Results from a Phase 1b (OX1222) Dose-Finding Study of OXi4503 Combined with Cytarabine in Patients with Relapsed/Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome

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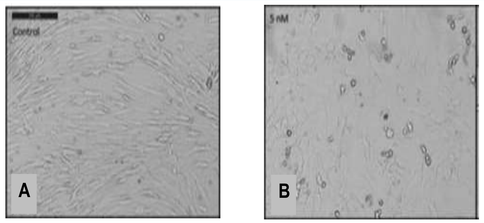
Introduction

- OXi4503 (combretastatin A1-diphosphate or CA1P) is a phosphate pro-drug of combretastatin A1 (CA1) which has a dual mechanism of action involving vascular targeting effects and direct cytotoxic effects
- **Effects on leukemia vasculature and leukemic cell attachment:** Once administered *in vivo* OXi4503 is activated to CA1 by phosphatase enzymes.
  - CA1 binds to and depolymerizes tubulin which causes endothelial cells to become spherical in shape and internalize adhesion molecules[1]
  - Endothelial cell changes lead to AML cell detachment, initiation of cell cycling and higher response to cytarabine (Figure 1)[1]
- **Cytotoxic effects:** CA1 can also be oxidized by myeloperoxidase in myeloblasts to a reactive orthoquinone species with the production of oxygen radicals that result in direct cytotoxic effects.
- OXi4503 alone induces AML remission *in vivo*[2] and also increases the sensitivity of AML cells to cytotoxic agents such as cytarabine[1]

Figure 1: Morphology of BMEC after CA1 Exposure



Morphology of bone marrow endothelial cells (BMEC) after combretastatin exposure. Brightfield images of bone marrow endothelial cells taken 24 hours after (A) no treatment or (B) treatment with treatment with 5 nM CA1.[1]

Methods

Study OX1222 (NCT02576301) is a Phase 1b dose escalation study of OXi4503 as a single agent (presented previously) followed by combination with cytarabine with subsequent combination phase 2 cohorts in patients with AML or MDS (Figure 2)

Primary Objective
- To determine the MTD of OXi4503 (Figure 2) in combination with intermediate dose cytarabine (1mg/m^2/day x 5 days) chemotherapy

Secondary Endpoints
- To assess the safety and tolerability of OXi4503 in combination with cytarabine
- To assess preliminary survival benefit of this regimen
- To determine the pharmacodynamics profiles of OXi4503 and its metabolites and cytarabine

Drug Administration Schedule
- OXi4503 administered IV over 10 minutes on Days 1 and 4 of a 28 day cycle
- Cytarabine administered over 2 hours daily on Days 1-5 of the 28 day cycle
- On Days 1 and 4 cytarabine was administered 4 hours after the end of the OXi4503 treatment
- Combination induction treatment may be repeated after 28 days for up to 2 induction cycles in the event of residual AML if the subject has achieved >50% bone marrow blast reduction from baseline

Study Cohorts
- Cohorts of up to 4 subjects were enrolled
  - A cohort may be expanded up to 6 subjects if a dose limiting toxicity (DLT) is observed in 1 subject

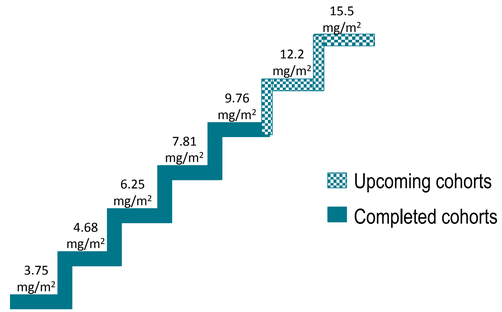
DLT: Observations for DLT take place during Cycle 1 for a minimum of 28 days and include
- Any grade >3 drug related non-hematologic toxicity (with some exceptions)
- Hematologic toxicities: Grade 4 neutropenia and/or thrombocytopenia (thought to be due to marrow hypoplasia not leukemic burden) that does not recover to <grade 3 within 6 weeks

Inclusion Criteria
- Patients with relapsed/refractory AML or MDS (following failure of at least 1 prior hypomethylating agent)
- Good organ function
- ECOG performance status of 0-2
- Normal values for PT and INR (based on bleeding events observed with single-agent OXi4503)

Methods (cont.)

Exclusion Criteria
- Acute promyelocytic leukemia
- Absolute peripheral blood myeloblast count >20,000/mm3
- Uncontrolled hypertension
- Prolonged QTc
- History of recent significant CV events
- History of hemorrhagic stroke
- Any requirement for full dose anti-coagulation

Figure 2: OX1222 Phase 1b Study Schema



Results

Cohort Demographics (Table 1): A total of 22 patients (21 evaluable) with relapsed/refractory AML were enrolled

Table 1: Demographics

Demographics		Cohort 1 (3.75 mg/m^2)	Cohort 2 (4.68 mg/m^2)	Cohort 3 (6.25 mg/m^2)	Cohort 4 (7.81 mg/m^2)	Cohort 5 (9.76 mg/m^2)
N		7	4	4	3	4
Age (median)		61	60	63	67	71
Gender	Male	42.9%	100%	75%	66.7%	75%
	Female	57.1%	0%	25%	33.3%	25%
ECOG Status	0	0	0	1	0	1
	1	6	3	2	3	2
	2	1	1	1	0	1
Prior AML/MDS Treatment Lines (median)		5	4	2	3	3

Table 2: Summary of Responses

Cohort (Dose)	N	CR (N)	PR Rate	ORR
Cohort 1 (3.75 mg/m^2)	6	1 (17%)	0 (0%)	1 (17%)
Cohort 2 (4.68 mg/m^2)	4	1 (25%)	0 (0%)	1 (25%)
Cohort 3 (6.25 mg/m^2)	4	1 (25%)	1 (25%)	2 (50%)
Cohort 4 (7.81 mg/m^2)	3	0 (0%)	1 (33%)	1 (33%)
Cohort 5 (9.76 mg/m^2)	4	2 (50%)	0 (0%)	2 (50%)

Table 2: Treatment-Related* AEs (≥ Grade 3)

Adverse Events	N	%
Neutrophil count decrease	5	28
Platelet count decrease	5	28
Febrile neutropenia	4	22
Anemia	3	17
White blood cell count decreased	2	11

* At least possibly related.

Table 3: Characteristics of Responders

Cohort (Dose)	Age	Cytogenetics	Cycles*	Best Response; Duration
Cohort 1 (3.75 mg/m^2)	59	inv(3), del(5)	2	Complete Remission (cytogenetic); 13 months
Cohort 2 (4.68 mg/m^2)	65	Trisomy 8	2	Complete Remission (morphologic); 7 months
Cohort 3 (6.25 mg/m^2)	66	TP53, del(5q, 7q), Trisomy 8	2	Complete Remission (molecular); 6 months
Cohort 5 (9.76 mg/m^2)	78	ETV6, SETBP1, U2AF1; VUS in DNMT3A	1	Complete Remission (morphologic); patient withdrew before cycle 2
Cohort 5 (9.76 mg/m^2)	68	Trisomy 8, inv(16) t(16;16); CBFB rearrangement	1	Complete Remission (cytogenetic); 3 months

* Number of cycles to achieve CR.

Discussion

OXi4503 is a potent anti-vasculature agent that has been demonstrated in animal models to disrupt tumor vasculature and downregulate vascular adhesion molecules, resulting in the release of leukemic cells into the periphery and activation of their cell cycle.[1,2] In addition to its effects on tumor vasculature, OXi4503 directly kills leukemic cells, thus representing a new dual-mechanism approach to the treatment of this disease.[2] Finally, animal data also show that an additive effect of OXi4503 when combined with cytarabine in eradicating leukemic cells.[1] In the first 5 cohorts of this phase 2 clinical study of OXi4503 combined with cytarabine, there is initial evidence supporting the safety and efficacy of OXi4503 for the treatment of patients with relapsed/refractory AML or myelodysplastic syndromes. This combination regimen was well-tolerated in all patients treated to date, and the maximum tolerated dose has yet to be defined. In all dose-cohorts at least one patient experienced either a complete remission or partial remission, with clear evidence of a dose-response: 50% (2/4) of patients at the highest dose cohort (9.78 mg/m^2) showed a complete remission after only 1 cycle of therapy, while patients at lower doses had relatively fewer responses after 2 cycles of therapy. Further study of this combination regimen at higher doses of OXi4503 is planned until the maximum tolerated dose is reached.

Conclusion

- OXi4503 in combination with cytarabine (1 g/m^2/day) is generally well tolerated in all dose cohorts to date
- MTD of OXi4503 has yet to be reached
- Preliminary evidence demonstrates activity in heavily pretreated, relapsed/refractory AML patients
- This Phase 1b study is currently on recruitment hold pending funding. The next dose cohort will be 12.2 mg/m^2 plus cytarabine (1g/m^2/day)

References

1) Bosse RC et al. *Exp Hematol.* 2016;44(5):363-377
2) Madlambayan GJ et al. *Blood*. 2010;116(9):1539-1547.

Disclosures

There are no relationships to disclose.