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Blood 142 (2023) 5783

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

PRT2527, a Novel Highly Selective Cyclin-Dependent Kinase 9 (CDK9) Inhibitor, Has Potent Antitumor Activity in Combination with BTK and BCL2 Inhibition in Various Lymphoid Malignancies

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CDK9 is a master regulator of transcription that modulates transcription elongation via phosphorylation of RNA polymerase II. Short-term inhibition of CDK9 depletes short-lived transcripts and labile proteins such as MCL1, BFL1 and MYC to promote cancer cell death.

We previously described PRT2527, a novel, potent, highly selective CDK9 inhibitor with anti-leukemic activity in various pre-clinical models. PRT2527 is currently under evaluation in a Phase I clinical trial in patients with relapsed/refractory hematologic malignancies (NCT05159518).

Here we demonstrate PRT2527 potently inhibits cancer growth and induces cell death in various models of Diffuse Large B Cell Lymphoma (DLBCL), Mantle Cell Lymphoma (MCL) and Chronic Lymphocytic Leukemia (CLL), through depletion of MCL1, BFL1 and MYC. We also show that combination of PRT2527 with BTK inhibitors (BTKi) or BCL2 inhibitors (BCL2i) leads to more robust and durable responses in multiple pre-clinical models. In these studies, the combination of PRT2527 with BTKi or BCL2i was well tolerated.

Mechanistically, we show that in cell lines, BTK inhibition upregulates BMF, an endogenous inhibitor of BCL2 and BCL-xL, driving cells towards MCL1 and BFL1 dependency. Concurrent depletion of MCL1 and BFL1 with PRT2527 led to complete inhibition of Bcl-2- family mediated survival signaling, potently inducing cell death. In a similar fashion, Venetoclax-driven BCL2 inhibition also potentiated the anti-tumor activity of PRT2527. Consistent with our findings in vitro, we confirmed potent combinatorial inhibition of tumor growth by PRT2527, administered once weekly, and BTKi or BCL2i, administered daily, in CDX and PDX *in vivo* models of DLBCL and MCL. We observed reduced BFL1 and MCL1 as well as increased BMF in tumors of mice treated with BTKi and PRT2527 suggesting complete Bcl-2 family inhibition. We also demonstrated enhanced induction of apoptosis by PRT2527 in primary CLL patient samples simultaneously treated with BTKi or BCL2i.

Additionally, we demonstrated that PRT2527 potently inhibits growth in Ibrutinib-resistant MCL cell lines. Further work characterizing PRT2527 as monotherapy and in combination with BTKi and BCL2i in *in vivo* models of BTKi-resistant MCL and CLL is currently ongoing.

Altogether these data provide a rationale for evaluating PRT2527 in combination with BTK and BCL2 inhibitors for the treatment of patients with relapsed/refractory hematologic malignancies.

Disclosures Fultang: *Prelude Therapeutics Inc.:* Current Employment. **Schwab:** *Prelude Therapeutics Inc.:* Current Employment. **McAneny-Droz:** *Prelude Therapeutics Inc.:* Current Employment. **Heiser:** *Prelude Therapeutics Inc.:* Current Employment. **Scherle:** *Prelude Therapeutics Inc.:* Current Employment. **Bhagwat:** *Prelude Therapeutics Inc.:* Current Employment.

https://doi.org/10.1182/blood-2023-190093

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