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Blood 142 (2023) 1442–1443

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

Dynamic Single-Cell Profiling Reveals Novel Immune Regulatory Mechanism of ITK Inhibitor Soquelitinib in Refractory T Cell Lymphoma

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Introduction

Interleukin 2 inducible T cell kinase (ITK) plays an important role in the T cell receptor (TCR) signaling pathway. The highly selective covalent ITK inhibitor, soquelitinib (formerly known as CPI-818), is being evaluated as a monotherapy in an ongoing Phase 1/1b trial in patients with refractory T-cell lymphoma (TCL) (NCT03952078). Single cell RNA-sequencing and flow cytometry were performed on patient samples to identify potential prognostic biomarkers and to study immune regulatory mechanisms.

Methods

Paired peripheral blood and tumor tissue samples were collected from 3 responding TCL patients treated with soquelitinib. Dynamic single cell RNA-seq and flow cytometry studies were performed and changes in gene expression profiling and signature gene enrichment were analyzed at baseline and on treatment.

Results

Single cell RNA-seq of mRNA expression demonstrated that soquelitinib induced expression of cytotoxic genes (PRF1, GZMB, GZMK, GZMA, GZMH, GNLY and NKG7) and effector genes (IFNG, EOMES, CST7), and reduced exhaustion genes (PDCD1, LAG3, CTLA4, HAVCR2) in normal CD8+ cells. KEGG and GSEA enrichment analysis revealed that Interferon-Gamma, IL-2-STAT5 and TNF-alpha related signaling pathways were upregulated; the protein-protein interaction network analysis revealed that the hub gene TBX21 might play a central regulatory role. KEGG enrichment analysis also demonstrated that soquelitinib treatment significantly decreased DNA replication and cell cycle signaling in malignant T cells, and that normal CD4+ Treg cells within tumor microenvironment and peripheral blood were significantly reduced post soquelitinib treatment.

Flow cytometry analysis of the peripheral blood and intratumoral T cell subpopulations confirmed that the normal CD4+ and CD8+ T cells, especially Th1 cells and CD8+ terminally differentiated T effector memory cells were significantly increased and CD4+ Treg cells were decreased compared to baseline levels following soquelitinib treatment.

In addition, human T cell differentiation studies and EL4 syngeneic tumor bearing mice studies confirmed the immunomodulatory effect of soquelitinib in the tumor microenvironment *in vitro* and *in vivo*. Similar results were also observed in the murine syngeneic B cell lymphoma A20, breast cancer 4T1 and colon cancer CT26.WT models.

Conclusions

Our findings reveal a novel immune regulatory mechanism by which the ITK inhibitor soquelitinib induced normal CD4+ Th1 cells and CD8+ TEMRA cells and reduced CD4+ Treg cells in the tumor microenvironment in responding patients. These findings demonstrate the potential of soquelitinib as a novel immunotherapy for the treatment of T-cell lymphomas and solid tumors.

Disclosures Guo: *Angel Pharmaceutical:* Current Employment. **Li:** *Angel Pharmaceutical:* Current Employment. **Hsu:** *Corvus Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company. **Miller:** *Corvus Pharmaceuticals:* Current Employment, Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees; *Bolt Biotherapeutics:* Current equity holder in publicly-traded company, Membership on an entity's Board of Directors or advisory committees.

https://doi.org/10.1182/blood-2023-174421