

A Phase 2 Trial of Voreloxin in Women with Platinum-Resistant Ovarian Cancer

H. Hirte¹, W. McGuire², R. Edwards³, A. Husain⁴, P. Hoskins⁵, J. Michels⁶, U. Matulonis⁷, C. Sexton⁸, K. Mahadoon⁹, J. Fox⁸, G. Michelson⁸

¹Juravinski Cancer Centre, Hamilton, ON, Canada; ²Weinberg Cancer Center, Baltimore, MD; ³University of Pittsburgh, Pittsburgh, PA; ⁴Stanford University, Palo Alto, CA; ⁵BC Cancer Agency – Vancouver, BC;

⁶BC Cancer Agency - Victoria, BC; ⁷Dana Farber Cancer Center, Boston, MA; ⁸Sunesis Pharmaceuticals, Inc., South San Francisco, CA

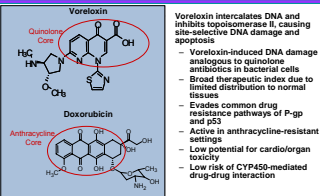


ABSTRACT - UPDATED

Voreloxin is a first-in-class Anticancer Quinolone Derivative (AQD) that intercalates DNA and inhibits topoisomerase II, inducing apoptosis. Clinical activity has been observed in ovarian cancer and in acute myeloid leukemia. Results are reported from a fully enrolled ongoing Phase 2 study of 3 dose levels of single agent voreloxin in patients with primary or secondary platinum-resistant or refractory ovarian cancer. **Study Design:** Patients may have received up to 3 prior platinum regimens plus one additional non-platinum cytotoxic regimen. An ECOG PS of 0-1 was required. Patients received 48 mg/m² q3weeks (Cohort A, N=65), or 60 mg/m² q4weeks (Cohort B, n=37), or 75 mg/m² q4weeks (Cohort C, N=35 patients) by short (≤10 min) IV infusion. **Results:** Objective responses were observed in all cohorts with similar response rates. Four CRs and 11 PRs were achieved in 143 patients for an overall response rate (ORR) of 11%. Seventy-four patients (52%) experienced disease control (CR + PR + SD for ≥ 12 weeks). Median PFS is 84 days (95% CI 63 – 104 days). The study included 44 women who had failed prior Doxil[®] treatment in addition to platinum-based therapies. Four PRs were seen in Doxil-failures (9% ORR), and 28 (64%) of these patients achieved disease control. Median PFS is 90 days (95% CI 83 – 133 days) for women who have failed Doxil. Final median PFS is available for Cohort A (48 mg/m² q3weeks); estimates for Cohorts B (60 mg/m² q4weeks) and C (75 mg/m² q4 weeks) are considered preliminary as patients remain on study. The median PFS for Cohort A was 82 days (95% CI 52 – 98 days). The median PFS for Cohort B appears similar, 84 days (95% CI 54 – 161 days). The median PFS for Cohort C has increased to 109 days (95% CI 54 – 187 days). There was a significant difference in PFS among the 3 dose cohorts (p = 0.019, logrank test). PFS was significantly greater in the 60 and 75 mg/m² cohorts vs 48 mg/m². Six patients remain on study in Cohort B; 10 patients continue on study in Cohort C. Overall, the adverse event profile was similar across cohorts and the drug was generally well-tolerated. However, febrile neutropenia was increased in Cohort C (75 mg/m² q4 weeks). The incidence of febrile neutropenia was < 10% in Cohorts A and B, and 26% in Cohort C. The febrile neutropenia was clinically manageable and was within the range of other commonly used agents. Across all cohorts, the most common Grade 3 or higher adverse events were neutropenia (26%), fatigue (15%), febrile neutropenia (12%), anemia (10%), nausea (7%), vomiting (5%), and hypokalemia (6%). **Conclusions:** Objective responses (4 CRs, 11 PRs) were observed in all cohorts with similar response rates (11%). Seventy-four patients (52%) experienced disease control (CR + PR + SD for ≥ 12 weeks). There was a significant difference in PFS among the 3 dose cohorts (p = 0.019, logrank test). PFS was significantly greater in the 60 and 75 mg/m² cohorts vs 48 mg/m². Forty-four patients (29%) had failed Doxil in addition to having demonstrated resistance to prior platinum-based therapies. Four PR were observed (ORR 9%) with 64% experiencing disease control (CR + PR + SD for ≥ 12 weeks). PFS was not statistically different between Doxil-failures and non-Doxil-failures. Overall, the adverse event profile was similar across cohorts and the drug was generally well-tolerated but febrile neutropenia increased to 26% Cohort C. The febrile neutropenia was clinically manageable and was within the range of other commonly used agents. Sixteen patients remain on study in Cohorts B and C.

VORELOXIN ANTICANCER QUINOLONE DERIVATIVE (AQD)

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



STUDY OBJECTIVES AND TRIAL DESIGN

Population: Platinum-resistant Ovarian cancer	Progression within six months of completing platinum-based chemotherapy or progression while on platinum-based therapy Patient could have failed additional non-platinum based therapy		
Objectives	Objective response by GOG-RECIST; duration of response; median PFS; safety		
Voreloxin Regimens	Safety profile supported testing increased dose intensity		
	N	Dose	Dose Intensity mg/m ² /week
	65	48 mg/m ² q3wk	16
	37	60 mg/m ² q4wk	15
	35	75 mg/m ² q4wk	19

DEMOGRAPHICS

	48 mg/m ² q3 weeks N=69	60 mg/m ² q4 weeks N=39	75 mg/m ² q4 weeks N=35	Total N=143 N (%)
1 st platinum-resistant	43%	59%	26%	43%
2 nd platinum-resistant	57%	41%	74%	57%
Prior Therapies				
Doxil [®] (Caelyx [®])	36%	23%	31%	44 (31%)
Gemcitabine	26%	18%	37%	38 (27%)
Topotecan	10%	5%	14%	14 (10%)
Bevacizumab	7%	6%	6%	8 (6%)
Histology				
Serous Cystadenocarcinoma	62%	51%	51%	81 (57%)
Papillary serous	9%	18%	23%	21 (15%)
Clear cell	12%	15%	17%	20 (14%)
Endometrioid	4%	6%	8 (6%)	
Adenocarcinoma, NOS	13%	8%	3%	13 (9%)

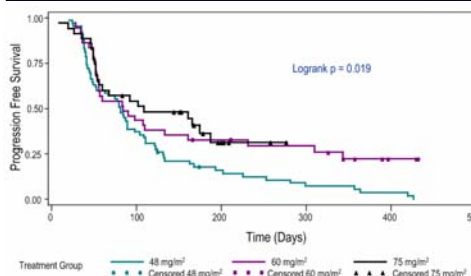
GRADE 3 OR HIGHER AEs ≥ 10%

	48 mg/m ² q3 weeks N=65	60 mg/m ² q4 weeks N=37	75 mg/m ² q4 weeks N=35
Reporting Grade 3 or Higher AEs	37 (57%)	20 (54%)	28 (80%)
Febrile Neutropenia	6 (9%)	2 (5%)	9 (26%)
Neutropenia	12 (19%)	8 (22%)	15 (43%)
Anemia	5 (8%)	7 (19%)	1 (3%)
Nausea	3 (5%)	3 (8%)	3 (9%)
Vomiting	4 (6%)	1 (3%)	2 (6%)
Intestinal Obstruction	1 (2%)	3 (8%)	3 (9%)
Fatigue	10 (15%)	4 (11%)	7 (20%)
Asthenia	1 (2%)	1 (3%)	2 (6%)
Infections	5 (8%)	1 (3%)	3 (9%)
Hypokalemia	1 (1.5%)	4 (11%)	3 (9%)
Anorexia	1 (1.5%)	1 (3%)	3 (9%)
Dehydration	1 (1.5%)	0 (0%)	2 (6%)
Dose Delays or Reductions	18 (28%)	6 (16%)	11 (31%)

OUTCOME

	48 mg/m ² q3 weeks N=65	60 mg/m ² q4 weeks N=37	75 mg/m ² q4 weeks N=35	Total N=137
Patients Remaining on Study	0	6	10	16
Objective Responses	2 CR, 5 PR	2 CR, 2 PR	4 PR	4CR, 11 PR
Objective Response Rate	11%	11%	11%	11%
Disease Control ≥ 12 weeks	38 (59%)	16 (43%)	20 (57%)	54%
Median Cycles Received	4	3	4	4
Median PFS	82 days	84 days	109 days	84 days
Doxil Failure Patients	N=24 (35%)	N=9 (23%)	N=11 (31%)	N=44 (32%)
Objective Responses	2 PR	0	2 PR	4 PR
Objective Response Rate				9%
Disease Control ≥ 12 weeks	18 (75%)	2 (22%)	8 (73%)	64%
Median Cycles Received				4
PFS				90 days

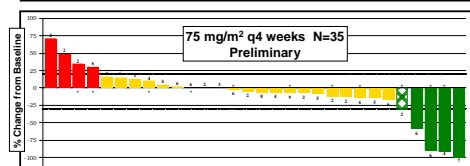
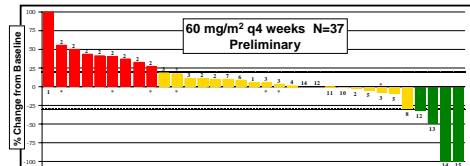
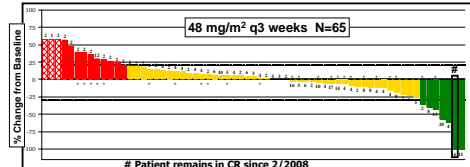
HIGHER DOSE COHORTS HAVE IMPROVED OVERALL PFS



For patients who have not progressed, PFS is censored at the date of last disease assessment.

- There was a significant difference in PFS among the 3 dose cohorts (p = 0.019, logrank test). PFS was significantly greater in the 60 and 75 mg/m² cohorts vs 48 mg/m².
- The improvement in PFS suggests a benefit to higher dose voreloxin irrespective of response rate.

DISEASE ASSESSMENT: WATERFALL PLOTS OF BEST RESPONSE (GOG-RECIST)



■ PD ■ SD □ PR target lesion only ■ CR or PR * Doxil[®] failure patients Number by bar is cycles received

CONCLUSIONS

- Voreloxin, a first-in-class Anticancer Quinolone Derivative (AQD), given as a single agent demonstrates clinical activity in platinum-resistant ovarian cancer as well as in patients who have progressed on Doxil.
- Voreloxin was generally well tolerated in this difficult to treat patient population.
- The increased incidence febrile neutropenia seen at 75 mg/m² (26%) was manageable and similar to other approved agents.
- The overall ORR of 11% and median PFS of 84 days is similar to other commonly used agents in platinum-resistant patients.
- ORR for Doxil failures was 9% with 64% experiencing disease control (CR + PR + SD for ≥ 12 weeks) and PFS was not statistically different from those who had failed Doxil (p = 0.73).
- Median PFS appears increased (109 days) in the 75 mg/m² cohort vs the lower dose cohorts (82-84 days).
- There was a significant difference in PFS among the 3 dose cohorts (p = 0.019, logrank test). PFS was significantly greater in the 60 and 75 mg/m² cohorts vs 48 mg/m².
- Further development of voreloxin, as a single agent or in combination, is warranted in platinum-sensitive and resistant ovarian cancer, including the Doxil-failure setting.