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

Abstract # 1835

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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), 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 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.

AIM OF THE STUDY

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-540, KM-H2, L-428).

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 inhibition of the mean (±SEM) growth of L-540, 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 S phase (TGR-1202: 25 ± 1%; BV: 23 ± 1%; TGR-1202/BV: 9 ± 1%, mean ±SEM) (**Fig. 3A**).
  - marked Cyclin 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-540, KM-H2, and L-428 cell lines (**Fig. 2B**).
- In addition, TGR-1202 alone induced a marked time-dependent inhibition of PI3K/Akt pathway (**Fig. 4A**) and dephosphorylation of GSK-3β, Aurora kinases, and stathmin (**Fig. 4B**).
- TGR-1202/BV treatment resulted in a potent synergistic microtubule disruption (mean values of α-tubulin inhibition of 40%, P ≤.0001) (**Fig. 5**).
- TGR-1202/BV was found to interfere with the mitotic spindle integrity (**Fig. 4B, 5**).

Fig. 2 - TGR-1202/BV: Cell Viability and Cell Death – Annexin-V/PI staining

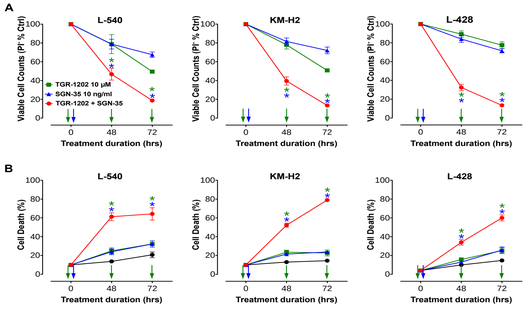


Fig. 1 – A-B) TGR-1202 single agent: Cell Viability and Cell Death – Annexin-V/PI staining. C) BV single agent dose-effect: Cell Viability

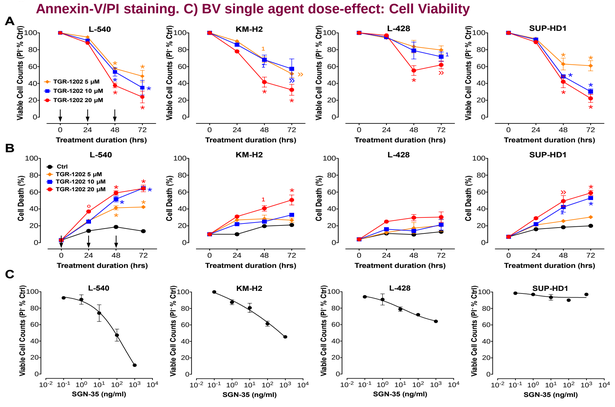


Fig. 3 –Cell Cycle and Immunofluorescence – PI, Cyclin B1 and p21 staining

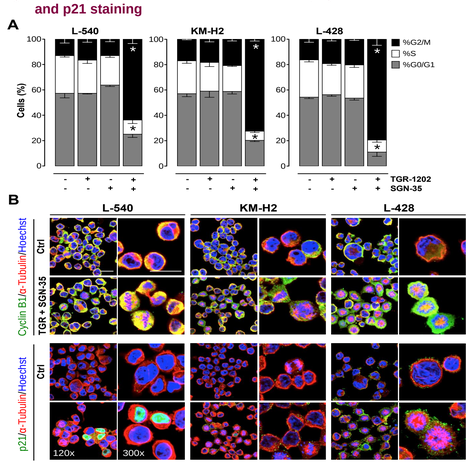


Fig. 4 – Targeting PI3K/Akt and microtubule pathways

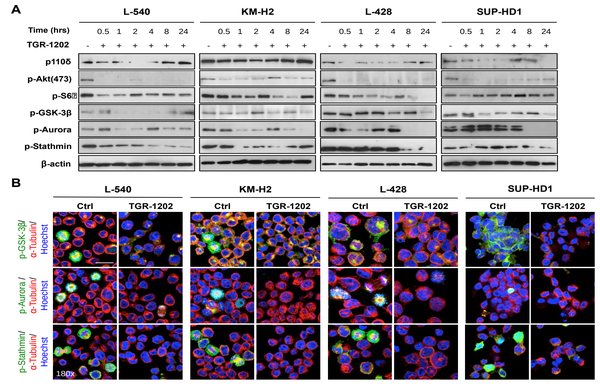
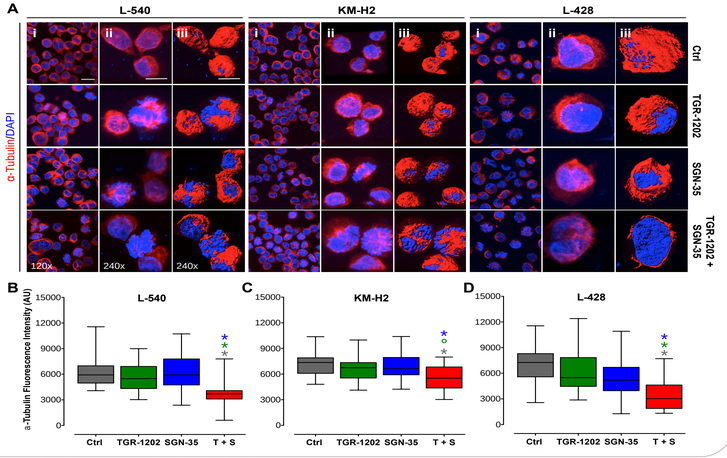


Fig. 5 – Microtubule Disruption – Immunofluorescence and Volumetric rendering of α-tubulin



CONCLUSIONS

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.

REFERENCES

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DISCLOSURES

P. Sportelli: Employment & Equity Ownership – TG Therapeutics

S. Viswanadha: Employment – Incozen Therapeutics