treated; 5 of 62 patients treated who exceeded 60 days post-first induction day.

Early First Relapse Characteristics of Complete Remissions

Complete Remissions in patients with CR1 of ≤ 12 months

| PT | Ara-C | Vore-loxin | Age | Cyto. | CR1 mo. | Previous Leukemia Tx | Outcome | Survival days |
|------|-------|------------|-----|-------|---------|---|--------------------|---------------------|
| 1104 | CIV | 80 | 63 | U | 3 | Lenalidomide, dauno/cytarabine, CPX-351 | CR relapse day 163 | 258+ |
| 1105 | CIV | 80 | 45 | I | 11 | Cytarabine/dauno/etoposide, dauno/cytarabine | CR to BMT | 332+ |
| 1112 | CIV | 80 | 71 | I | 6 | Dauno/cytarabine/cyclosporin, vidaza | CR to sepsis | death day 74 |
| 1303 | Bolus | 80 | 60 | I | 12 | ECOG1900/dauno/cytarabine, autologous HST post-busulfan/cylophosphamide | CR to BMT | 192+ |
| 1309 | Bolus | 90 | 55 | U | 5 | Idarubicin/daunomycin | CR* to BMT | 147+ |

* Heme recovery but no recovery marrow prior to transplant

+ Patient alive as of last follow up.

Primary Refractory Characteristics of Complete Remissions to Date

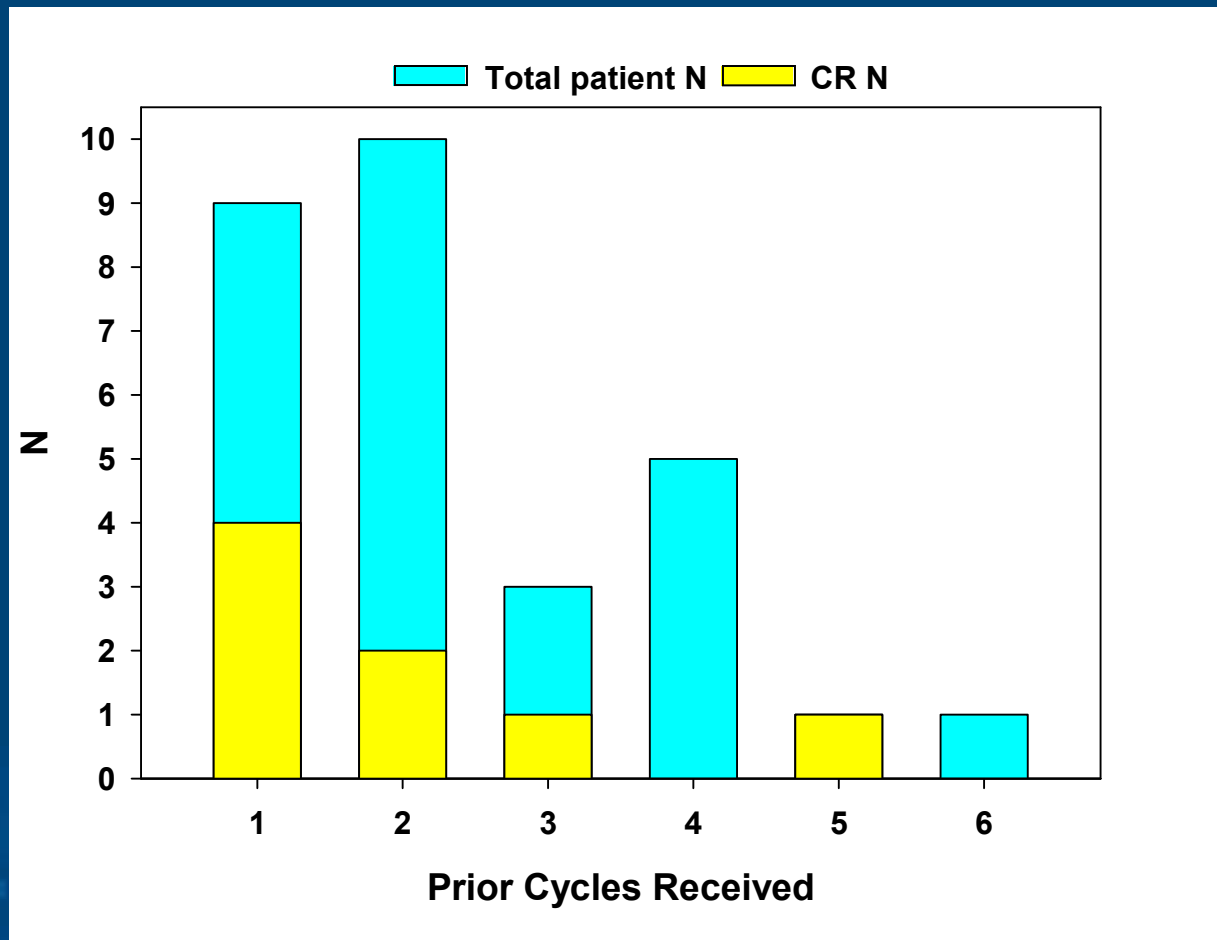
Complete Remissions achieved by patients who failed 1-5 treatment cycles

| PT | Ara-C | Vore-loxin | Age | Cyto-Genetics | Previous Leukemia Hx/Tx | Outcome | Survival days |
|------|-------|------------|-----|---------------|--|---------------------------------|---------------|
| 1029 | CIV | 80 | 56 | I | AHD; decitabine/decadron; cytarabine/dauno | CR to BMT | 401+ |
| 1037 | CIV | 90 | 47 | I | decitabine;7+3, 5+2, HIDAC | CR to BMT | 358+ |
| 1207 | Bolus | 80 | 46 | U | decitabine, 7+3, MRD allo | CR, decitabine consolidation | 267+ |
| 1212 | Bolus | 80 | 39 | F | HiDAC, MEC, MEC | CR* to BMT | 257+ |
| 1214 | Bolus | 90 | 70 | Not av. | sAML (NHL, MDS), tipifarnib, etoposide | CR to BMT | 255+ |
| 1402 | Bolus | 90 | 58 | Not av. | 3+7 | CR to BMT | 119+ |
| 1408 | Bolus | 90 | 71 | I | Fludarabine/cytarabine/ mitoxantrone | CRp likely BMT | 47+ |
| 1413 | Bolus | 90 | 60 | I | 7+3, 5+2 | CR | 38+ |

* Heme recovery but no recovery marrow prior to transplant

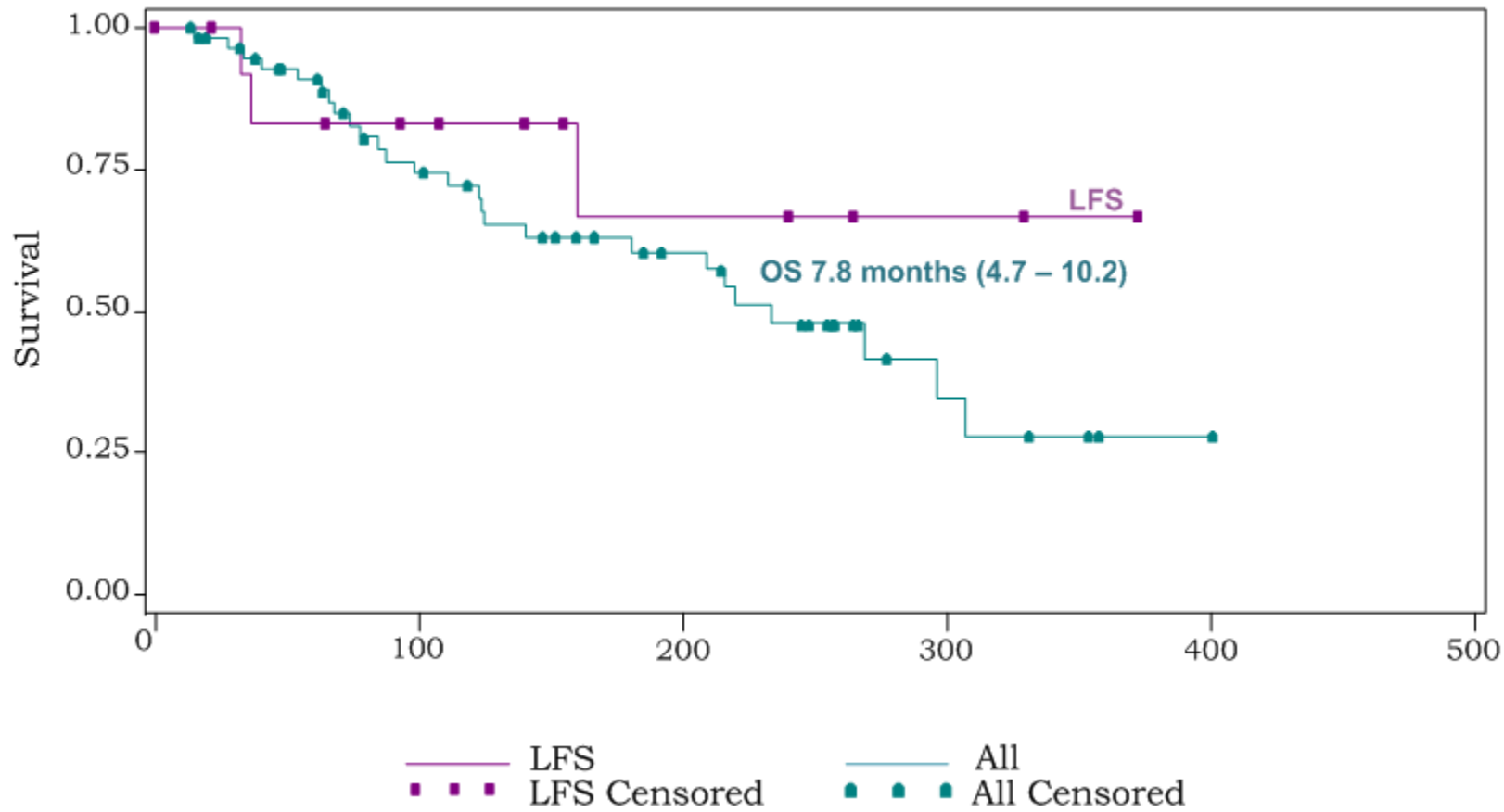
+ Patient alive as of last follow up.

CR Achieved in Primary Refractory Patients with 1-5 Cycles of Prior Therapy



Voreloxin Combination Survival Data Compare Favorably to Historical Outcomes

Historical median overall survival is ~4 - 6 months (Litzow 2009, Giles 2009)



LFS is defined as interval to relapse or death.

Voreloxin Profile Favorable Relative to Outcomes of Recent Studies in Similar Populations

Survival in relapsed/refractory setting also influenced by factors other than CR rate

| | Voreloxin/ Cytarabine N = 63 | Litzow 2009 N=82 | Giles 2009 | |
|------------------------------|---|--|---|---|
| | | | N=178 | N=90 |
| Patient Pop. | Prim. Refractory 1 st Relapse CR1 >3 months ≤ 24 months | Prim. Refractory Early 1 st Relapse CR1 ≤ 12 months | First Relapse CR1 >3 months ≤ 24 months | First Relapse CR1 >3 months ≤ 24 months |
| Tx | Voreloxin IDAC Cytarabine | IDAC cytarabine GO or lipo. dauno or cyclophosph/ topotecan | Laromustine HiDAC CIV cytarabine | HiDAC CIV cytarabine |
| CR+ CRp | 31% ¹ | 8% ³ | 35% | 19% |
| Median Overall Survival (OS) | 7.8 months ² | 3.4 months | 4.3 months | 5.9 months |
| 30-day mortality | 2% | 6% | 11% | 2% |
| 60-day mortality | 8% | ~30% ⁴ | ~30% ⁴ | ~15% ⁴ |

¹ Response rate and preliminary median OS 24% and 7.2 months in primary refractory/early 1st relapse population

²Preliminary ³No CR in CR1 < 6 mo. ⁴Estimated from K-M curve

Conclusions

- Voreloxin in combination with bolus or CIV cytarabine is well tolerated in relapsed/refractory patient population
- Promising activity observed in primary refractory and first relapse population
 - Low 30- and 60-day all-cause mortality
 - Preliminary CR rate 31%
 - Preliminary median overall survival 7.8 months
 - Compares well with recent data showing median survival approximately 4-6 months

Acknowledgements

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