Abstract
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The PI3K-δ Inhibitor TGR-1202 In Combination with Brentuximab Vedotin (SGN-35) Synergistically Inhibits Tubulin Polymerization and Exerts Potent Antitumor Effects in NOD/SCID Mice with Hodgkin Lymphoma Cell Line Xenografts

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BACKGROUND

- The phosphatidylinositol 3-kinase (PI3K) pathway is consistently activated in relapsed/refractory Hodgkin lymphoma (HL), suggesting that TGR-1202, a novel inhibitor of the delta isoform of PI3K (PI3K-δ), currently in clinical development for patients with hematologic malignancies, might represent an attractive therapeutic option.
- The anti-CD30 monoclonal antibody brentuximab vedotin (BV) conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) has recently been reported to induce an overall response rate of 75% in relapsed/refractory HL, but is associated with limited response duration.
- Combination therapies aimed at enhancing the anti-tumor activity of BV and avoiding potential toxicity may have significant clinical impact in the treatment of relapsed/refractory HL.

AIM OF THE STUDY

To investigate the in vitro activity and mechanism(s) of action of TGR-1202 in combination with BV by using three HL cell lines (L-540, KM-H2, L-428).

METHODS & RESULTS

IN VITRO

TGR-1202 in combination with BV was associated with:

- synergistic inhibition of the mean (±SEM) growth of HL cell lines (**Fig. 1**).
- 3-fold increase in induction of cell death in all HL cell lines (**Fig. 2**).
- G2/M cell cycle arrest and 3-fold reduction in number of cells in S phase (**Fig. 3**).
- marked Cyclin B1 and p21 overexpression (**Fig. 4**).
- potent synergistic microtubule disruption (**Fig. 5A**) and significant time-dependent tubulin depolymerization (**Fig. 5B**).

Fig. 1 – Cell Viability

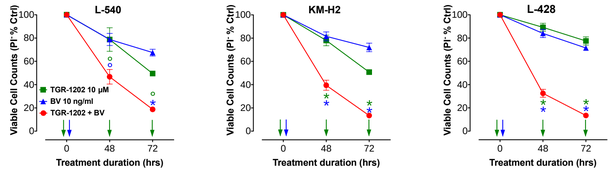


Fig. 2 – Cell death: Annexin-V/PI staining

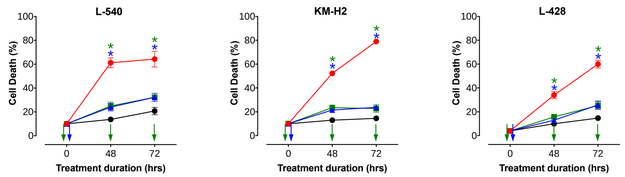


Fig. 3 – Cell Cycle

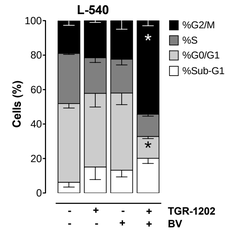


Fig. 4 – Cyclin B1 and p21 staining

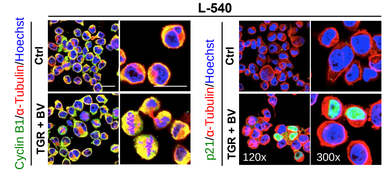
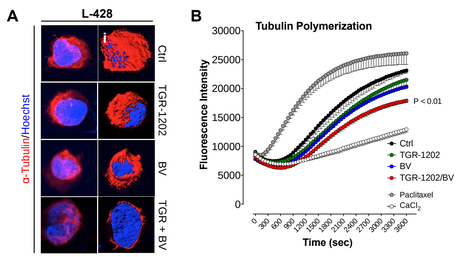


Fig. 5 – A) Microtubule Disruption and B) Tubulin polymerization assay



IN VIVO

Effects of the combined TGR-1202/BV treatment:

- Tumor growth inhibition
  - 55% vs controls and single agents (**Fig. 6**).
- Tumor necrosis
  - 5-fold increase vs controls (**Fig. 7**).
- Microtubule Disruption (**Fig. 8**).

Fig. 6 - Tumor Growth Inhibition (TGI)

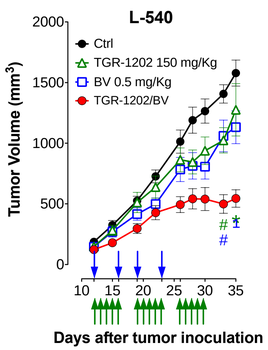


Fig. 7 – Tumor Necrosis

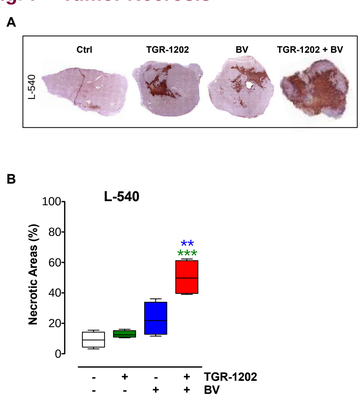
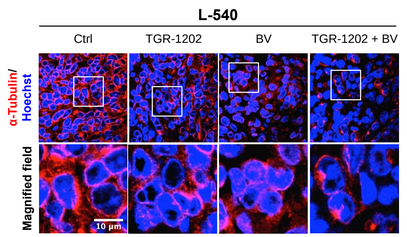


Fig. 8 – In Vivo Microtubule Disruption



CONCLUSIONS

In all HL cell lines, TGR-1202/BV induced potent anti-tumor effects with the novel PI3K-δ inhibitor TGR-1202 enhancing the anti-tumor activity of BV:

In vitro – increase drug-induced apoptosis and tubulin disruption.

In vivo – inhibition of tumor growth.

A Phase I multi-center study is ongoing evaluating the combination of TGR-1202 and BV in patients with relapsed/refractory HL, and this data supports continued evaluation and elucidates potential mechanisms for synergistic activity of the combination.

REFERENCES

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3. De, J. and Brown, R. **Int J Clin Exp Med** 3(1), 55-68 (2010)

DISCLOSURES

S. Viswanadha: Employment – Incozen Therapeutics.

Swaroop Vakkalanka: Employment – Rhizen Pharmaceuticals

P. Sportelli: Employment & Equity Ownership – TG Therapeutics