BET-BROMODOMAIN (BRD) INHIBITOR OTX015: FINAL RESULTS OF THE DOSE-FINDING PART OF A PHASE I STUDY IN HEMATOLOGIC MALIGNANCIES

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Background: OTX015 (Oncoethix) is a small molecule that specifically binds to BRDs 2, 3 and 4, thereby inhibiting binding to acetylated histones, resulting in downregulation of several oncogenes driven by super-enhancers. The therapeutic potential of BRD inhibitors has been demonstrated in several preclinical models including hematologic malignancies.

Methods: The primary end point of this dose escalation study (3 + 3 design) was to establish the Phase 2 recommended dose (P2RD) and schedule in two independent cohorts of patients (pts) with either relapsed/refractory acute leukemia (AL) or other hematologic malignancies (OHM). OTX015 was given orally, daily (qd), with 1 bidaily (bid) dose level (DL) explored, continuously in OHM or for 14 days ON/7 days OFF in AL.

Results: From January 2013 to August 2014, 41 pts with AL (AML 37; ALL 3) or high-risk myelodysplastic syndrome (HR-MDS 1) and 45 pts with OHM (22 diffuse large B-cell lymphoma [DLBCL], 11 other lymphomas, 12 multiple myeloma) were enrolled over 7 DLs from 10 to 160 mg. Dose-limiting toxicities (DLT) during the first treatment cycle were observed at doses >120 mg in AL (diarrhea, asthenia) and doses >80 mg in OHM (primarily thrombocytopenia). Additionally, both AL and OHM pts treated at >80 mg experienced grade 1-2 gastrointestinal events (diarrhea, dysgeusia) that hampered compliance, though not meeting DLT criteria. PK showed dose-proportional OTX015 exposure (AUC0-24h) up to 120 mg qd; trough plasma concentrations at 80 mg qd reached the GI50 cut-off of 500 nM for sensitive tumor cell lines in vitro. Two complete remissions (CR) and 1 CR with incomplete recovery (CRi) were observed in pts with relapsed/refractory HR-MDS or AML secondary to MDS and 2 CR and 1 partial response in DLBCL pts. OTX015 P2RD was determined as 80 mg qd with a 14 days ON/7 days OFF schedule, based on kinetics of platelet nadir and recovery.

Conclusion: OTX015 is an orally available molecule showing dose-proportional exposure up to 120 mg qd with a favorable tolerance profile, and evidence of clinical activity in refractory DLBCL and AML/HR-MDS. Expansion cohorts in AML secondary to MDS, de novo AML and DLBCL at the P2RD are ongoing.