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 (PI3Kδ)-, 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).

**REFERENCES**


**CONCLUSIONS**

In all HL cell lines, TGR-1202/BV induced potent anti-tumor effects with the novel PI3Kδ 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.

**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).

**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).

**DISCLOSURES**

P. Sportelli: Employment & Equity Ownership – TG Therapeutics