Birinapant (TL32711), a Small Molecule Smac Mimetic, Induces Regressions in Childhood Acute Lymphoblastic Leukemia (ALL) Xenografts That Express TNFα and Synergizes with TNFα – A Report from the Pediatric Preclinical Testing Program (PPTP)

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Abstract #3565

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Birinapant is a small molecule mimetic of Smac that potently and specifically antagonizes multiple inhibitors of apoptosis proteins (IAPs).

Birinapant rapidly degrades cIAPs and enables cytokines (TNF, TRAIL) to activate the extrinsic apoptosis pathway, while it rapidly turns off the canonical NF-κB survival pathway, causing cancer cell death.

Preclinical studies using adult cancer models have shown that birinapant can be a potent single agent in selected models and that it has potent antitumor activity when combined with chemotherapies and death receptor ligands.

**Numerical Data:**

- **Birinapant Activity is In Vivo Activity (ALL Xenografts)**
- **BIRINAPANT IN VITRO METHODS**
- **BIRINAPANT IN VIVO METHODS**
- **Examples of Birinapant in Vivo Activity (ALL Xenografts)**

**VIVERO RESULTS**

- **Birinapant was well tolerated in vivo.**
- **Birinapant induced significant differences in event-free survival (EFS) distribution compared to control in 3 of 3 (100%) of the B-precursor ALL xenografts, but in none of the solid tumor or ALCL xenografts.**
- **Objective responses were not observed for the solid tumor and ALCL xenografts.**
- **For the ALL panel one xenograft (ALL-17) achieved a complete response (CR) and another (ALL-2) achieved a maintained CR, with treated animals remaining in remission at day 42, approximately 30 days after their last treatment with birinapant.

**CONCLUSIONS**

- **Birinapant showed little single agent in vitro activity against ALL cell lines, though its activity was markedly potentiated by the addition of exogenous TNFα for these cell lines.**
- **In vivo, birinapant showed remission-inducing activity against 2 of 3 ALL xenografts, with one of these showing a maintained CR.**
- **TNFα is mechanistically associated with the activity of Smac mimetics, and the initial PPTP in vivo data for ALL xenografts are consistent with a relationship between TNFα expression and responsiveness to birinapant.**
- **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.**