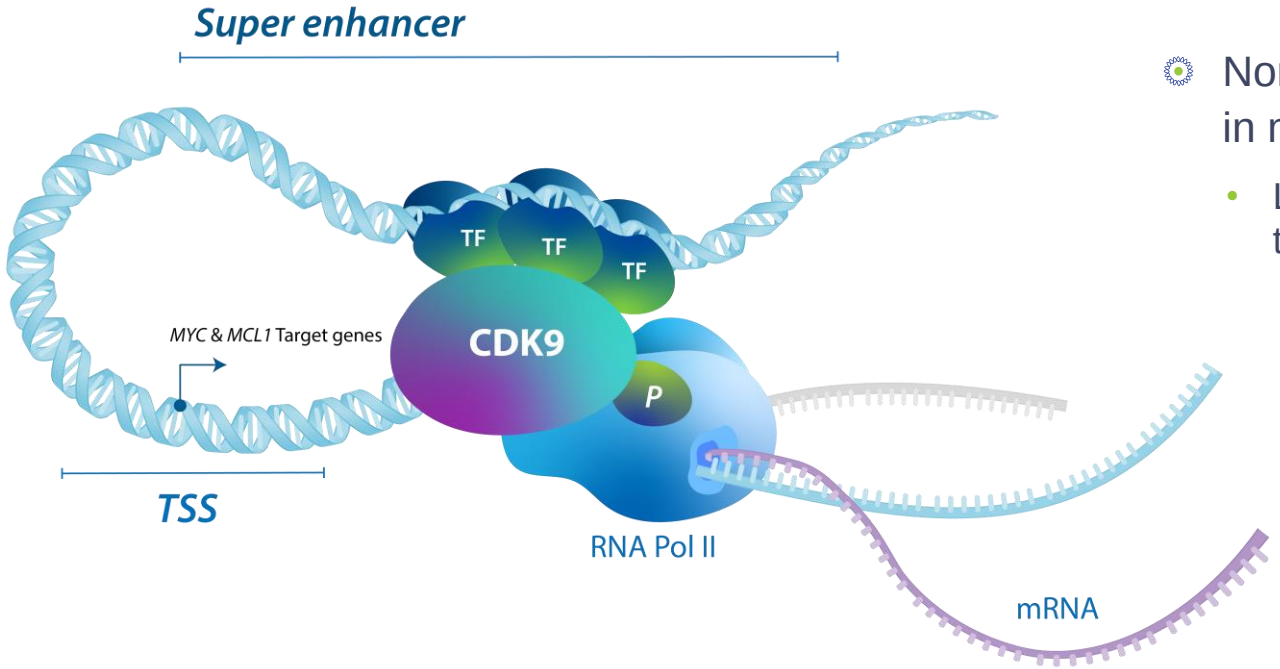
PRT2527, a Novel, Highly Selective Cyclin-Dependent Kinase 9 (CDK9) Inhibitor, Has Potent Anti-Leukemic Activity in Preclinical Models of Lymphoid Malignancies

Neha Bhagwat[1], Bruce Ruggeri[1], Yang Zhang[1], Yaron Mosesson[2], Clare Killick-Cole[2], Veena Jagannathan[2], Peggy Scherle[1]

Affiliations: [1]Prelude Therapeutics Inc. Wilmington, DE; [2]Champions Oncology, Rockville, MD.

CDK9: Targeting Cancer Through Transcriptional Regulation

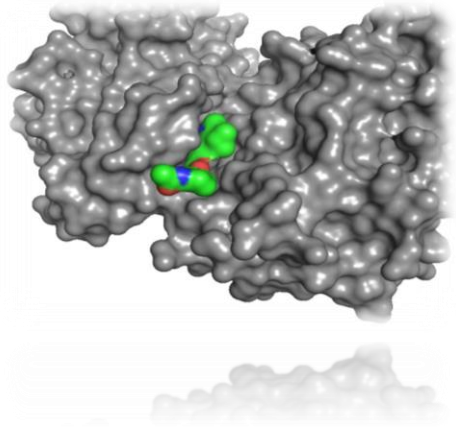


- CDK9 phosphorylates RNA Pol II and regulates transcription
- Regulates expression of several immediate early genes driving oncogenesis and resistance (i.e. *MYC*, *MCL1*)
- Non-selective CDK9 inhibitors have demonstrated clinical activity in multiple tumor types but poor tolerability
  - Lack of selectivity and potency vs other CDKs is believed to contribute to low therapeutic window

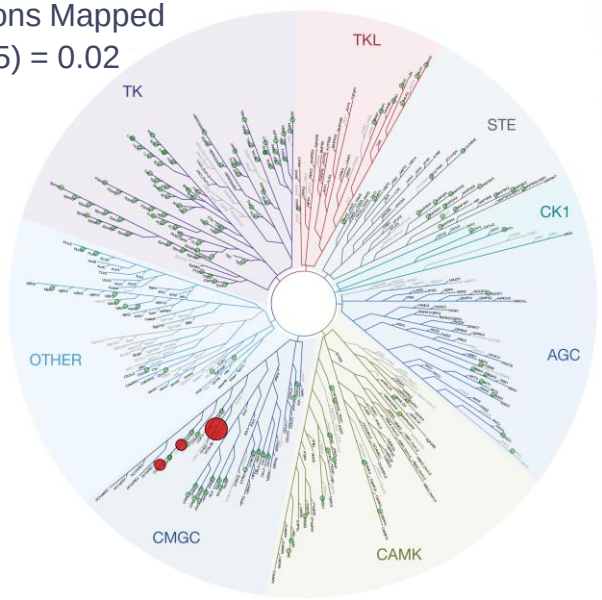
Highly-selective CDK9 inhibitors may have broad applicability in hematological malignancies and solid tumors

PRT2527: Potent and Highly Selective CDK9 Inhibitor Candidate

Highly Selective, ATP Competitive CDK9 Inhibitor Candidate



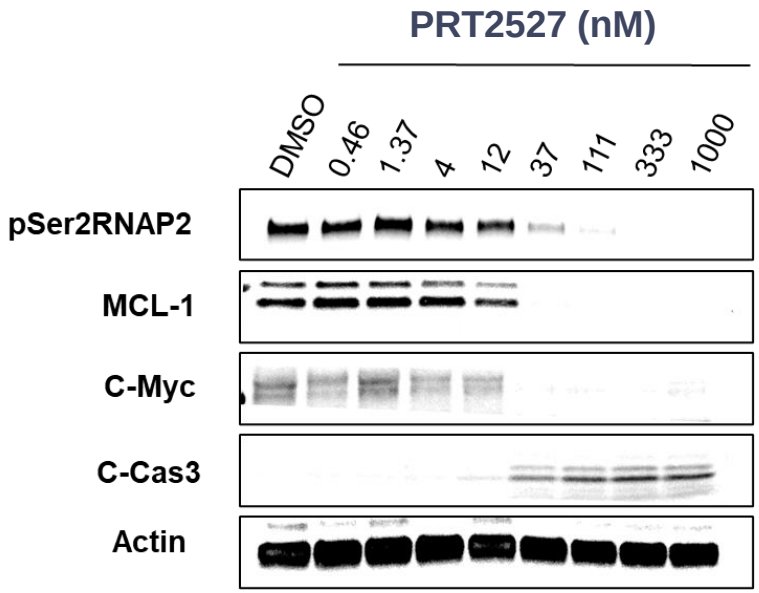
PRT2527
177 Assays tested
3 Interactions Mapped
S-Score(35) = 0.02

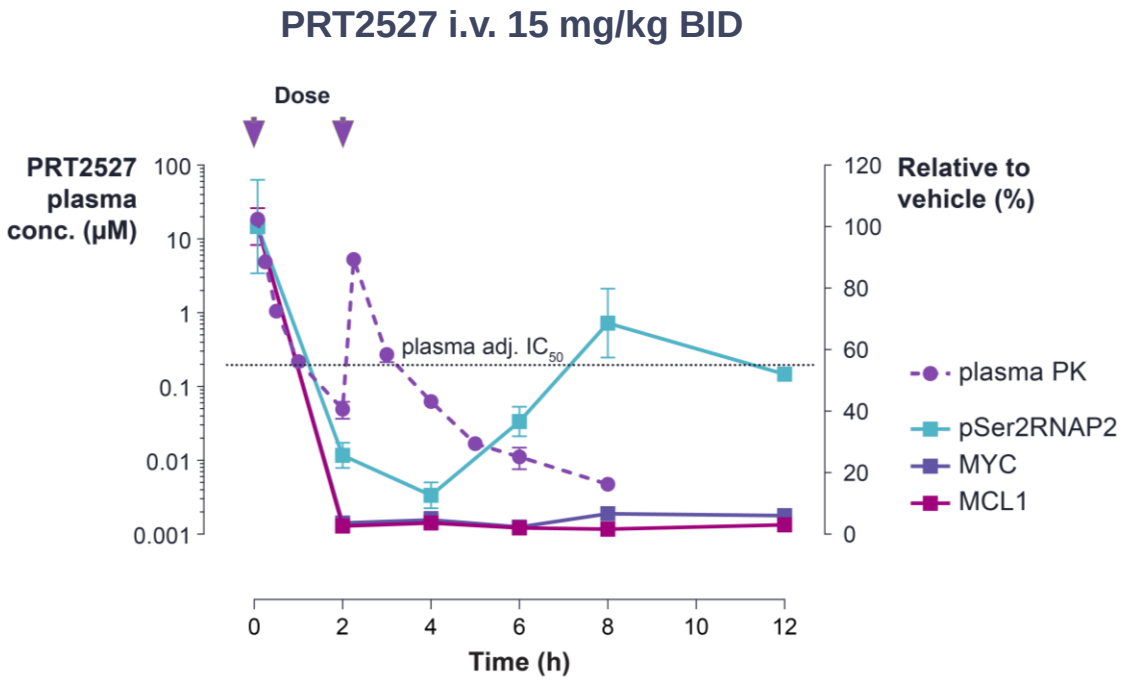


Compound		PRT2527
Biochemical* IC_{50} (nM)	**CDK9**	0.95
Proliferation* IC_{50} (nM)		18
Plasma* IC_{50} (nM)		196
Fold Selectivity CDK9 *vs* Other Isoforms	**CDK1**	73x
	CDK2	340x
	CDK3	35x
	CDK4	250x
	CDK5	>1000x
	CDK6	>1000x
	CDK7	>1000x

<10x 10 -100x >100x

PRT2527 Treatment Induces Depletion of MCL1 and MYC in Preclinical Models



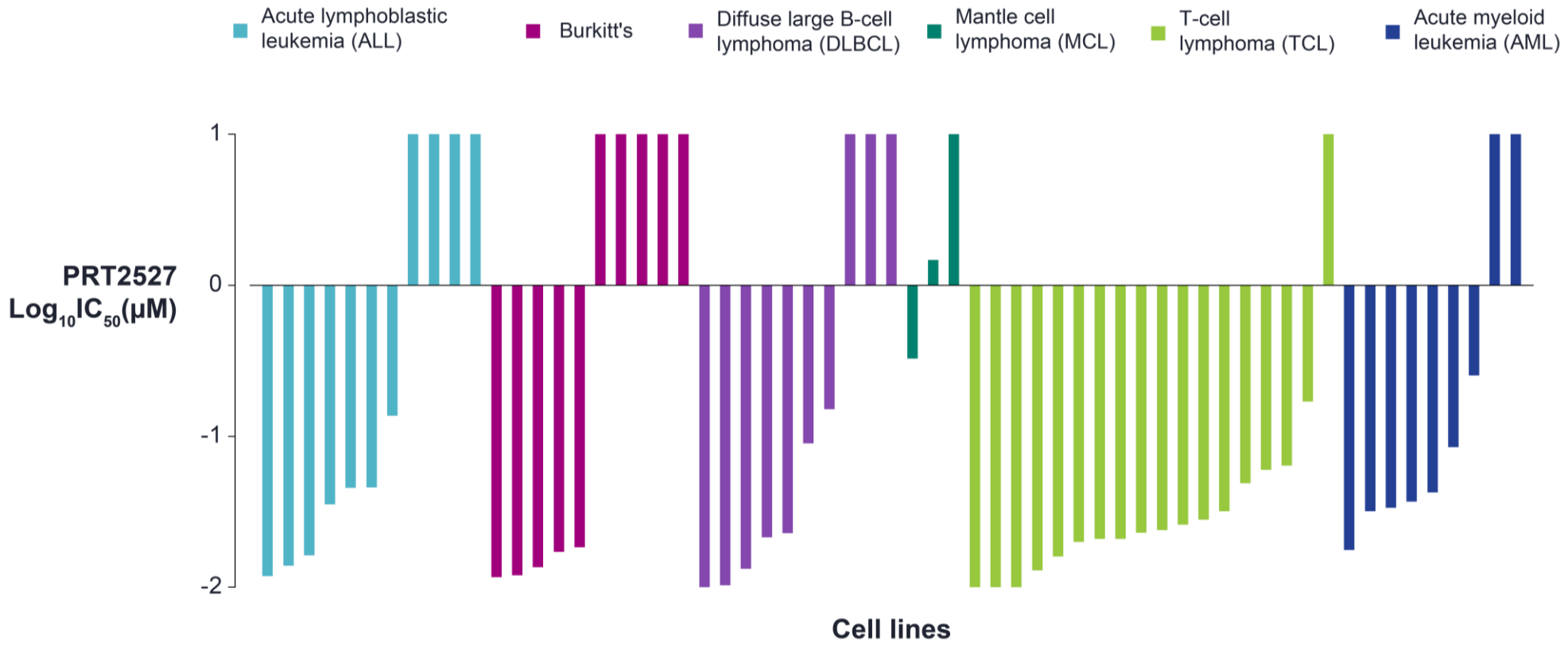


Transient treatment of MV4-11 cells with PRT2527 for 4 hours leads to inhibition of phospho-RNAPol2, and depletion of MCL1 and MYC, along with induction of cleaved Caspase-3 in vitro

IV administration of PRT2527 at 15 mg/kg BID (q2h) achieves ~ 3h coverage over plasma-protein binding IC_{50} and induces depletion of MCL1 and MYC in MV4-11 tumor tissue

ASH Annual Meeting 2022
Abstract No. 210

PRT2527 demonstrates broad anti-proliferative activity in hematologic malignancy cell lines



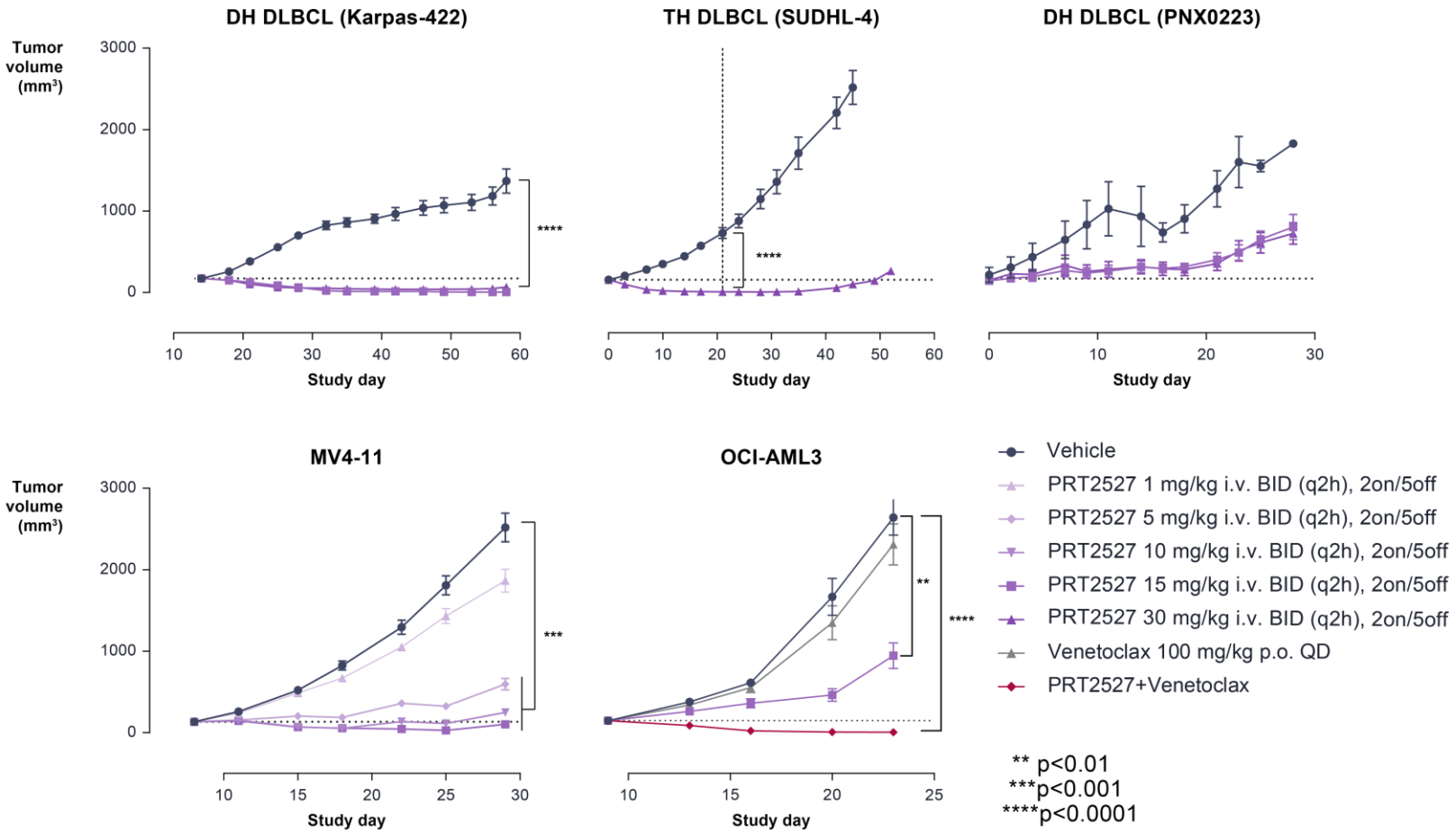
Median IC_{50} – 45 nM

PRT2527 is Highly Efficacious *In Vivo* in CDX and PDX Models of Hematologic Malignancies

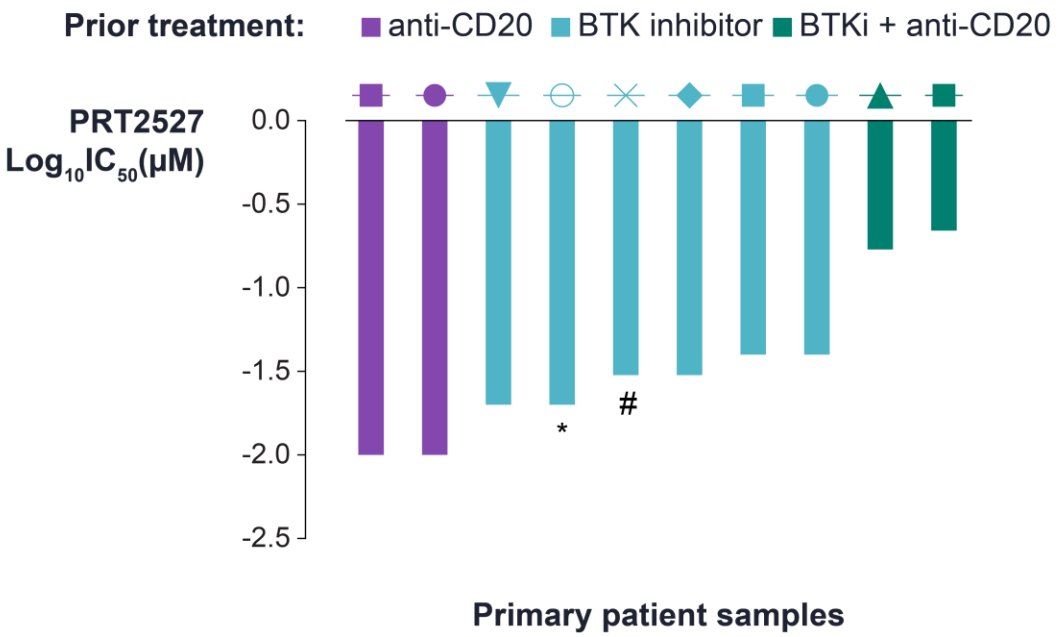
Intermittent IV administration of PRT2527 is highly efficacious in CDX/PDX double-hit/triple-hit DLBCL models with MYC translocation

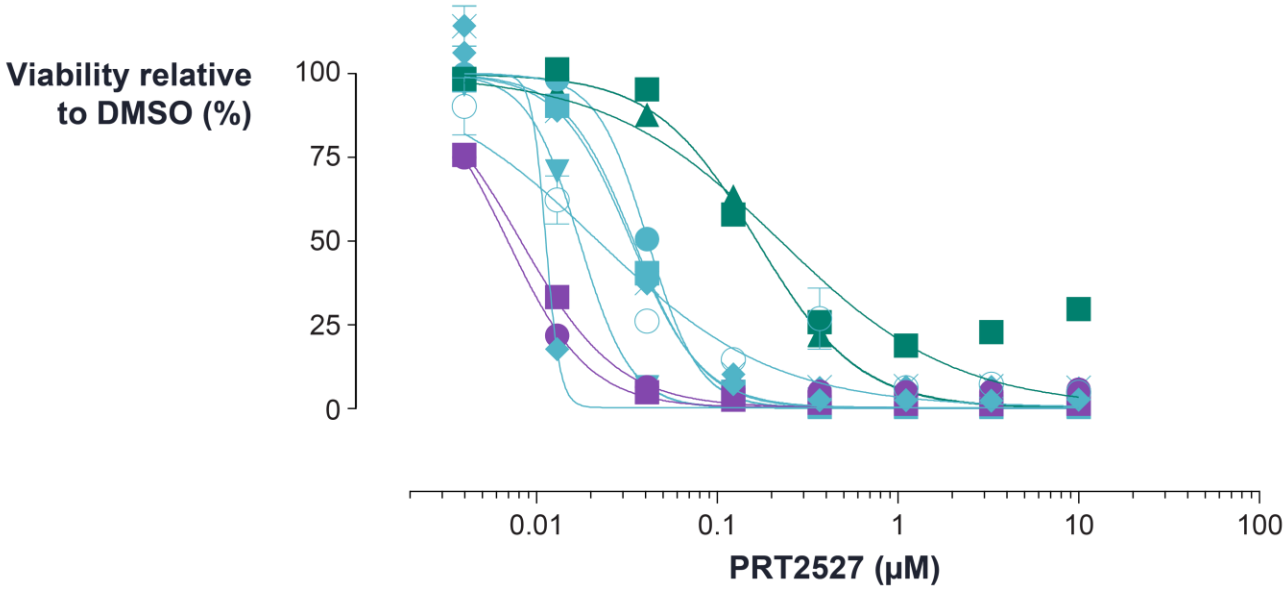
PRT2527 demonstrates anti-tumor activity in AML models

- Achieved complete regressions in combination with Venetoclax in a Venetoclax-insensitive model



PRT2527 is Potent in CLL Primary Cultures *Ex vivo*





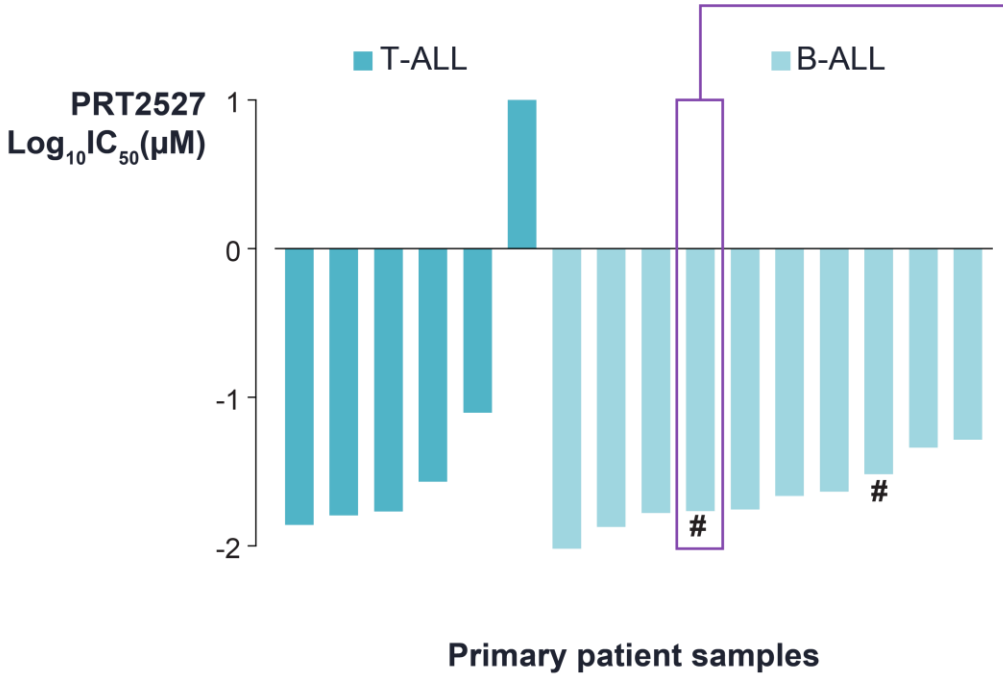
Median IC_{50} - 30 nM in a proliferation assay

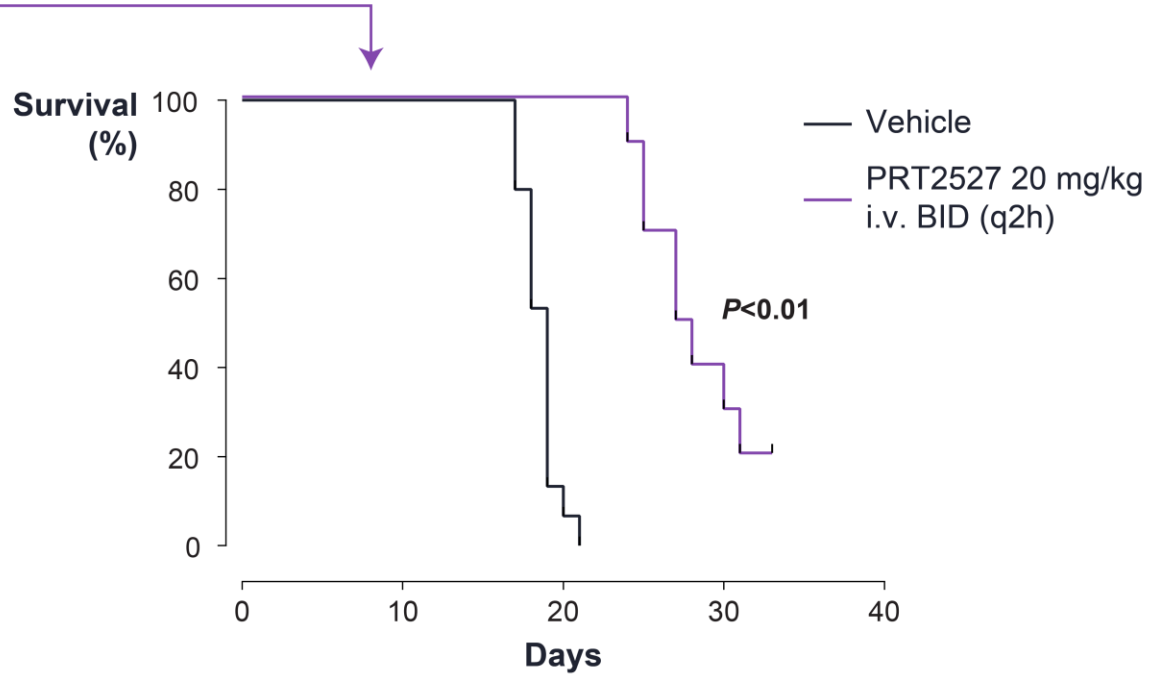
*Prior tx included FCR and an experimental autologous T-cell infusion

#Prior tx included Chlorambucil and Rituximab/Bendamustine

PRT2527 Demonstrates Significant Anti-Tumor Activity in Models of B-ALL and T-ALL

- PRT2527 activity in ALL was observed in 5/6 T-ALL and 10/10 B-ALL primary patient samples in an *ex vivo* assay
- Significant survival benefit observed with once weekly PRT2527 treatment in a highly aggressive KMT2A-rearranged systemic model of primary B-ALL in NSG mice



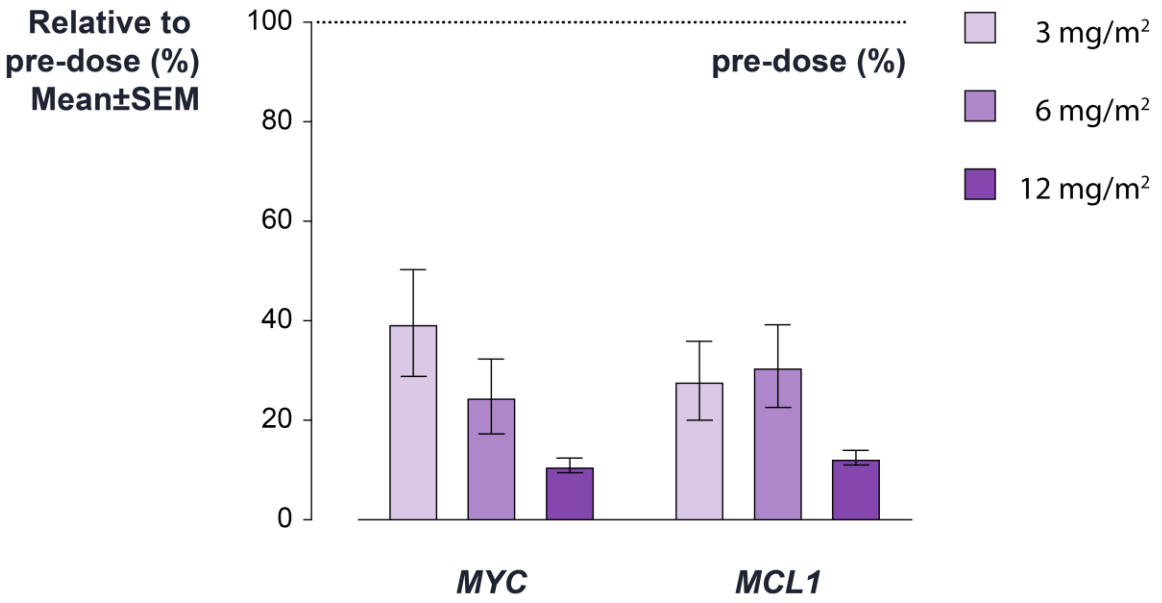


KMT2A rearranged

Phase 1 dose-escalation study of PRT2527 in advanced solid tumors (NCT05159518)

- Phase 1 dose escalation study of PRT2527 is ongoing and enrolling following tumor types
  - selected sarcomas displaying a gene fusion
  - Castrate resistant prostate cancer
  - HR+ HER2- breast cancer
  - Non-small cell lung cancer
  - Solid tumors with MYC amplification
- Nine patients have been treated in the first three dose levels (3, 6 and 12 mg/m^2 I.V. weekly), with no dose-limiting toxicities and acceptable tolerability.

- Dose-dependent inhibition of CDK9 transcription targets observed in PBMCs



HR+ Hormone receptor positive; HER2- Human epidermal growth factor negative

Summary

- PRT2527 is potent and selective CDK9 inhibitor that demonstrates robust activity in preclinical models of hematologic malignancies with once weekly dosing
  - Activity observed in models that are insensitive to current SoC as well as in combination with targeted agents
- PRT2527 was well-tolerated in preclinical toxicology studies
- Currently enrolling in a Phase 1 study in selected solid tumors (NCT05159518)
  - Demonstrates acceptable safety and PK profile and dose-dependent inhibition of PD biomarkers
- Planned Phase 1 study in aggressive B-cell lymphoma, MCL and CLL/SLL

Thank you

PRT2527, a Novel, Highly Selective Cyclin-Dependent Kinase 9 (CDK9) Inhibitor, Has Potent Anti-Leukemic Activity in Preclinical Models of Lymphoid Malignancies

Neha Bhagwat[1], Bruce Ruggeri[1], Yang Zhang[1], Yaron Mosesson[2], Clare Killick-Cole[2], Veena Jagannathan[2], Peggy Scherle[1]

Affiliations: [1]Prelude Therapeutics Inc. Wilmington, DE; [2]Champions Oncology, Rockville, MD.