The PI3K-δ Inhibitor TGR-1202 In Combination With Brentuximab Vedotin (SGN-35) Synergistically Induces G2/M Phase Arrest and Cell Death Via Inhibition Of Tubulin Polymerization in Hodgkin Lymphoma Cell Lines

Silvia L Locatelli,1,2 Silvia Tartari,1 Luca Rubino,1 Ercole Brusamolino,1 Luca Castagna,1 Srikanth Viswanadha,3 Peter Sportelli,4 Armando Santoro,1 and Carmelo Carlo-Stella,1,2

1Department of Oncology and Hematology, Humanitas Cancer Center, Humanitas Clinical and Research Center, Rozzano, Italy; 2Department of Medical Biotechnology and Translational Medicine, University of Milano, Milano, Italy; 3Incozen Therapeutics, Hyderabad, India; 4TG Therapeutics, Inc., New York, NY

Abstract # 1835

REFERENCES

METHODS & RESULTS

TGR-1202 and BV used as single agents induced time- and dose-dependent inhibition of cell proliferation and induction of cell death in HL cells (Fig. 1A-C).

- TGR-1202 in combination with BV was associated with:
  - synergistic growth of L-S40, KM-H2, and L-428 cell lines (TGR-1202: 40 ± 4%, BV: 30 ± 2%, TGR-1202/BV: 85 ± 1%) (Fig. 2A).
  - G2/M cell cycle arrest and 3-fold reduction of cells in 5 phase (TGR-1202: 25 ± 1%, BV: 23 ± 1%, TGR-1202/BV: 9 ± 1%, mean ± SEM) (Fig. 3A).
  - marked Cyt3 B1 and p21 overexpression (Fig. 3B).
  - 3-fold induction of cell death (TGR-1202: 27 ± 2%, BV: 27 ± 2%; TGR-1202/BV: 75 ± 2%) in L-S40, KM-H2, and L-428 cell lines (Fig. 3B).

In addition, TGR-1202 alone induced a marked time-dependent inhibition of PI3K/Akt pathway (Fig. 4A) and dephosphorylation of GSK3-β, Aurora kinase, and siltalin (Fig. 4B).

- TGR-1202/BV treatment resulted in a poten synergistic microtubule disruption (mean values of α-tubulin inhibition of 40%, P < 0.0001) (Fig. 5).
- TGR-1202/BV was found to interfere with the mitotic spindle integrity (Fig. 4B, 5).

In all HL cell lines, TGR-1202/BV treatment induced potent anti-tumor effects.

Novel PI3K-δ inhibitor TGR-1202 enhances the anti-tumor activity of BV by increasing drug-induced apoptosis and tubulin disruption in all HL cell lines analyzed in the present study.

Our data provides a strong rationale for evaluating TGR-1202 in combination with BV in patients with relapsed/refractory HL.

CONCLUSIONS

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), 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 71% in relapsed/refractory HL, but is associated with limited response duration.

Combination therapies aimed at enhancing the anti-tumor activity of BV and reducing its side effects may have significant clinical impact in the treatment of relapsed/refractory HL.

The present study was aimed at investigating the activity and mechanism(s) of action of the PI3K-δ inhibitor TGR-1202, in combination with BV in non-clinical models of HL.

To investigate in vitro the activity and mechanism(s) of action of TGR-1202 in combination with BV by using three HL cell lines (L-S40, KM-H2, L-428).

AIM OF THE STUDY

CONCLUSIONS

REFERENCES

DISCLOSURES

P. Sportelli: Employment & Equity Ownership – TG Therapeutics
S. Venkatraman: Employment – Incozen Therapeutics