ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
SCIENZE MEDICHE E CHIRURGICHE

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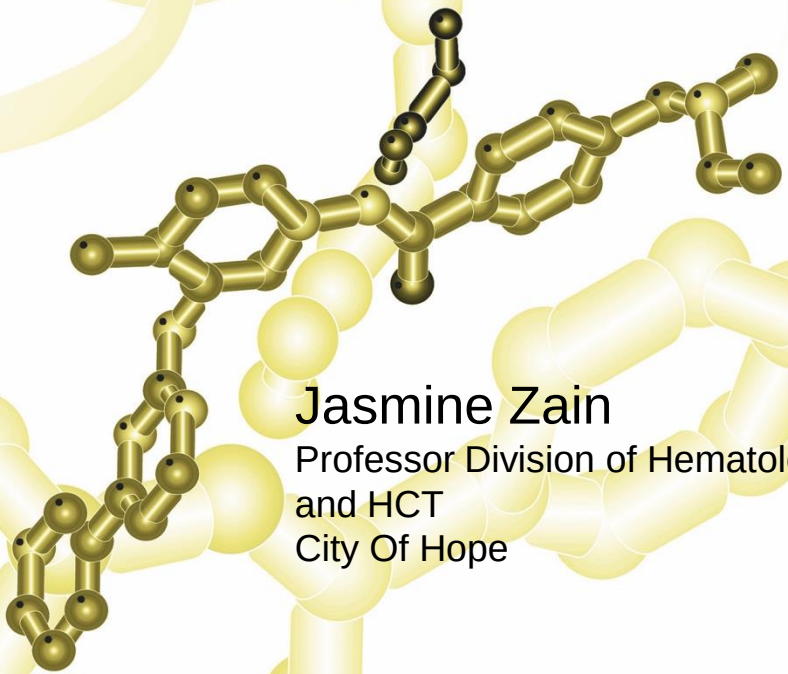

New Drugs in Hematology

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President: Pier Luigi Zinzani
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Bologna,
Royal Hotel Carlton
January 15-17, 2024

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

Disclosures of Jasmine Zain

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Seattle Genetics	Yes						
Dreon - Bio	Yes					Yes	
Myeloid	Yes		Yes				
Astex	Yes						
Secura Bio	Yes		Yes				
Kiyowa Kirin					Yes		
CRSPR	Yes						

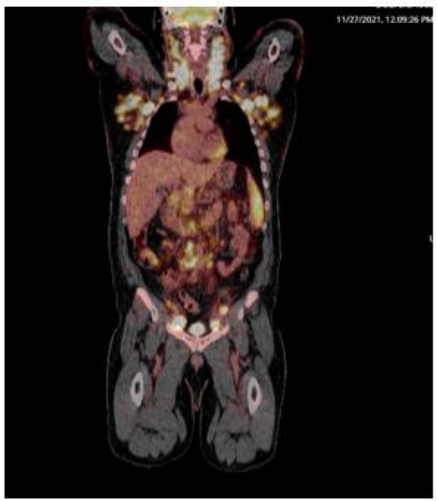
CDK 9 inhibitors

Novel therapeutic agents with a broad range of activity in multiple malignancies

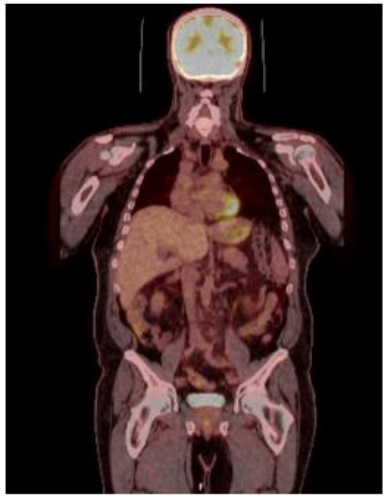
Focus on lymphoma –T cell lymphoma, B cell

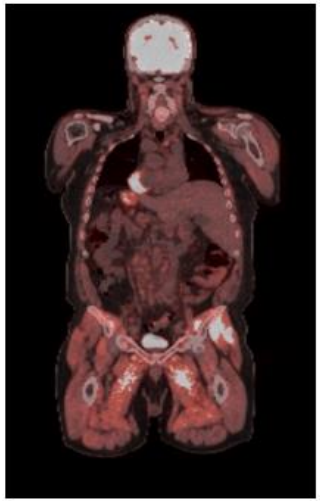
Future directions

56 year- dxed with AITL in 2021- BV + CHP x 6
High dose therapy and ASCT 4/4/22
Relapsed October 2022
Started AZD 4573 on 12/30/22
Currently on going – side effects, transaminitis during C2, fatigue, muscle pain



October 2022


March 2023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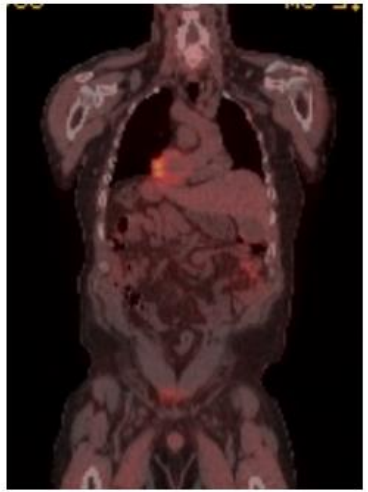
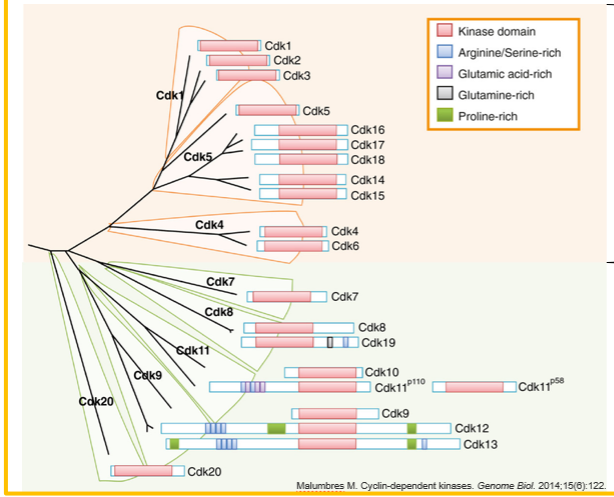
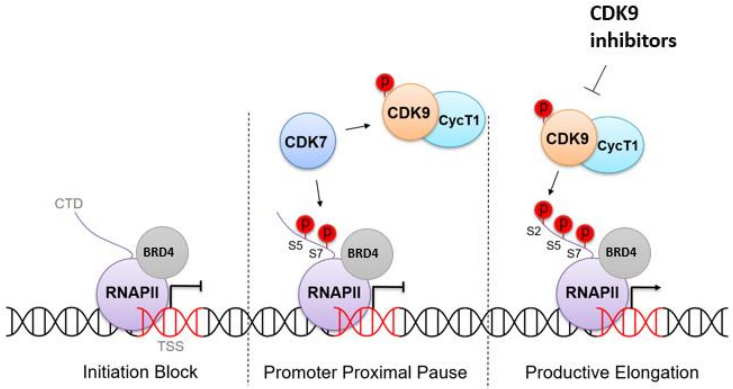

October 2023

Cyclin-dependent kinases

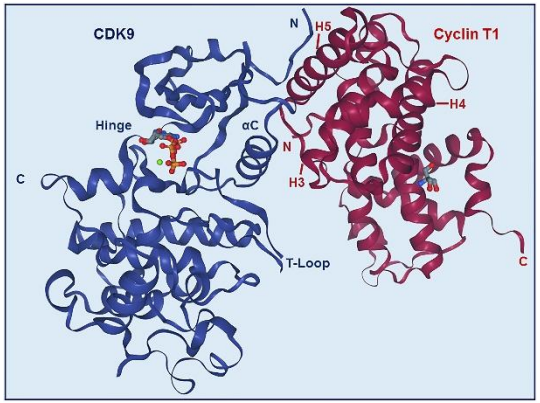


2 broad categories of CDK

Transcriptional CDKs: CDK7 and CDK9



Transcriptional regulators – release RNAPII from pause to release at the promotor – proximal region



Structure of CDK9 and cyclin T1-

Regulation by acetylation, ubiquitination

`Control of transcriptional elongation and termination

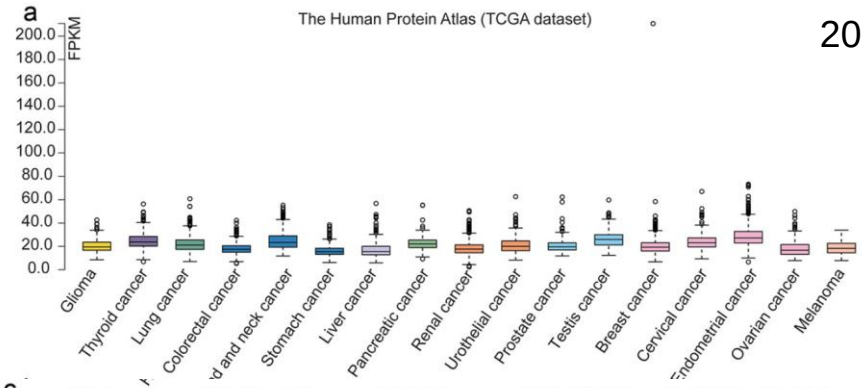
`Cell cycle progression

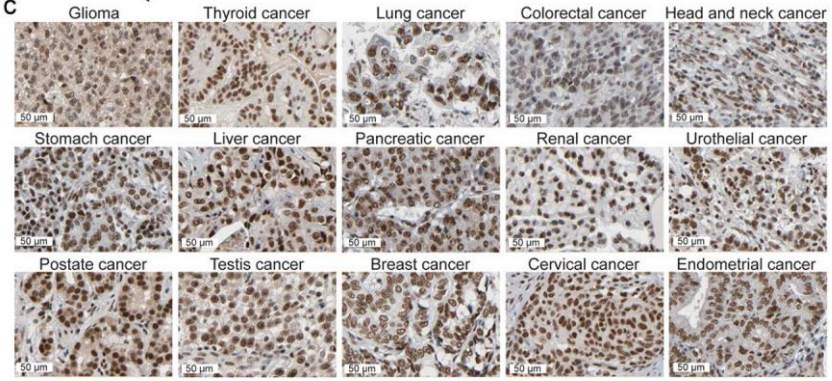
` Cellular Differentiation

`DNA repair

`Epigenetic modification (silencing)

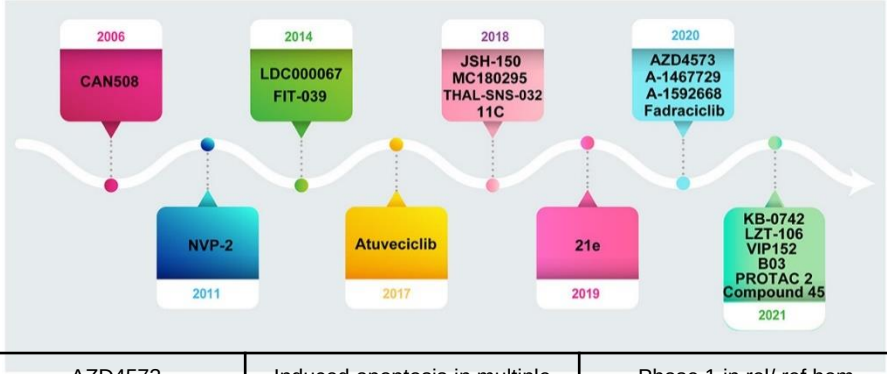
Anshabo et al :Front. Oncology 2021



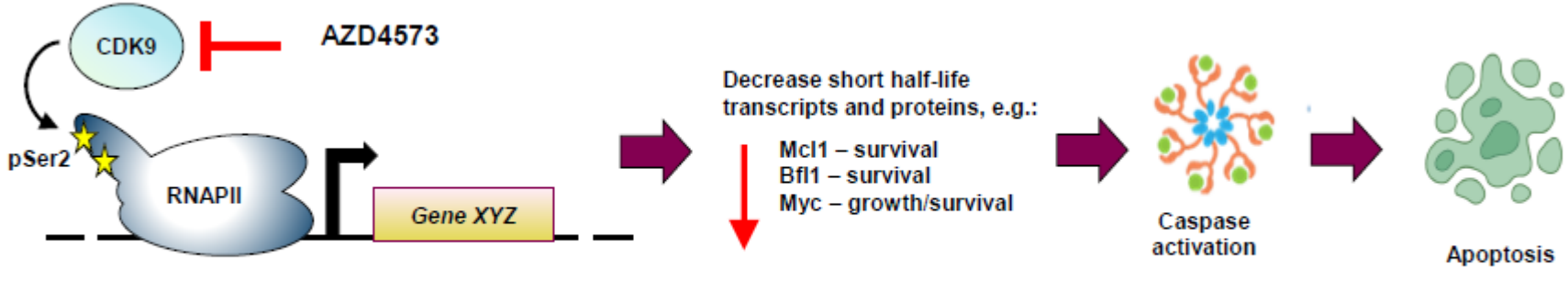


CDK9 expression in various tumors

20 selective CDK9 inhibitors and degraders in development



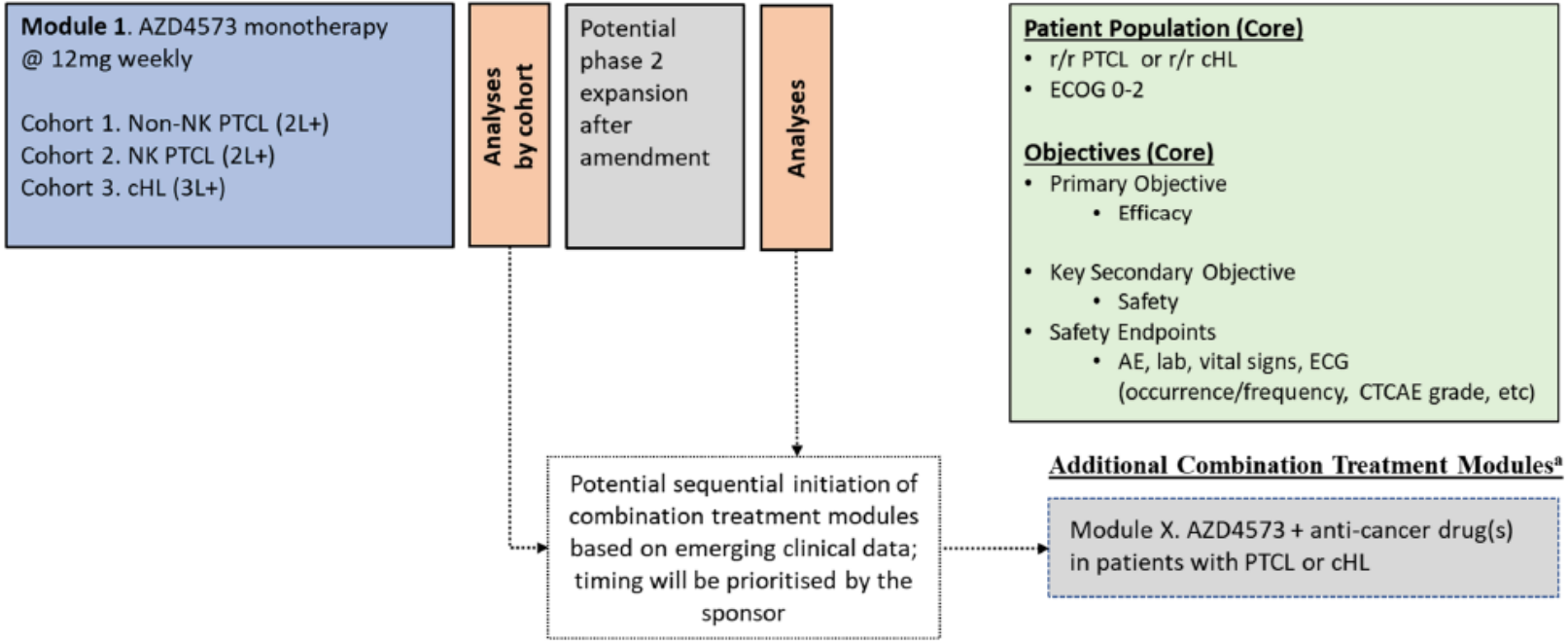
AZD4573	Induced apoptosis in multiple cell lines	Phase 1 in rel/ ref hem malignancies Phase II alone or in combination in PTCL and HL Combinaiton studies
CYC065 (Fadraciclib)	Reduces cell viability and induces apoptosis in multiple cell lines	Phase I/II clinical trial in leukemia Phase I/II in advances solid tumors and lymphomas
Voruciclib	Decreases MIC ,MCL-1	Phase I in combination with Venetoclax and prednisone in RR lymphoid malignancies
VIP-152		Orphan drug designation for DH lymphomas

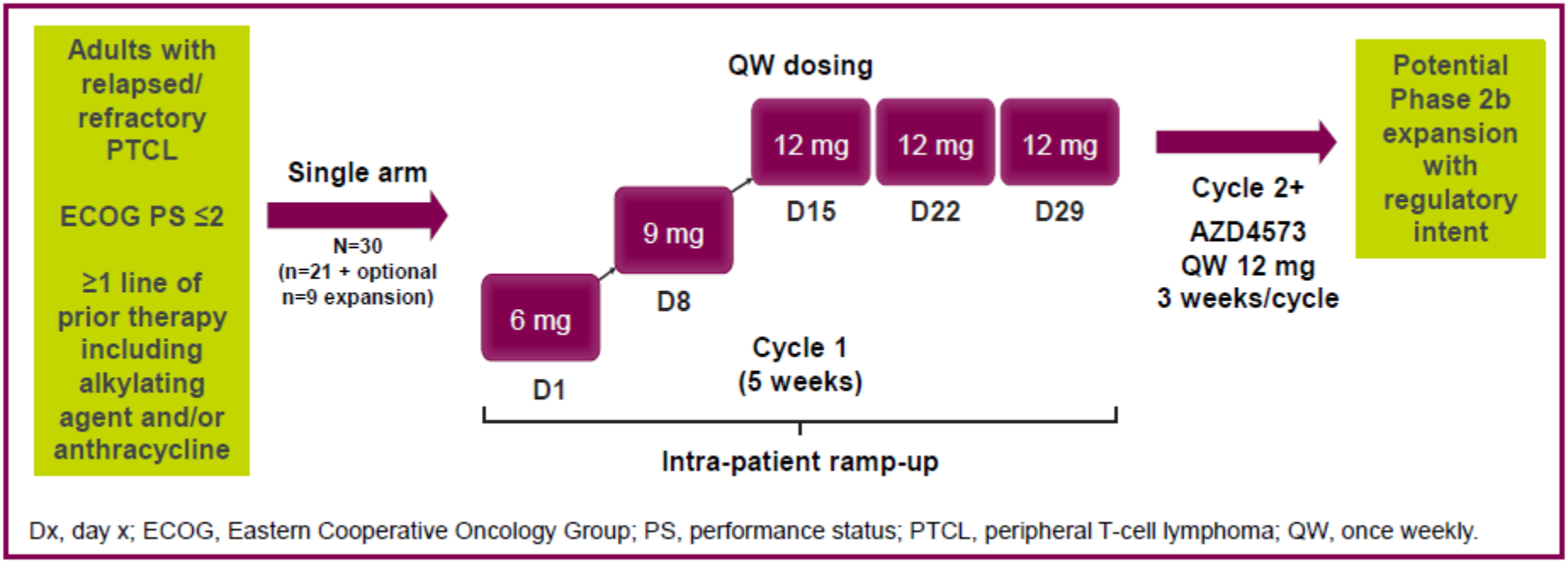


CDK9, cyclin dependent kinase 9; pSer2, phospho-serine 2; RNAPII, RNA polymerase II

- -AZD4573 – Selective and potent CDK 9 inhibitor
- - Rapid depletion of MCL-1, BFL-1, Myc leading to apoptosis
- - High MCL-1 and BFL-1 levels observed in primary PTCL cell models-
- - AZD4573 reduced disease burden and increased survival in PDX models of PTCL
- -Phase I study – 12mg IV Q week recommended dose
- -Manageable safety profile – diarrhea, fever , nausea, LFT elevation

Figure 1 **AZD4573 Modular Phase II CSP in r/r PTCL and r/r cHL**





Dx, day x; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PTCL, peripheral T-cell lymphoma; QW, once weekly.

T- cell lymphoma cohort- Primary end point - ORR

Table 1. Patient and disease characteristics

	AZD4573 monotherapy 12 mg QW (N=23)
Median age (range), years	62.0 (45–83)
Male / female, n (%)	15 (65.2) / 8 (34.8)
Race, Black or African American / Asian / White, n (%)	1 (4.3) / 3 (13.0) / 14 (60.9)
Median number of prior lines of treatment, n (range)	3.0 (1–9)
Previous treatments, n (%)	
Autologous haematopoietic stem cell transplantation	5 (21.7)
Allogeneic haematopoietic stem cell transplantation	1 (4.3)
T-cell lymphoma subtype, n (%)	
AITL	7 (30.4)
TFH, non-AITL	3 (13.0)
PTCL NOS	7 (30.4)
ALCL, ALK-negative	5 (13.0)
MEITL	1 (4.3)

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; MEITL, monomorphic epitheliotropic intestinal T-cell lymphoma; NOS, not otherwise specified; PTCL, peripheral T-cell lymphoma; QW, once weekly; TFH, T-follicular helper

Interim analysis

	ORR	CRR
>1 target dose	3/17 (17.6%0	3/17 (17.6%)
> 2 cycles	3/9 (33%)	3/9 (33 %)

Figure 3. Response assessment (full analysis set)

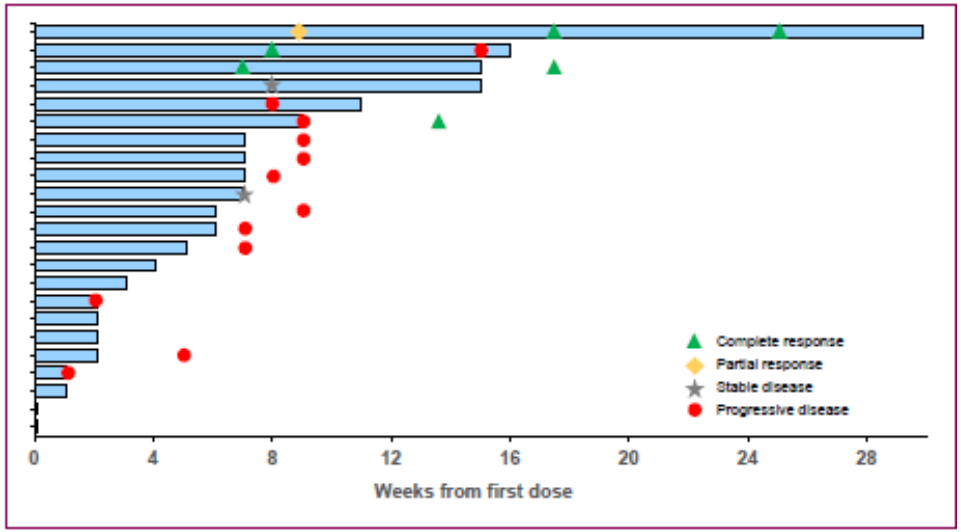


Table 4. Grade ≥3 TEAEs occurring in ≥5% of patients

	AZD4573 monotherapy 12 mg QW (N=23)
Any Grade ≥3 TEAE	19 (82.6)
Neutropenia	12 (52.2)
AST increased	6 (26.1)
White blood cell count decreased	5 (21.7)
Neutrophil count decreased	3 (13.0)
ALT increased	3 (13.0)
Septic shock	2 (8.7)
Anaemia	2 (8.7)
Drug induced liver injury	2 (8.7)
Thrombocytopenia	2 (8.7)
Acute kidney injury	2 (8.7)
Gamma-glutamyltransferase increase	2 (8.7)
Lymphocyte count decreased	2 (8.7)

Presented at EHA 2023 and ICML 2023-

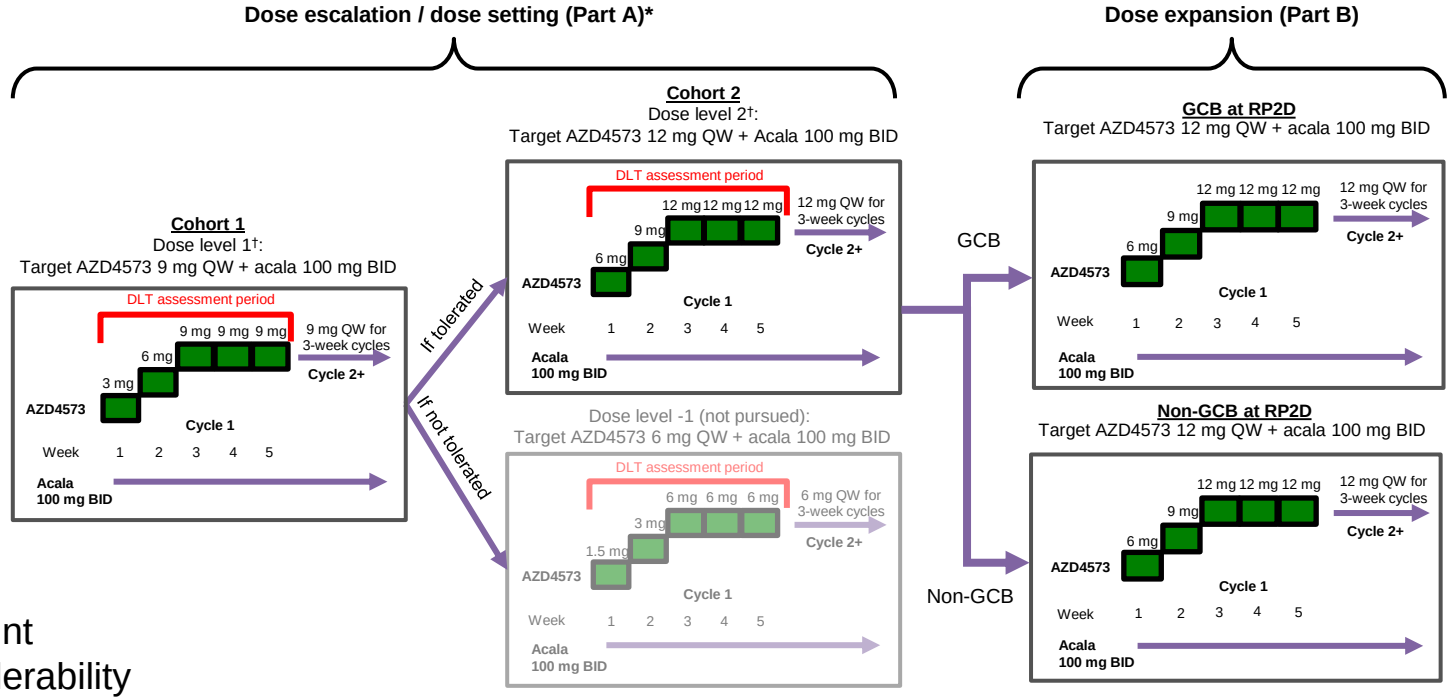
A multicenter, open-label, Phase 1b/2a study of AZD4573 + acalabrutinib in patients with relapsed/refractory DLBCL

Adults with relapsed/refractory DLBCL

ECOG PS ≤2

Failure of ≥2 prior treatments

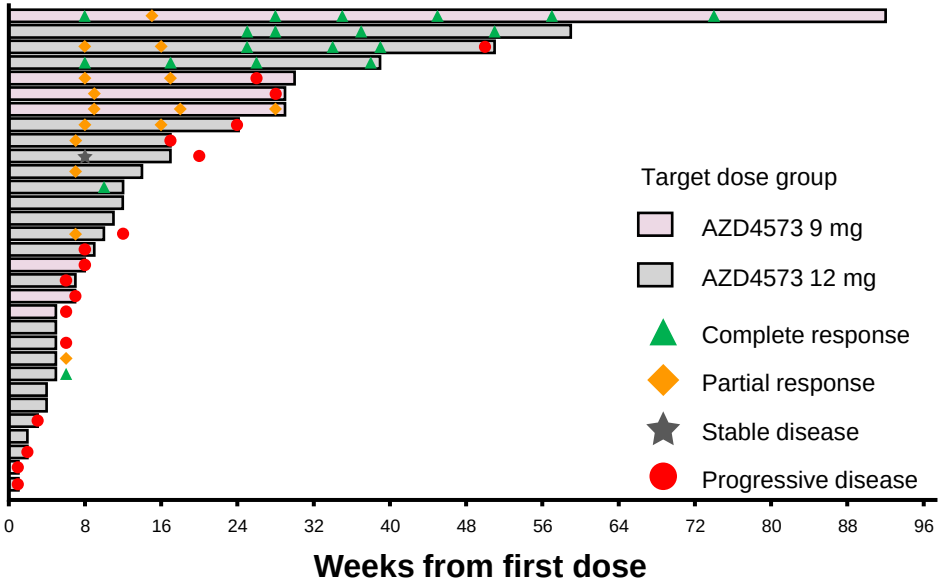
No prior antilymphoma therapy within 14 days of first dose of study treatment, and no prior BTK inhibitors



Primary end point
1-Safety and tolerability
2- ORR

- Overall, median duration of response (DoR) was 4.4, with 43.6% of patients remaining in response after 9 months.
- The median DoR in patients with complete response (CR) or partial response (PR) was 9.9 months and 3.9 months, respectively.

	AZD4573 9 mg QW + acalabrutinib 100 mg BID (n=8)	AZD4573 12 mg QW + acalabrutinib 100 mg BID (n=23)	Total (N=29)
ORR (CR + PR), % (95% CI)	50.0 (15.7–84.3)	47.6 (25.7–70.2)	48.3 (29.4–67.5)
CR, n (%)	1 (12.5)	5 (23.8)	6 (20.7)
Median DoR, months (95% CI)	4.4 (4.1–NR)	3.7 (1.1–NR)	4.4 (2.3–NR)
Median PFS, months (95% CI)	3.9 (0.3–NR)	3.6 (1.4–5.5)	3.6 (1.5–5.8)
Median OS, months (95% CI)	NR	9.1 (3.7–NR)	NR



Danilov A et al, ICML 2023

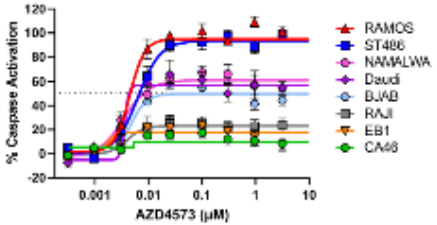
AE, n (%)	AZD4573 9 mg QW + acalabrutinib 100 mg BID (n=8)		AZD4573 12 mg QW + acalabrutinib 100 mg BID (n=23)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	8 (100.0)	8 (100.0)	18 (78.3)	17 (73.9)
Nausea	3 (37.5)	0	11 (47.8)	0
ALT increased	3 (37.5)	2 (25.0)	10 (43.5)	6 (26.1)
AST increased	2 (25.0)	2 (25.0)	11 (47.8)	6 (26.1)
Thrombocytopenia	4 (50.0)	2 (25.0)	9 (39.1)	5 (21.7)
Anemia	2 (25.0)	0	8 (34.8)	6 (26.1)
Diarrhea	2 (25.0)	0	8 (34.8)	1 (4.3)
Fatigue	2 (25.0)	0	6 (26.1)	0
Vomiting	0	0	7 (30.4)	1 (4.3)

*Grade 4 AEs were reported in 14 cases possibly related to AZD4573 and 9 cases possibly related to acalabrutinib. Grade 5 AEs were reported in 2 patients; neither one was related to treatment.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; QW, once weekly

- Neutropenia was manageable with granulocyte colony-stimulating factor; 7/31 patients (22.6%) had Grade ≥3 infections.
- Alanine aminotransferase, aspartate aminotransferase and bilirubin elevations were mainly due to down-modulation of hepatic transporter proteins and reduced enzyme clearance rather than direct hepatocellular injury; all were short-lived with spontaneous resolution.

Burkitt's Lymphoma (BL) is characterized by over expression of MYC and MCL1.

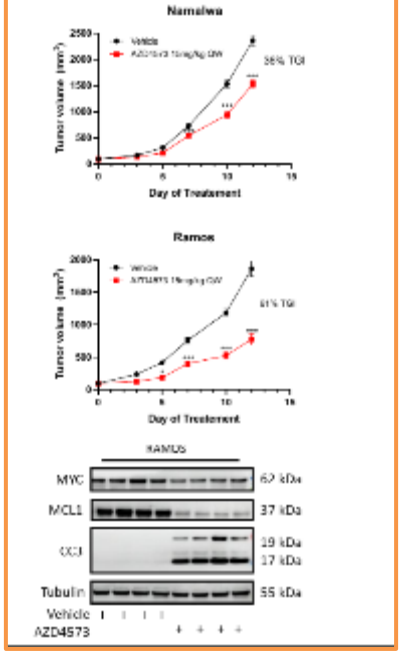
AZD4573 shows evidence of *in vitro* monotherapy activity in BL cell lines



Cell line	Caspase EC50	Max Caspase Activation (%)
RAMOS	80nM	101.1
ST486	110nM	93.45
NAMALWA	120nM	61.01
Daudi	100nM	56.79
BJAB	140nM	49.58
RAJI	>10μM	23.24
EB1	>10μM	17.71
CA46	>10μM	12.72

Cell line treated for 6hrs

AZD4573 decreases MCL1 and MYC leading to tumor growth inhibition in BL xenograft models

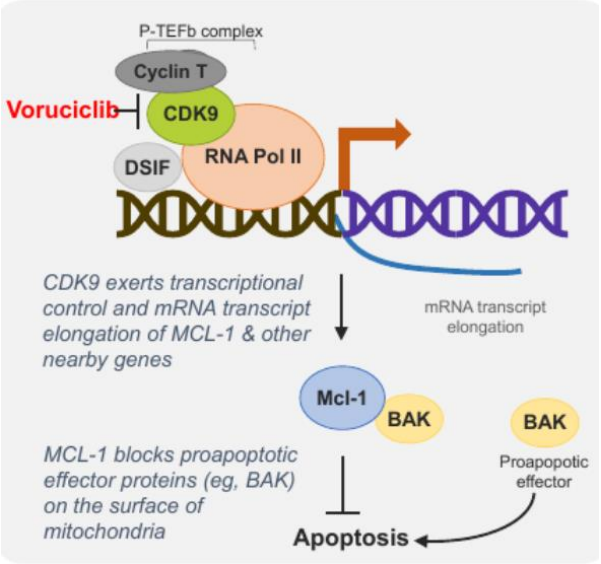


- CDK9 inhibition induced cell death in BL cell lines
- Treatment with AZD4573 decreased pSer2-RNAPII and depleted MCL1 and MYC and induced apoptosis by cleavage of Caspase 3
- AZD4573 resistant cell lines (< 30% CC3) had higher levels of BCL2 and BCLxL
- AZD4573 treatment led to decreased tumor growth in BL xenograft models

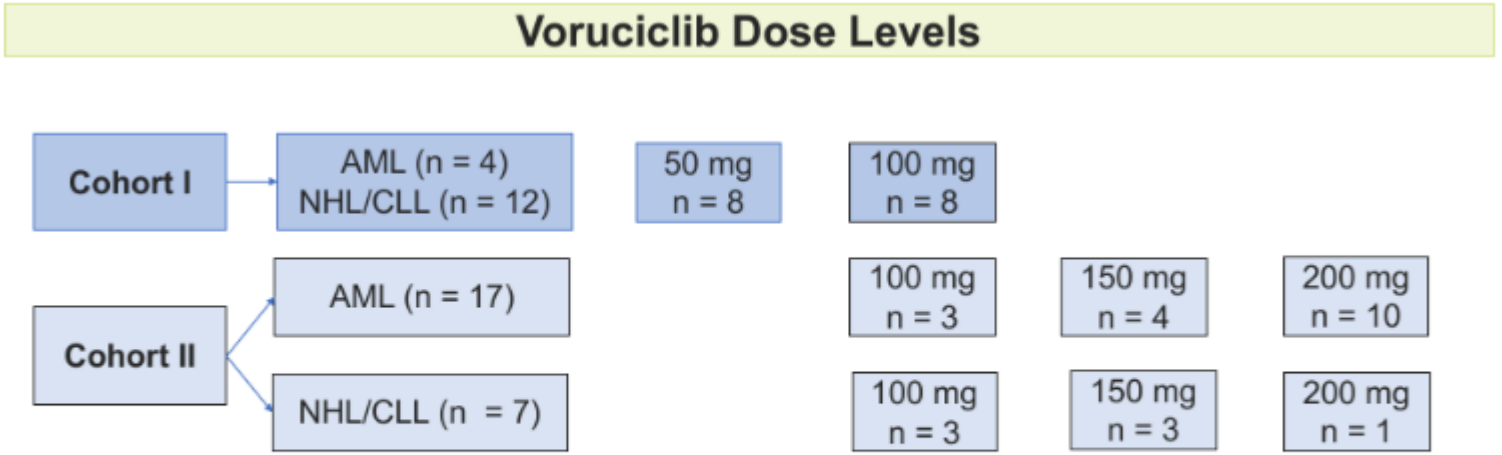
Potter et al; ASH 2023

Phase I study of Voruciclib in RR NHL or AML

- Higher affinity and longer resistance time
- Indirectly suppresses MCL-1
- Combination of Voruciclib and Venetoclax show synergy and improve survival in mouse models of AML and DLBCL
- MTD 350 mg daily dosing or 600 mg days 1-14 on a 21day cycle



Phase 1 study of Voruciclib in RR AML of B cell NHL



- Dose escalation in Cohort II stopped at 200 mg to focus on evaluation of venetoclax combination
- Median duration of exposure = 5 weeks (range 1-22)

Efficacy

AML (n = 21)

- 1 patient (5%) at 100 mg achieved a morphologic leukemia-free state
  - 81 yo female with adverse risk AML, TP53 and NPM1 mutation, enrolled in the study after failure of 4 prior lines of therapy
- 9 patients had disease stabilization, which lasted ≥3 months in 2 and qualified as stable disease by ELN 2017

B-cell malignancies (n = 19)

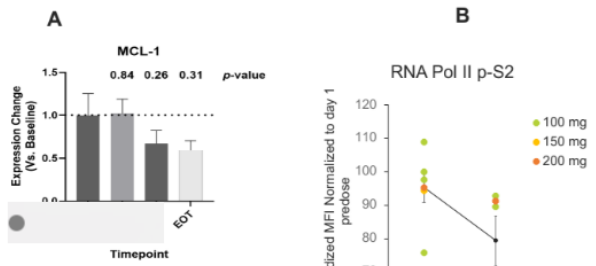
- No objective responses observed
- 4 patients had stable disease (SD) with reduction in SPD (Table)

Change in SPD in Patients with B-cell Malignancies with SD

Diagnosis	No. of Prior Therapies	Therapy Duration (weeks)	Baseline SPD (cm^2)	Change SPD (%)
FL	2	18	49.8	-49%
DLBCL	3	16	14.5	-28%
CLL	5	22	74.5	-7%
MZL	4	22	28.4	-4%

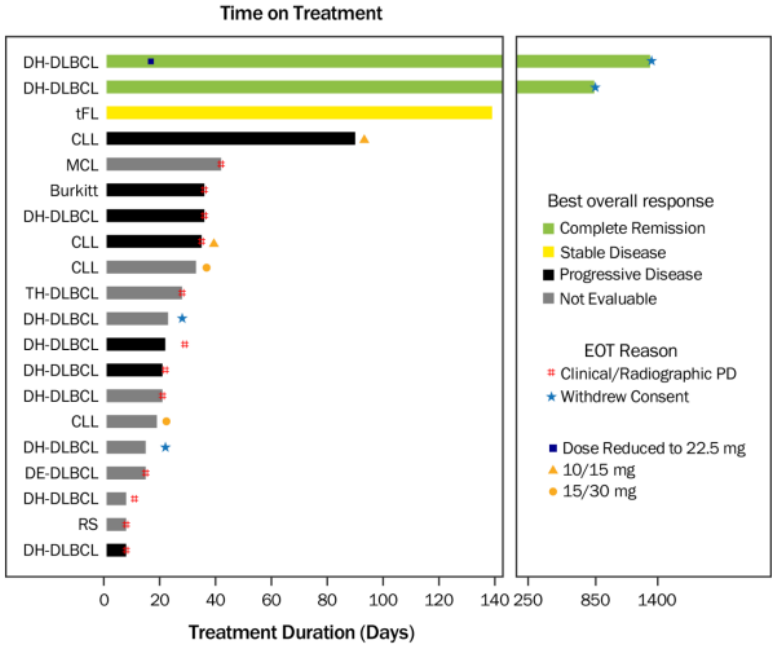
Davis et al :ASH 2023

On target effect



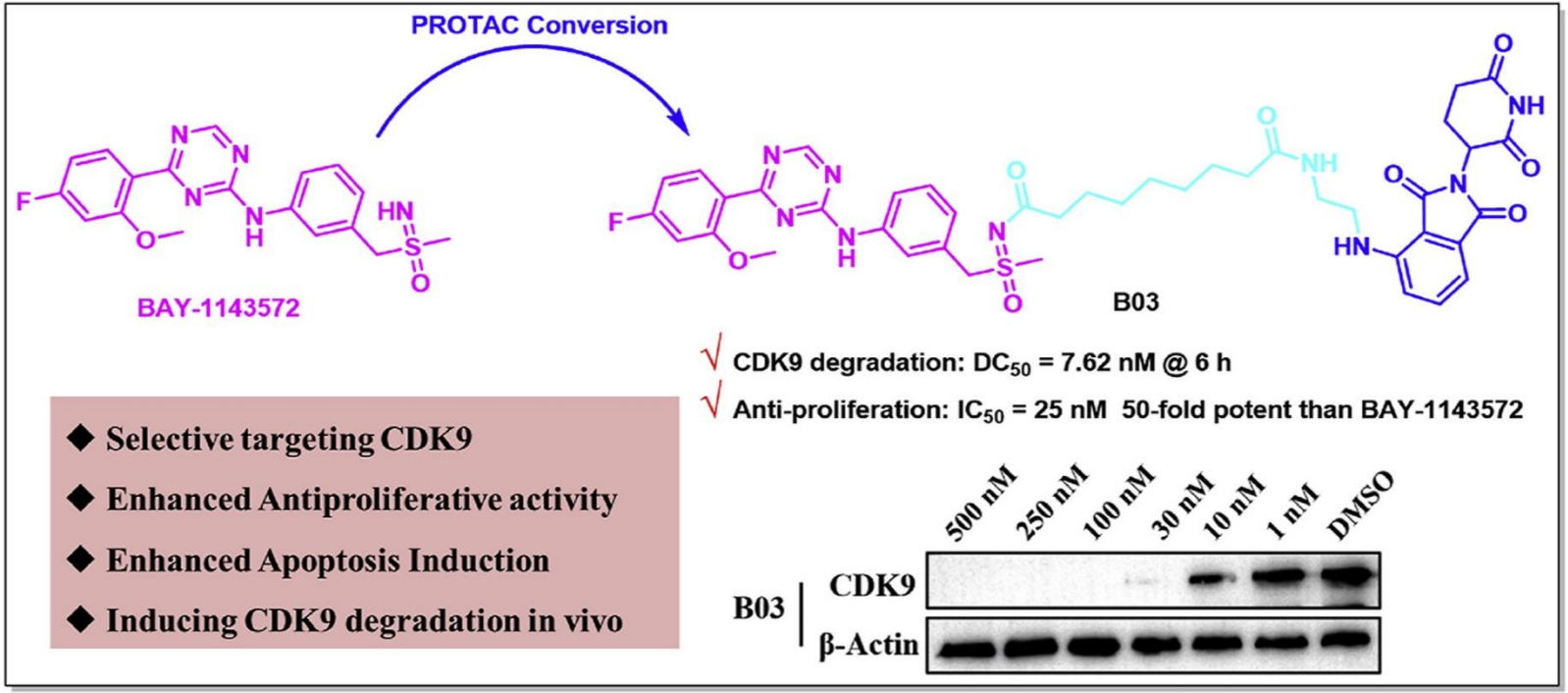
- No DLTs reported so far
- No evidence of overlapping toxicity
- Enrollment continues on the combination arm

- Enitociclib (VIP152)
- Being evaluated in aggressive B cell lymphomas
- Promising activity in DH- DLBCL and CLL (orphan drug designation for DH-DLBCL)
- Mild GIT toxicity and hematologic toxicity
- Preclinical data shows that it can over come variety of therapeutic resistance in MCL PDX models



Shadman et al – 2022
Lee et al – ASH 2023

CDK9- DEGRADERS



CONCLUSIONS AND FUTURE DIRECTIONS

CDK-9 inhibitors are promising as anticancer a gents

Single agent activity is limited but lend to combinations both to enhance efficacy and overcome and prevent resistance- (Acalibrutinib, venetoclax)

For T cell lymphomas, there is promising activity but need further preclinical data to design rational combinaions. (consider antiapoptotic agents, bromodomain inhibtors, PI3kinase inhibitors, epigenetic agents

CDK 9 degraders need further evaluation in hem malignancies due to increased specificity which may increase potency without increasing toxicity

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