**Abstract #3565**

**PhD**

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by TetraLogic Pharmaceuticals. Testing was supported by NCI NO1CM42216.

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**METHODS**

- **BIRINAPANT** was tested against the 23 cell lines of the PPTP in vitro panel (including 1 AML and 5 ALL lines) using 96 hour exposure at concentrations from 1.0 nM to 3.0 μM, both as a single agent and in combination with TNFα (10 ng/mL) or TRAIL (10 ng/mL).

**IN VITRO ACTIVITY**

- Only 4 of 23 PPTP cell lines showed IC50 values < 3 μM, including 4 of rhabdomyosarcoma cell lines, 1 of 5 ALL cell lines (CCR-FEM), the AML cell line Kasumi-1, and the anaplastic large cell lymphoma cell line Rh30.

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**RESULTS**

- **BIRINAPANT was well tolerated in vivo.**

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**CONCLUSIONS**

- BIRINAPANT is a small molecule mimic of Smac that potently and specifically antagonizes multiple inhibitors of apoptosis proteins (IAPs).

- BIRINAPANT rapidly degrades cIAPs and enables cytokines (TNFα, TRAIL) to activate the extrinsic apoptosis pathway, while it rapidly turns off the intrinsic apoptosis pathway, while it rapidly turns off the intrinsic apoptosis pathway.

- Preclinical studies using adult cancer models have shown that birinapant lines to regressions as a single agent in selected models and that it has potent antitumor activity when combined with chemotherapy and death receptor ligands.

**EXAMPLES OF BIRINAPANT IN VIVO ACTIVITY (ALL XENOGRANTS)**

- Given the mechanism of action of Smac mimetics, TNFα expression was examined for the PPTP xenografts using Affymetrix U133 Plus 2 expression data. TNFα expression was significantly higher for high-risk PPTP ALL xenografts compared to the PPTP solid tumor xenografts (ST) and to 15 normal tissues (NL, figure below, left).

- TNFα expression in ALL clinical specimens was examined using the TARGET ALL gene expression data (Affymetrix U133 Plus 2), with the observation that its expression was significantly higher for high-risk B-precursor ALL, compared to a set of normal tissues (NL), but with a wide range of TNFα expression among ALL cases (figure below, right).

- Lymphoxygen B and Lymphoxygen A also show significantly elevated expression in ALL xenografts and clinical specimens compared to normal tissues.

- Among the ALL xenografts tested with birinapant, the best responding xenograft (ALL-2) showed the highest TNFα expression. Karpos-299, which did not respond in vivo to TL32711, also showed high TNFα expression, but the two solid tumor xenografts tested in vivo did not.

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**REFERENCES**

- **TetraLogic Pharmaceuticals, Malvern, PA; Nationwide Children’s Hospital, Columbus, OH**

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**PPTP**

- The PPTP results suggest that birinapant may show high level activity against a subset of childhood ALL, and additional in vivo testing is ongoing to better identify predictive markers that can reliably select responsive cases.