ZEN-3365 is a novel BET bromodomain inhibitor for the treatment of hematologic malignancies and solid tumors
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Abstract
ZEN-3365 is an orally bioavailable small molecule discovered and developed from a BET bromodomain inhibitor platform. In vitro, ZEN-3365 binds BRD4(BD1) vs non-BET bromodomains with >20-fold selectivity, and binds both the first and second bromodomains of BRD2, BRD3, BRD4 and BRDT pan-selectively in a biochemical AlphaScreen assay, competing for binding to acetylated histone peptides with IC50 values of 8-36 nM. ZEN-3365 selectively displaces BRD4 protein from MYC and BCL-2 promoters and from super-enhancers in cells, resulting in inhibition of MYC and BCL-2 expression in acute myeloid leukemia (AML) and B-cell lymphoma cell lines with sub-uM IC50 values. In hematologic tumor types, including most lymphomas and many leukemias, ZEN-3365 inhibits proliferation (IC50 0.1 – 0.5 uM) and induces cell cycle arrest and apoptosis, consistent with inhibiting MYC and BCL-2 expression. In AML xenograft tumor models, ZEN-3365, administered orally, dose-dependently inhibits MYC and BCL-2 expression and can cause complete tumor regression with no regrowth for 6 months post cessation of dosing.

ZEN-3365 has also demonstrated strong activity against several solid tumor cell lines with sub-uM IC50 values, including breast, prostate, head and neck, and colorectal cell lines. Solid tumor xenograft studies conducted with ZEN-3365 have demonstrated that it is efficacious at well-tolerated doses. Robust PK/PD relationships have been established across a number of in vitro, in vivo and ex vivo systems for ZEN-3365 and will be explored further in the clinic. Promising target validation data, excellent pharmaceutical properties, clean off target selectivity profile, and robust activity of ZEN-3365 across a variety of hematologic malignancy and solid tumor settings support the clinical development of ZEN-3365 in both of these therapeutic indications.

Results

ZEN-3365 selectively inhibits BET proteins, oncogenic gene expression & proliferation

ZEN-3365 synergizes with AC220 and cytarabine to inhibit proliferation, induce apoptosis and reduce tumor growth

Table 1. Proliferation of MV4-11 cells treated with ZEN-3365 alone or in combination with cytarabine or AC220 (FLT3-ITD inhibitor): Chou-Talaly synergy indicated by values <0.3

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Combination Index</th>
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<tbody>
<tr>
<td>ZEN-3365 + cytarabine</td>
<td>0.3</td>
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<tr>
<td>ZEN-3365 + AC220</td>
<td>0.6</td>
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Conclusions

1. ZEN-3365 is novel and selective BET inhibitor that binds BET bromodomains in vitro and displaces BET proteins from chromatin in cells
2. ZEN-3365 inhibits BETi specific gene signature in multiple matrices including MYC and BCL-2
3. ZEN-3365 synergizes with cytarabine and FLT3 inhibitor (AC220) to inhibit MV4-11 cell proliferation
4. ZEN-3365 is orally bioavailable, maintains plasma concentrations for sufficient duration and causes tumor regression in MV4-11 xenografts
5. ZEN-3365 inhibits tumor growth in CRC and lung carcinoma xenografts

References
3. Zou et al. (2013) Brief treatment constitutively active NTRK-1 to cancer cells by binding to tyrosine-phosphorylated NCK. Oncogene 32, 3203-3213