Single agent activity and synergistic drug combinations of ixazomib in Preclinical Models of T-cell Lymphoma (TCL) and Hodgkin Lymphoma (HL)

Ravi Dashnamoorthy PhD[1], Afshin Beheshti PhD[1], Nassera Abermil MS, PharmD[1], Jaya Sharma MBBS, MD[1], Michael Coyle MD[1], Irawati Kandela PhD[2], Andrew Mazar PhD[2], Lynn Hlatky PhD[1], Andrew M. Evens DO, MSc[1]

[1]Tufts University School of Medicine and Molecular Oncology Research Institute, Tufts Cancer Center, Tufts Medical Center, Tufts University School of Medicine, Boston, MA, USA

[2]Feinberg School of Medicine, Northwestern University, Evanston, IL USA.

Introduction

We investigated the potency, biological mechanisms of action, and described the role of Myc in cell death and resistance to the investigational proteasome inhibitor, ixazomib, in TCL and HL *in vitro* and *in vivo* tumor models. In addition, we sought to identify molecular biomarkers that were associated with response/resistance to proteasome inhibitor, ixazomib

Methods

TCL cell lines (Jurkat, Hut78, HH) and HL cell lines (L428, L540, L1236) were treated with ixazomib for 24-72 hours, cell viability and apoptosis were analyzed by MTT and Annexin/PI by flow cytometry (FC).

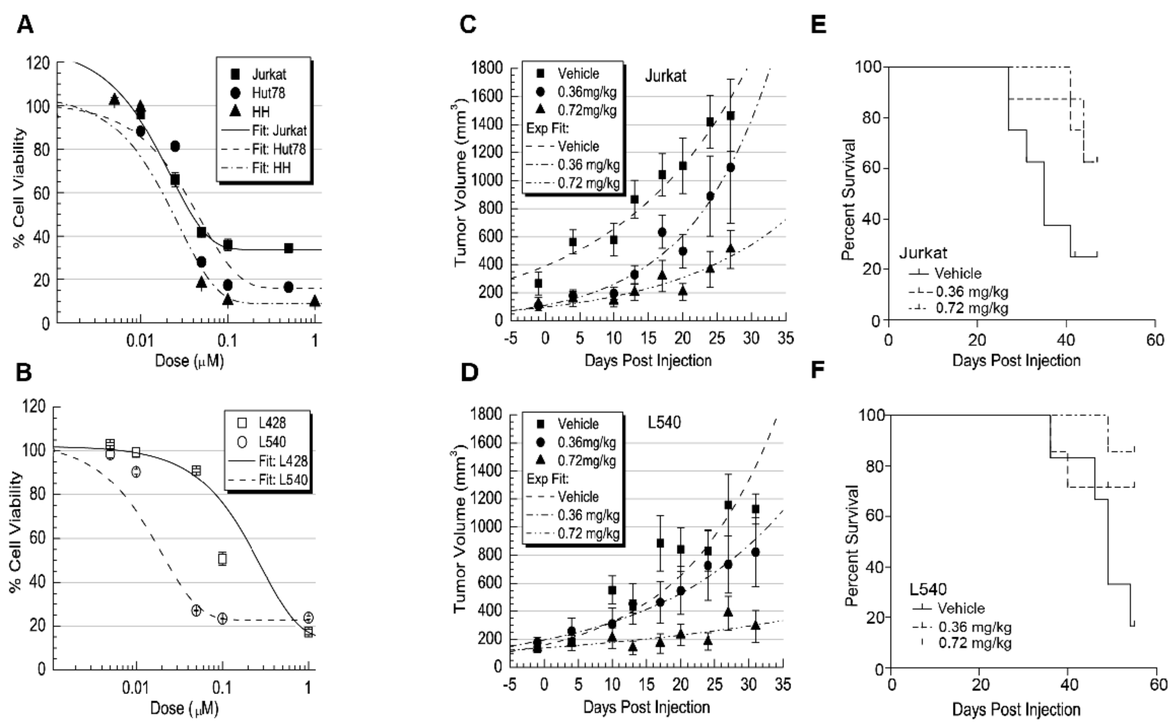
In vivo tumor growth inhibition and survival of tumor bearing SCID mice were determined using xenografts derived from Jurkat (TCL) and L540 (HL) cell lines.

Gene expression profiling (GEP) was performed using Human Affymetrix 2.0 HT array, which included Gene Set Enrichment Analysis (GSEA), for Jurkat, L540, and L428 cell lines. Significant genes where determined using FDR < 0.05.

Western blot, Chromatin IP-PCR, siRNA based transfection, and pharmacological inhibitors were used to assess biological function of apoptosis, MYC, oxidative stress, lysosomal activity and chromatin modifications, in the presence and/or absence of ixazomib.

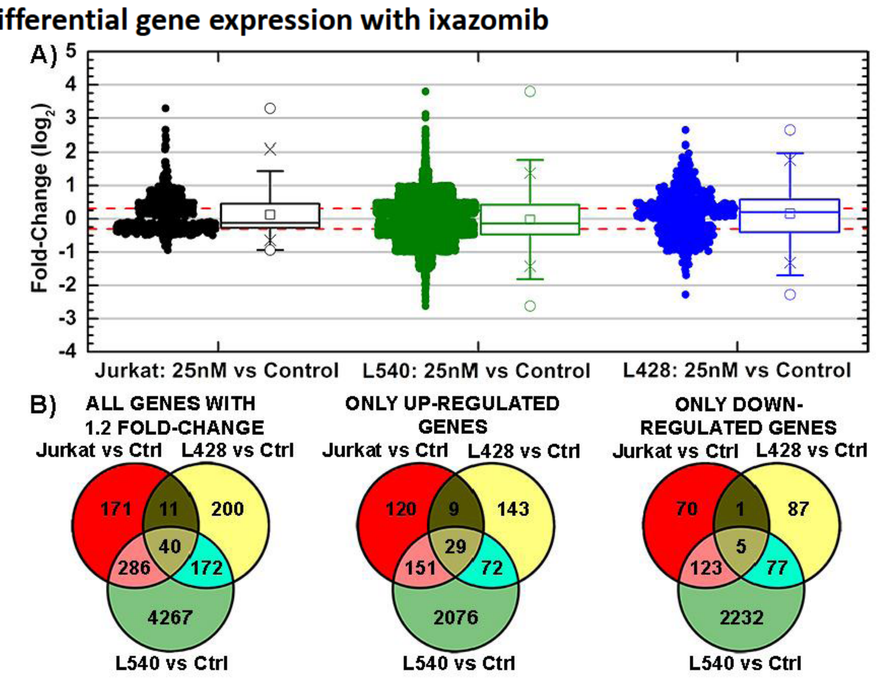
Results

1. Ixazomib induced potent cell death in vitro, and inhibited the growth of tumor xenografts in SCID mice

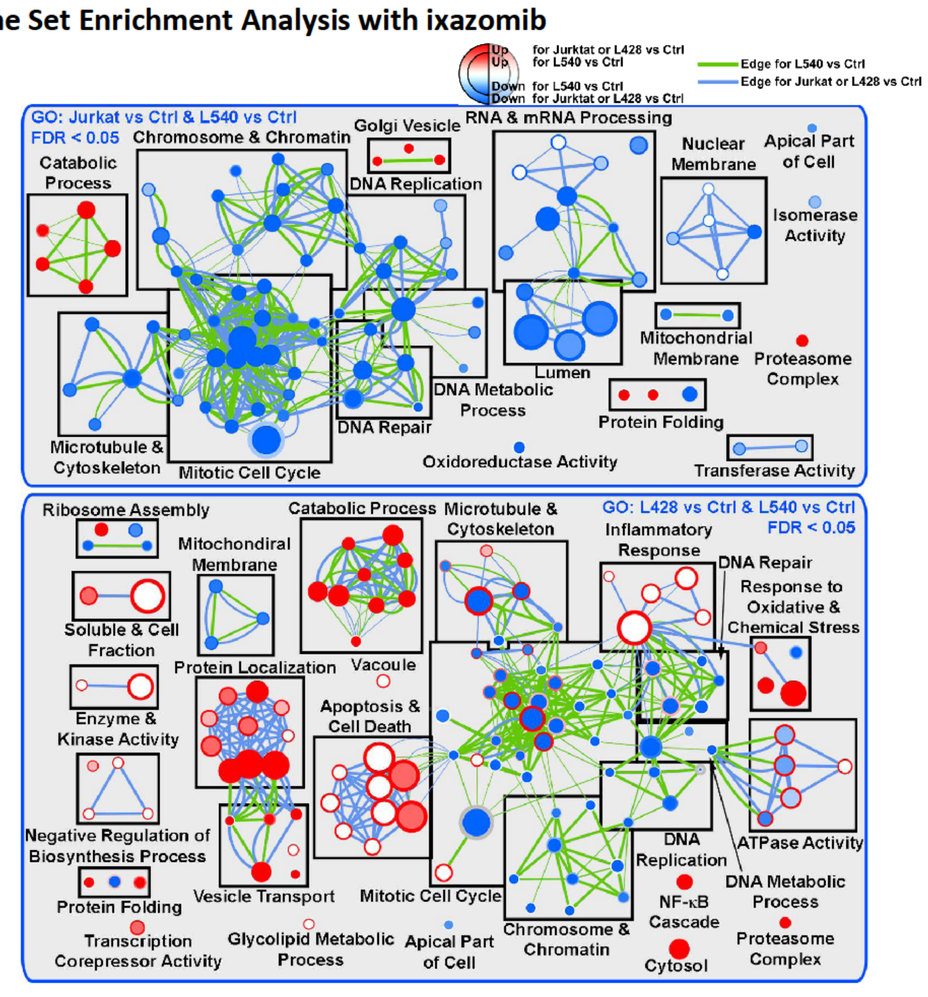


2. Identification of relevant biological pathways affected by ixazomib treatment by Gene Set Enrichment Analysis

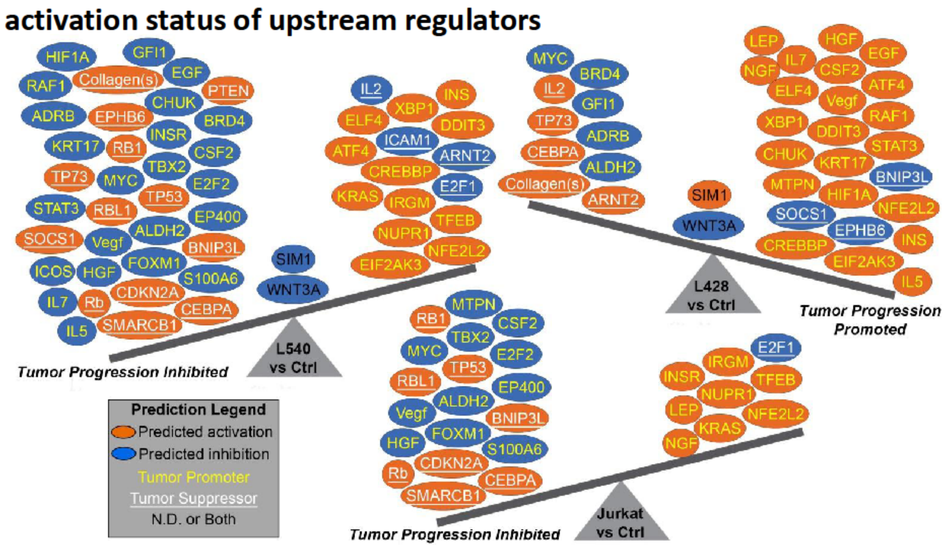
A-B) Differential gene expression with ixazomib



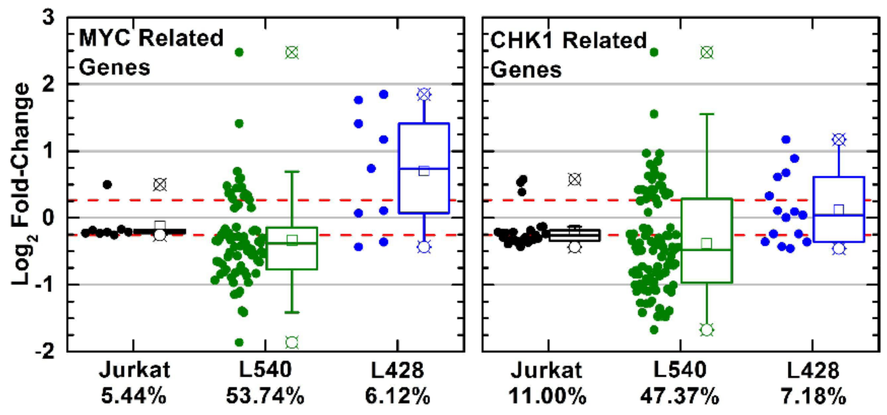
c) Gene Set Enrichment Analysis with ixazomib



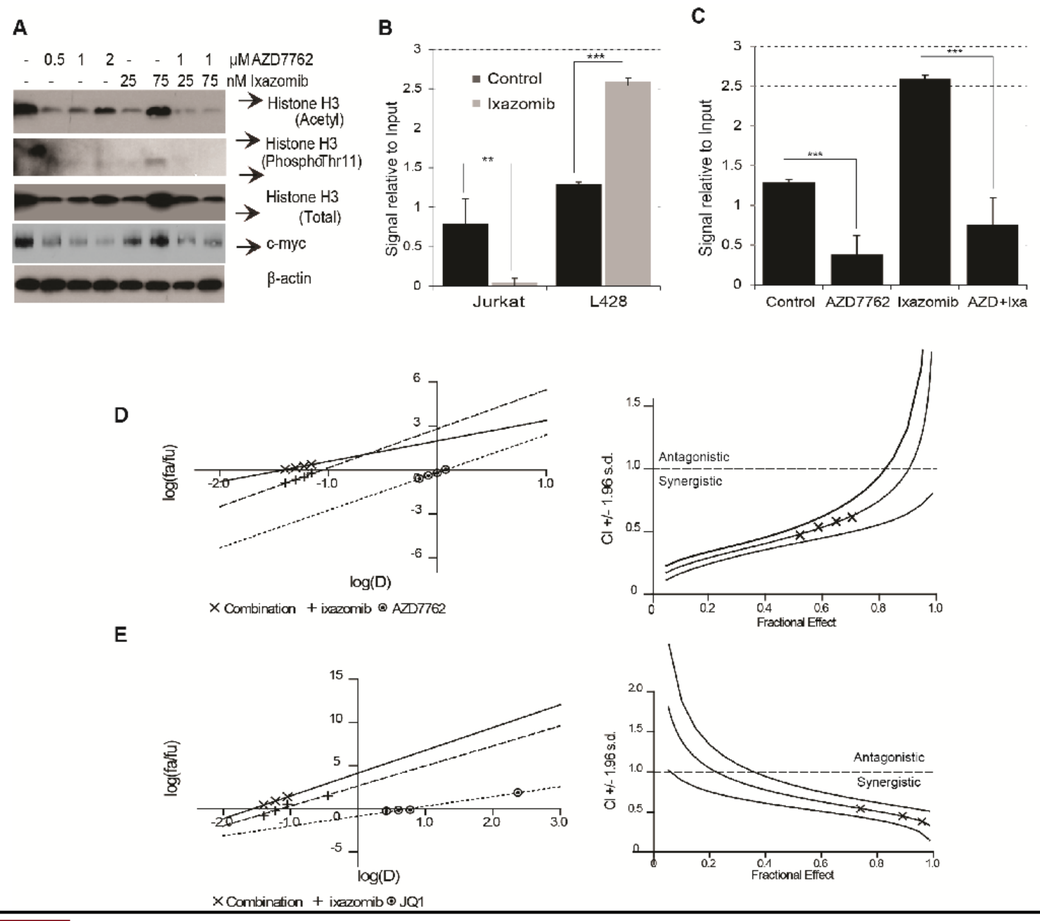
D) Predicted activation status of upstream regulators



3. Ixazomib regulation of MYC and CHK1 related pathways



4. (A-C Ixazomib induces CHK1 dependent MYC response by (ChIP assay) and (D-E) CHK1 and MYC inhibitors induce synergistic cell death in L428 HL cells



Conclusions

The investigational proteasome inhibitor, ixazomib, induced potent cell death at nanomolar and clinically achievable concentrations in TCL and HL cell lines and *in vivo* xenograft SCID models. Results from GEP with ixazomib showed global changes in gene expression consistent with inhibition of tumor progression, in both TCL and HL cells. Ixazomib treatment down-regulated Myc and its downstream substrates in TCL and HL cells. Resistance to ixazomib treatment appeared to occur through a Myc-dependent mechanism. In addition, we identified several potential novel biomarkers of ixazomib response/resistance in TCL and HL. Continued examination of ixazomib in lymphoma is warranted and rational combinations with Myc and HDAC inhibitors should be explored.

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Hodgkin lymphoma

Andrew Evens

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