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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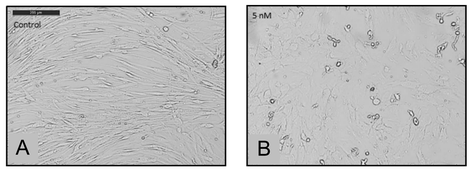
Introduction

- 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 endothelilal cells to become spherical in shape and internalize adeshion 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 chemosensitizes AML cells to cell cycle agents such as cytarabine[1]

Figure 1: Morphology of BMEC after CA1 Exposure

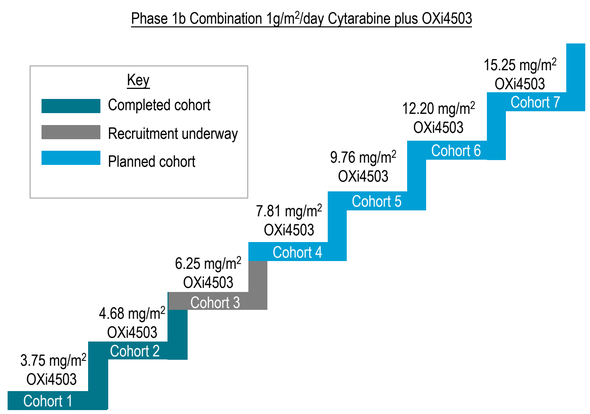


Morphology of bone marrow endothelial cells (BMEC) after combretastatin exposure. Brightfield images of bone marrow endothelial cells taken 24 hours after no treatment (A) or treatment with 5 nM CA1 (B)[1].

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 of the Phase 1b combination portion of the study**
  - To determine the MTD of OXi4503 (Figure 2) in combination with intermediate dose cytarabine (1mg/m^2/day) chemotherapy
- **Secondary endpoints**
  - To assess the safety and tolerability of OXi4503 in combination with 1 mg/m^2/day cytarabine
  - To assess preliminary survival benefit of this regimen
  - To determine the pharmacokinetic/ pharmacodynamics profiles of OXi4503 and its metabolites and cytarabine
- **Phase 1b combination portion 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 is 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 3 subjects will be enrolled
    - A cohort may be expanded up to 6 subjects if a DLT is observed in 1 subject

Figure 2: OX1222 Study Schema



Methods (continued)

- **Dose limiting toxicity (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
- **Key Inclusion Criteria:** The Phase 1b combination portion of the study was opened for patients with relapsed/refractory AML or MDS (following failure of at least 1 prior hypomethylating agent) who had:
  - Good organ function
  - ECOG performance status of 0-2
  - Normal values for PT and INR (based on bleeding events observed with single-agent OXi4503)
- **Key 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

Table 1: Patient Demographics

Demographics	Cohort 1 (OXi4503 3.75 mg/m^2)	Cohort 2 (OXi4503 4.68 mg/m^2)
N	6	4
Age (median)	51.5	54
Gender	50% Male; 50% Female	100% Male
Diagnosis	Relapsed/refractory AML	Relapsed/refractory AML
ECOG status	83% ECOG status 1 17% ECOG status 2	100% ECOG status 1
Cytogenetics risk group	Intermediate or adverse-risk	50% cytogenetics not performed 50% intermediate or adverse-risk
Prior therapy failure (median)	4.2	3.5

Results

- **Cohort 1: OXi4503 3.75mg/m^2**
  - Cohort demographics (Table 1)
    - Between December 2015 and May 2016, 7 patients with relapsed/refractory AML were enrolled (6 evaluable)
  - One patient achieved a morphological complete remission (mCR) after 2 cycles (Figure 3; Table 3)
  - One patient experienced a dose-limiting toxicity of hypofibrinogenemia, but no clinical evidence of bleeding
    - Following correction with cryoprecipitate, fibrinogen returned to normal and remained normal without further intervention
- **Cohort 2 OXi4503 4.68 mg/m^2**
  - Cohort demographics (Table 1)
    - Between June 2016 and August 2016, 4 patients with relapsed/refractory AML were enrolled (4 evaluable; Figure 4)
  - Of 22 adverse events (AEs), 11 were unrelated to treatment and 11 were possibly related (of which only 3 were ≥ grade 3; Table 2)
  - The combination treatment was generally well tolerated
  - One patient achieved a mCR after 2 cycles (Figure 4; Table 3)

Figure 3: Swimmer Plot Cohort 1 (3.75 mg/m^2)

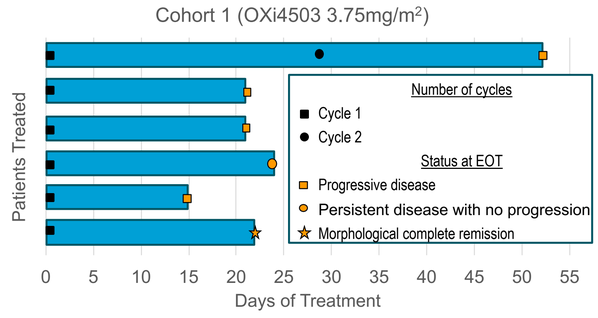


Figure 4: Swimmer Plot Cohort 2 (4.68 mg/m^2)

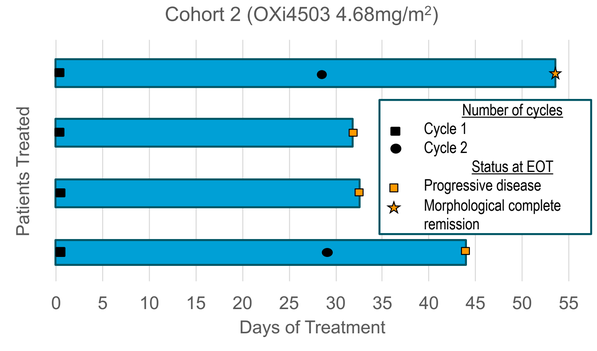


Table 2: Possible Treatment-Related AEs

Adverse Events possibly related to treatment	Cohort 1 (OXi4503 3.75 mg/m^2) N = 6	Cohort 2 (OXi4503 4.68 mg/m^2) N=4
	≥ grade 3	≥ grade 3
	N (%)	N (%)
Anemia	2 (33%)	1 (25%)
AST increase	2 (33%)	0
D-dimer increase	2 (33%)	0
Fibrinogen decrease	1 (17%)	0
Hypokalemia	1 (17%)	0
Neutropenia	2 (33%)	1 (25%)
Neutrophil count decrease	1 (17%)	0
Platelet count decrease	1 (17%)	0
Thrombocytopenia	1 (17%)	1 (25%)

Table 3: Patient Disease Status at End of Trial

	Evaluable Patients	Results
Cohort 1 (OXi4503 3.75 mg/m^2)	6	• Disease progression (n = 4) • Persistent disease with no progression (n=1) • Morphological complete remission (n = 1)
Cohort 2 (OXi4503 4.68 mg/m^2)	4	• Disease progression (n = 3) • Morphological complete remission (n = 1)

Conclusion

- OXi4503 in combination with cytarabine (1 g/m^2/day) is generally well tolerated through Cohort 1 (3.75 mg/m^2) and Cohort 2 (4.68 mg/m^2)
  - The dose escalation continues as MTD is yet to be reached
- Preliminary evidence demonstrates activity in heavily pretreated, relapsed/refractory AML patients
- The optimal dose of OXi4503/cytarabine is yet to be determined
- The following translational studies are currently being undertaken:
  - Myeloid gene mutation profiling
  - Bone marrow microvessel density before and after treatment
  - Bone marrow endothelial colony forming capacity before and after treatment
  - Bone marrow and peripheral blood angiogenic cytokine measurements before and after treatment
  - Adhesion molecule and cytokine receptor expressions on malignant myeloblasts
- This Phase 1b study continues to recruit patients into the Cohort 3 (OXi4503 6.25 mg/m^2) plus cytarabine (1g/m^2/day)
- Data from Cohort 3 (OXi4503 6.25 mg/m^2) are expected in January 2017

References

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

Disclosures

There are no relationships to disclose. Editorial support by Link Health Group.