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CDK9 Inhibitors

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Aggressive Lymphoma Workshop

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Disclosures

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- I have no personal financial relationships or interests with any proprietary entity producing healthcare goods/or services

- I have done consulting work for:
  - BeiGene: Clinical trial steering committee; Advisory board
  - Janssen/Pharmacyclics: Scientific Advisory Board
  - Kite: Scientific Advisory Board
  - Morphosys: Advisory Board
  - TG Therapeutics: Advisory Board
  - AbbVie: Advisory Board
- I have received grants from:
  - ORIEN Network

- I do have research funding from below:
  - AbbVie: investigator initiated trial
  - AbbVie/Roche/Genentech: Institutional PI on industry sponsored trial
  - Infinity: Institutional PI on industry sponsored trial
  - Acerta/AstraZeneca: Institutional PI on industry sponsored trial
  - TG therapeutics: Institutional PI on industry sponsored trial
  - BeiGene: Institutional PI on industry sponsored trial
  - Kite: Institutional PI on industry sponsored trial
  - Xencor: Institutional PI on industry sponsored trial
  - SeaGen: Institutional PI on industry sponsored trial
  - Merck: Investigator initiated trial
  - VelosBio/Merck: institutional PI on industry sponsored trial

I will be discussing approved treatments

Outline

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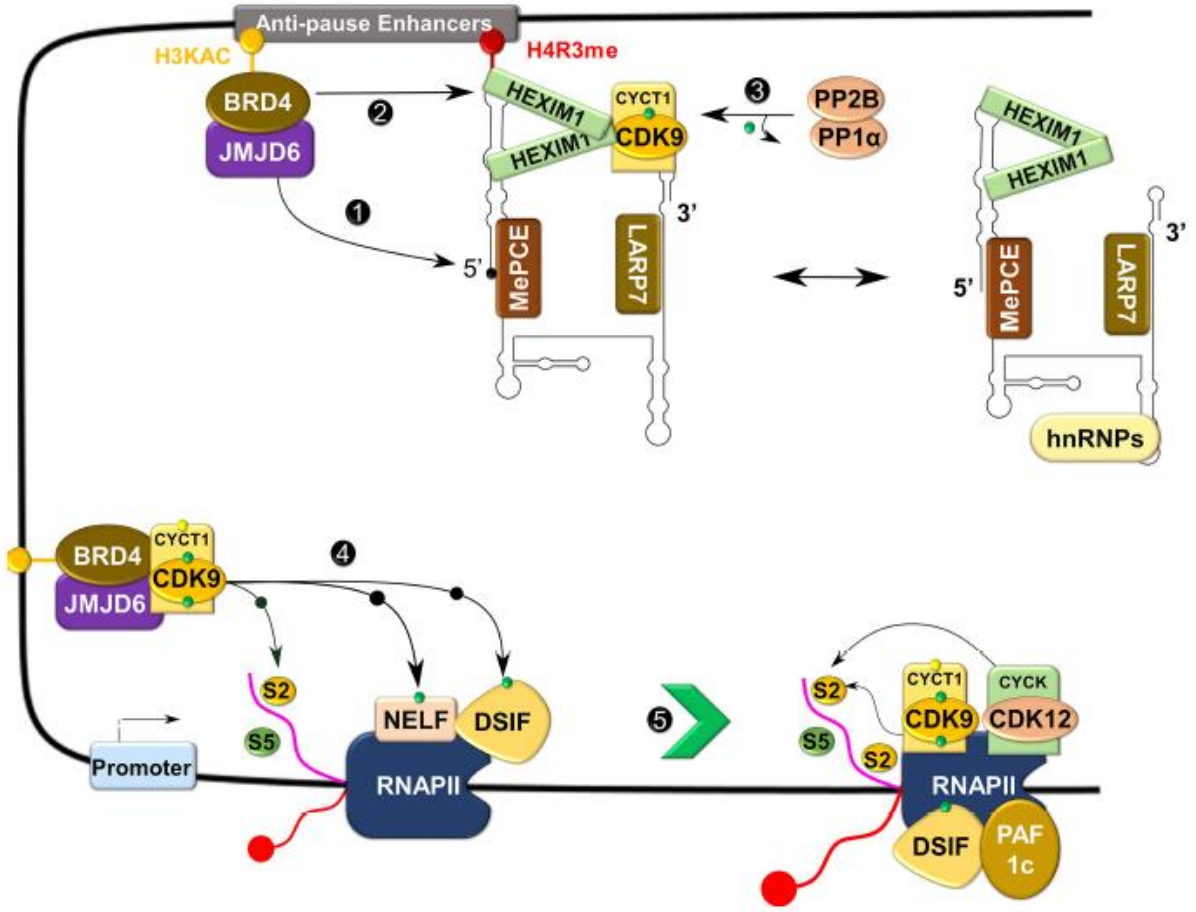
- Biologic activity of CDK9 in normal cells and cancer.
- Regulation of CDK9
- Clinical experience with CDK9 inhibitors
    - VIP152 (Enitociclib)
    - AZD4573
    - PRT2527

Biologic Activity



- Complexes with Cyclin T1 forming P-TEFb
- When active, binds to BRD4 complex on promoter regions
- CDK9 phosphorylates and binds members of RNAP II complex which is paused in translation
- Allowing elongation and final translation

Anshabo AT et al, Frontiers in Oncology, vol 11, May 2021

Biologic Activity—normal functions

- CDK9/Cyclin T1 complex (P-TEFb) controls transcription elongation and termination through RNAP II
- Limited role in cell cycle progression (different than other CDK/Cyclin complexes)
- Required for differentiation of lymphocytes (and others)
- CDK9 also has a role in DNA damage repair (though through Cyclin K, not T1)

- NOTE that TAT, and HIV-1 protein, hijacks P-TEFb to promote HIV transcription

Biologic Activity—functions in Cancer

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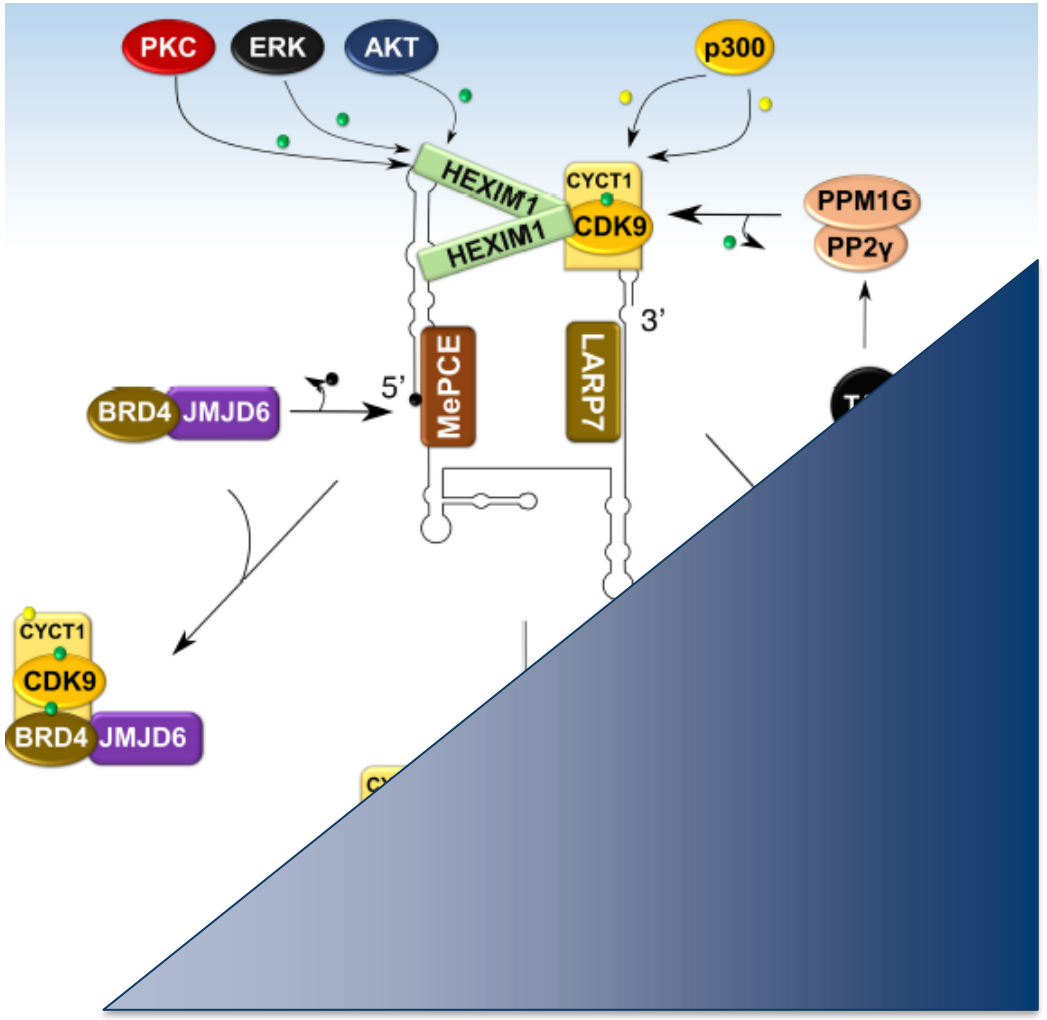
- In Lymphomas and CLL, P-TEFb controls *mcl-1* and *c-myc* transcription
    - MCL-1 is a anti-apoptotic protein and gets over expressed in venetoclax acquired and primary resistance.
    - MYC recruits P-TEFb to the promoter thus many genes are regulated by MYC through P-TEFb
- Suspected that it is important in
    - CLL through MCL-1
    - DLBCL through MYC
    - Aggressive T- and NK-cell lymphomas through MYC and MCL-1

Regulation of CDK9

- CDK9 is sequestered by 7SK snRNP complex
    - Binding partners are phosphorylated by PKC, AKT and ERK which releases P-TEFb
- CDK9 is regulated by phosphorylation
    - Serine and Threonine at various spots, which typically promote activity
- Acetylation helps release CDK9 from 7SK
- Ubiquitination and proteosome mediated degradation removes the protein



Anshabo AT et al, Frontiers in Oncology, vol 11, May 2021

Inhibiting CDK9

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- Several inhibitors have been available but are not as selective for CDK9 (inhibit other CDKs)
    - Flavopiridol (Alvocidib)
    - Dinaciclib
    - Therapeutic window has been too low and efficacy was limited.
- Newer generation inhibitors are more selective to CDK9 and are showing promise
    - VIP152
    - AZD4573
    - PRT2527

VIP152 (Enitociclib)

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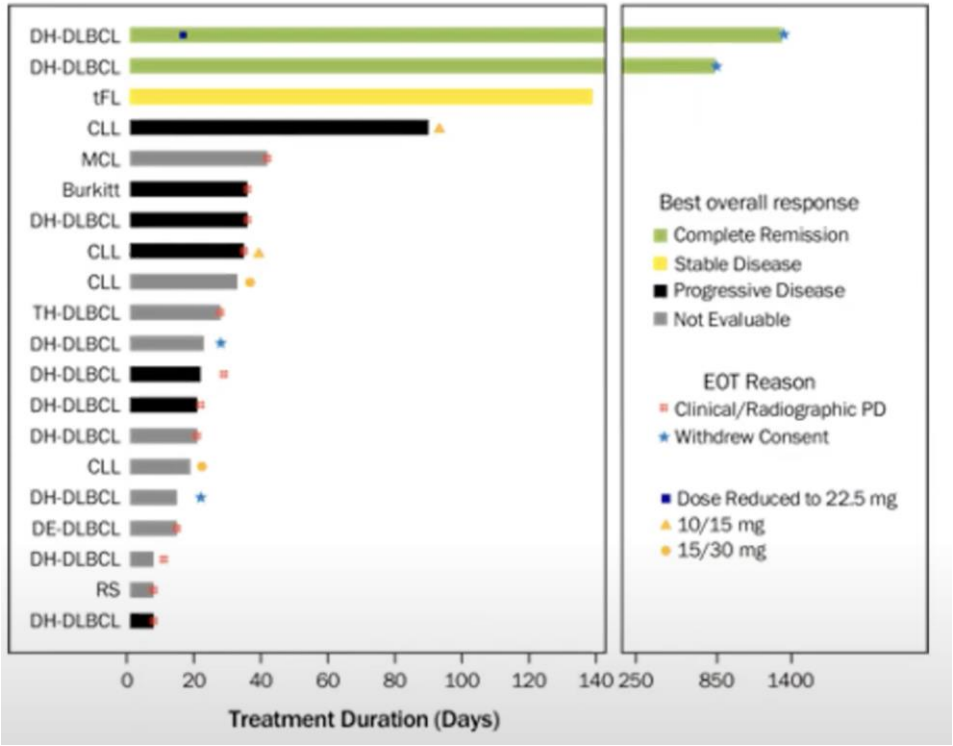
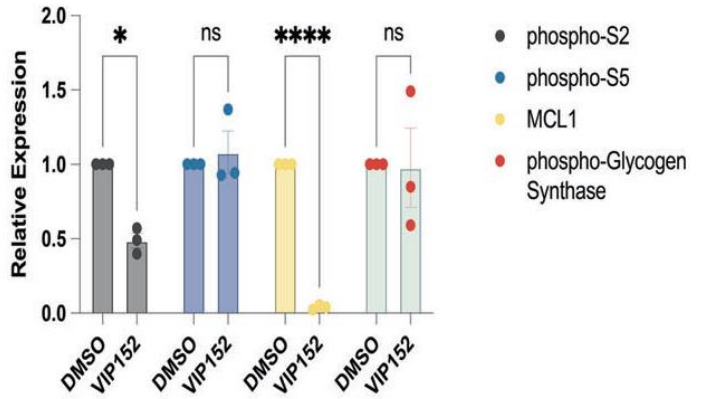
- Weekly dosing
- Phase I study in CLL/NHL
- Good toxicity, Neutropenia and low grade GI



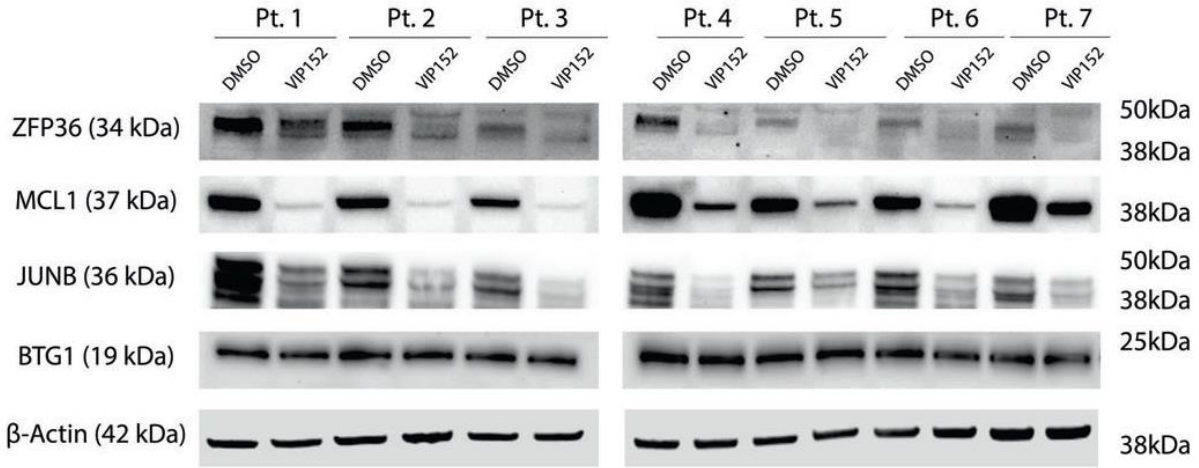
Shadman, M et al, ASH 2022

B)

Cell line



CLL Patient samples



Sher S, et al, Leukemia 2023

AZD4573

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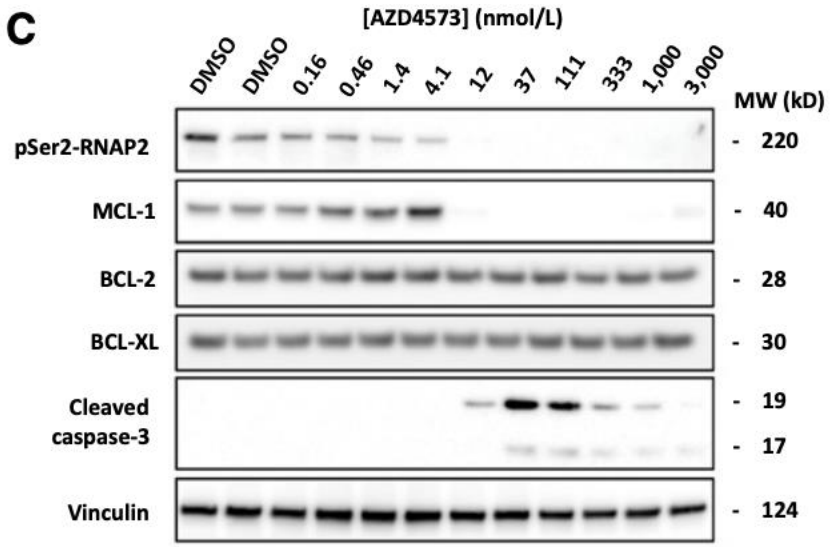
- Weekly dosing in trials moving forward
- Hematologic malignancies
    - 22 Pts with lymphoma/myeloma
    - 22 pts with leukemia (incl CLL)
- 12mg for lymphoma/myeloma and 9mg in leukemia
    - 18mg not tolerated and 12 mg caused TLS for leukemia

Table 1. Most common treatment-related adverse events (≥20% incidence at any CTCAE grade)

	Total (N=44)	
Preferred term, n (%)	**All Grades**	**Grades 3-5**
Diarrhea	22 (50.0)	4 (9.1)
Nausea	21 (47.7)	0
Tumor lysis syndrome	18 (40.9)	18 (40.9)
Neutropenia	14 (43.2)	13 (29.5)
Vomiting	13 (29.5)	2 (4.5)
Alanine aminotransferase increased	12 (27.3)	6 (13.6)
Blood bilirubin increased	12 (27.3)	4 (9.1)
Aspartate aminotransferase increased	10 (22.7)	8 (18.2)
Hypokalemia	9 (20.5)	0
Pyrexia	9 (20.5)	2 (4.5)

Brummendorf TH et al, ASH 2022

Cell line



Ongoing clinical study combining with Acalabrutinib in DLBCL with promising early results

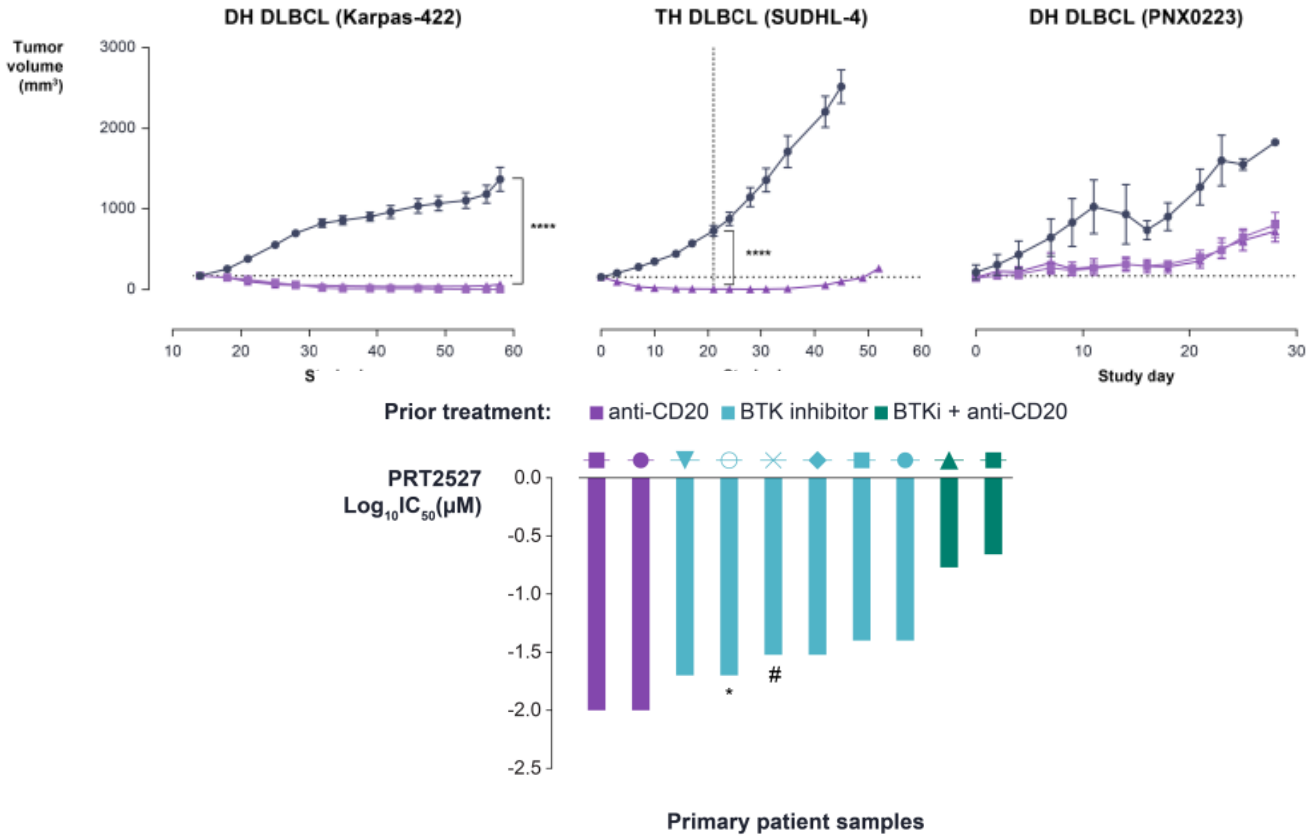
Cidado J et al CCR 2020

PRT2527

- Highly selective for CDK9

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



- IV Weekly Dosing

Phase I dose escalation in solid tumors showed 18mg/m2 IV weekly a promising dose

Moving forward in heme malignancies and in combination with BTKi

Phase I study on-going with various cell types

Henry et al AACR 2023

Thank you