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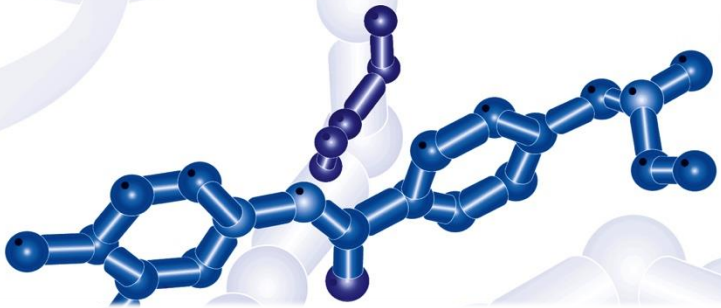

Mantle Cell Lymphoma Treatment with Pirtobrutinib and Combinations

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New Drugs in Hematology

President: Pier Luigi Zinzani

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Disclosures of Dr. Michael Wang

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BTK plays a central role in B-cell receptor signaling, crucial for malignant B-cell proliferation

Covalent BTKi	Covalent BTKi	Non-covalent BTKi	BTK degraders
Ibrutinib FDA: Withdrawn EMA: Approved	**Acalabrutinib** FDA: Approved EMA: Approved	**Pirtobrutinib** FDA: Approved EMA: Approved	**NX-2127** Phase I
	Zanubrutinib FDA: Approved EMA: Approved	**Nemtabrutinib** Phase II	**Bexobrutideg (NX-5948)** Phase I
			BGB-16673 Phase II

Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Previously Treated Mantle Cell Lymphoma: Updated Results from the Phase 1/2 BRUIN Study

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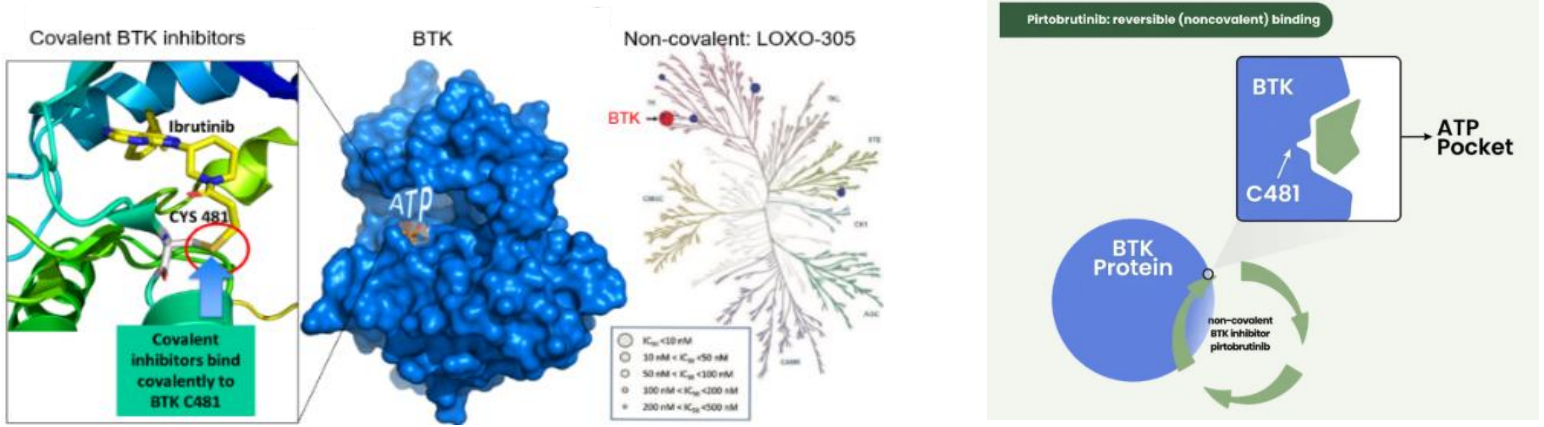
Non-covalent BTKi Pirtobrutinib (LOXO-305) vs. Covalent BTKi, Ibrutinib

A B C D



Pirtobrutinib binds to BTK in the ATP pocket and does not depend on Cys481.

Outcomes in MCL are Extremely Poor Following Covalent BTK Inhibitor Progression

- Covalent BTK inhibitor resistance in MCL and other lymphomas is incompletely understood[1-10]
- BTK C481-mutations are uncommon; bypass alterations & epigenetic changes implicated in some patients[7]
- *Overall survival* following covalent BTK inhibitor therapy is poor[3,4,11]

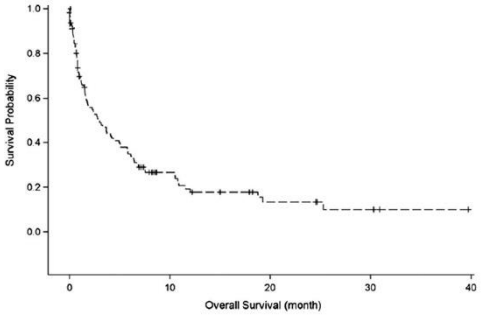


Fig 1[4]

Analysis of n = 114 global patients
Median OS = 2.9 months

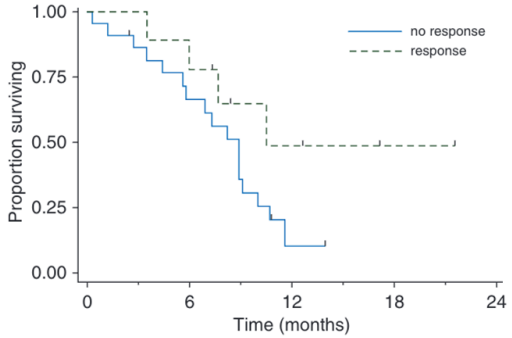


Fig 2[3]

Analysis of n = 31 US patients
Median OS = 8.4 months

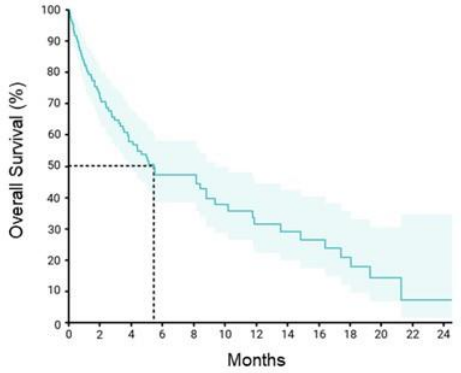


Fig 3[11]

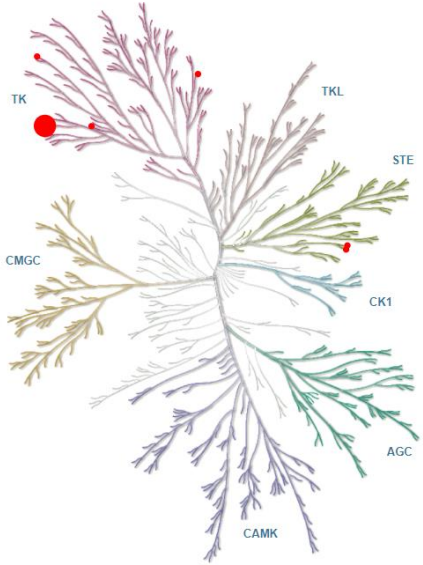
Analysis of n = 108 Japanese patients
Median OS = 5.46 months

[1]Hershkovitz-Rokah et al. *Br J. Haemtol.* 2018;181:306-19. [2]Wang et al. *N. Engl. J. Med.* 2013;369:507-16. [3]Cheah et al. *Ann. Oncol.* 2015;26:1175-79. [4]Martin et al. *Blood.* 2016;127:1559-63. [5]Dreyling et al. *Lancet.* 2016;387:770-8. [6]Epperla et al. *Hematol. Oncol.* 2017;35:528-35. [7]Ondrisova L and Mraz M, *Front. Oncol.* 2020;10. [8]O'Brien et al. *Clin Lymphoma Myeloma Leuk.* 2018;18:648-57. [9]Byrd et al. *Blood.* 2019;130(Suppl 1):4326. [10]Tam et al. *Blood.* 2020;136:2038-50. [11]Rai et al. *Clin Lymphoma Myeloma Leuk.* 2021; 21(Suppl 1):S407-S408.

Pirtobrutinib is a Highly Potent and Selective Non-Covalent (Reversible) BTK Inhibitor

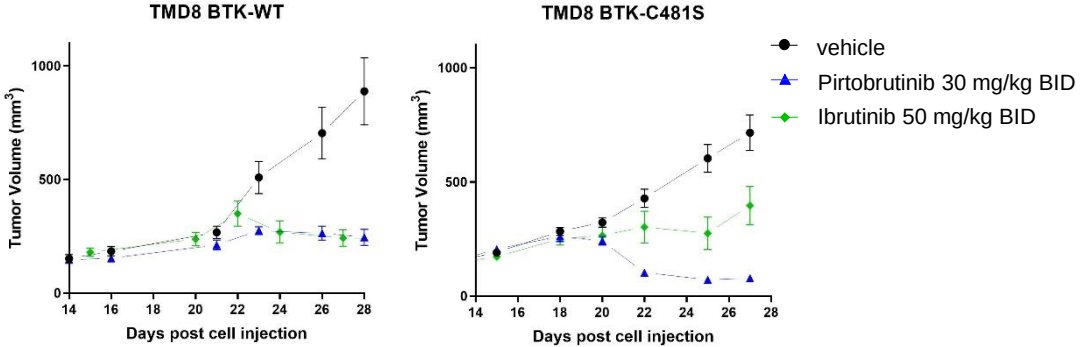
Kinome selectivity[1]

Highly selective for BTK



Xenograft models

In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[2]
- >300-fold selectivity for BTK vs 370 other kinases[2]
- Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[2]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[2]

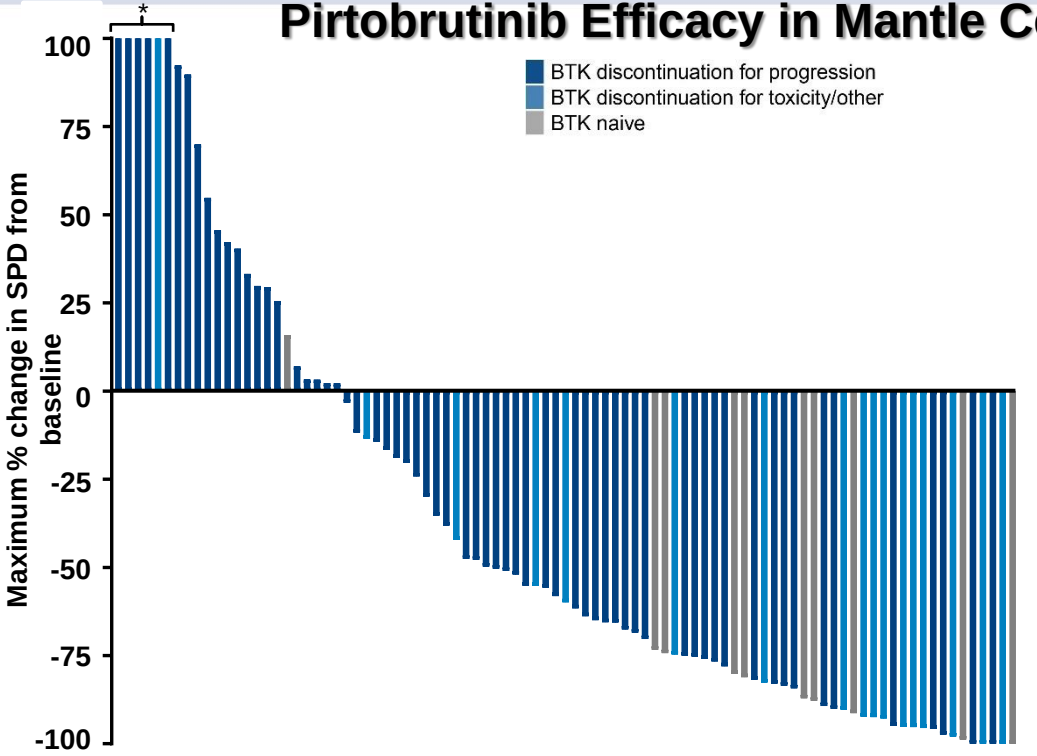
BID, twice-daily; BTK, Bruton tyrosine kinase. [1]Mato et al, *Lancet*, 2021:397:892-901. [2]Brandhuber BJ, et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

Patient Characteristics

Characteristics	MCL (n=134)
Median age (range), years	70 (46, 88)
Female / Male, n (%)	30 (22) / 104 (78)
Histology	
Classic	108 (81)
Pleomorphic/Blastoid	26 (19)
ECOG PS, n (%)	
0	82 (61)
1	50 (37)
2	2 (2)
Median number prior lines of systemic therapy (range)	3 (1, 9)
Prior therapy, n (%)	
BTK inhibitor	120 (90)
Anti-CD20 antibody	130 (97)
Chemotherapy	122 (91)
Stem cell transplant[b]	30 (22)
IMiD	23 (17)
BCL2 inhibitor	20 (15)
Proteasome inhibitor	17 (13)
CAR-T	7 (5)
PI3K inhibitor	5 (4)
Reason discontinued prior BTKi[a]	
Progressive disease	100 (83)
Toxicity/Other	20 (17)

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding. [a]Calculated as percent of patients who received prior BTK inhibitor. [b]3 patients had both auto and allo stem cell transplants.

Pirtobrutinib Efficacy in Mantle Cell Lymphoma



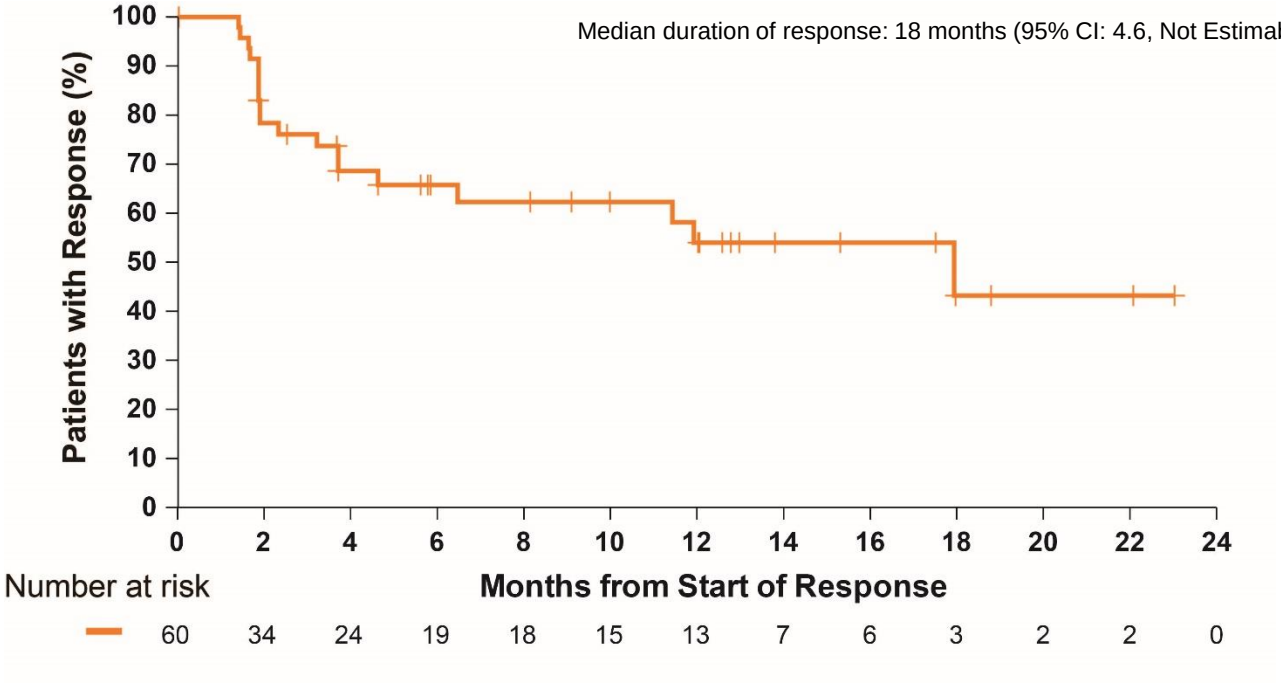
BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	**51% (41-61)**
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	**82% (48-98)**
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

Efficacy also seen in patients with prior:

- Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
- CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

Data cutoff date of 16 July 2021. Data for 20 MCL patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. *Indicates patients with >100% increase in SPD. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]ORR includes patients with a best response of CR and PR. Response status per Lugano 2014 criteria based on investigator assessment. Total % may be different than the sum of the individual components due to rounding.

Pirtobrutinib Duration of Response in Mantle Cell Lymphoma



- Median follow-up of 8.2 months (range, 1.0 - 27.9 months) for responding patients
- 60% (36 of 60) of responses are ongoing

Data cutoff date of 16 July 2021. Response status per Lugano 2014 criteria based on investigator assessment.

Pirtobrutinib Safety Profile

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

No DLTs reported and MTD not reached
96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily
1% (n=6) of patients permanently discontinued due to treatment-related AEs

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Represents 6 events (all grade 3), including 2 cases of post-operative bleeding, 1 case each of GI hemorrhage in the setting of sepsis, NSAID use, chronic peptic ulcer disease, and one case of subarachnoid hemorrhage in setting of traumatic bike accident. [h]Of 10 total afib/aflutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation, 2 in patients presenting with concurrent systemic infection, and 2 in patients with both.

Conclusions

- Pirtobrutinib demonstrates promising efficacy in MCL patients previously treated with BTK inhibitors, a population with extremely poor outcomes
- Favorable safety and tolerability are consistent with the design of pirtobrutinib as a highly selective and non-covalent (reversible) BTK inhibitor
- A randomized, global, phase 3 trial comparing pirtobrutinib with investigator's choice of covalent BTK inhibitors in BTK naïve relapsed MCL is ongoing (BRUIN MCL-321; NCT04662255)

Noncovalent BTKi: Pirtobrutinib combinations

Several trials assessing pirtobrutinib-based combinations in patients with MCL are currently recruiting

Study	Intervention	Primary endpoint
Phase II trial (NCT05529069)[1] R/R MCL (planned n = 30)	Pirtobrutinib + venetoclax	ORR and safety
Phase II GOlDiLOX trial (NCT05833763)[2] R/R MCL (planned n = 42)	Glofitamab + pirtobrutinib	CR rate
Phase II trial (NCT06263491)[3] Previously untreated low-/intermediate-risk MCL (planned n = 50)	Pirtobrutinib + rituximab	ORR at Cycle 3 and safety
Phase II GATE1 trial (NCT06522386)[4] Previously untreated MCL (planned n = 40)	Pirtobrutinib + rituximab and venetoclax	CR rate

BTKi, Bruton's tyrosine kinase inhibitor; CR, complete response; MCL, mantle cell lymphoma; ORR, overall response rate; R/R, relapsed/refractory.

1. ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT05529069. Accessed Jun 6, 2025; **2.** ClinicalTrials.gov https://clinicaltrials.gov/study/NCT05833763. Accessed Jun 6, 2025; **3.** ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06263491. Accessed Jun 6, 2025; **4.** ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT06522386. Accessed Jun 6, 2025.

The emergence of pirtobrutinib tolerant persister cells

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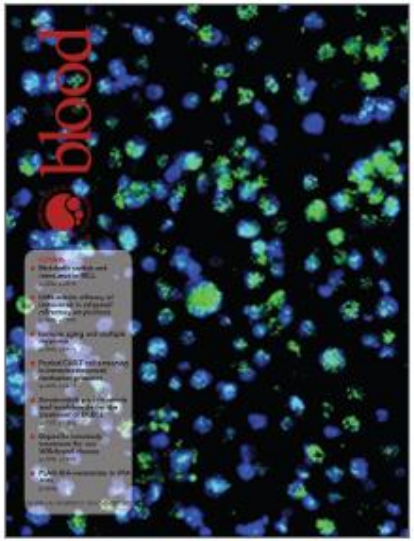
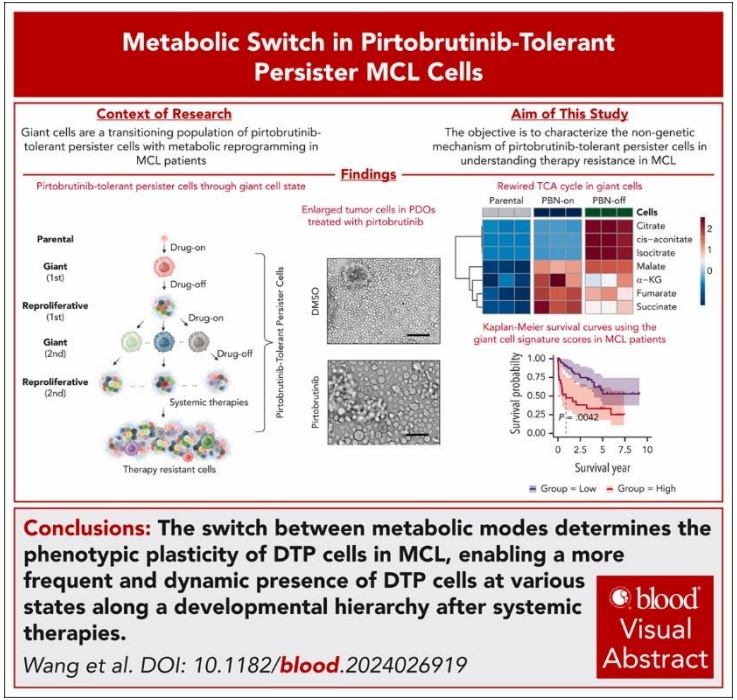




Dissecting Pirtobrutinib Resistance in Mantle Cell Lymphoma

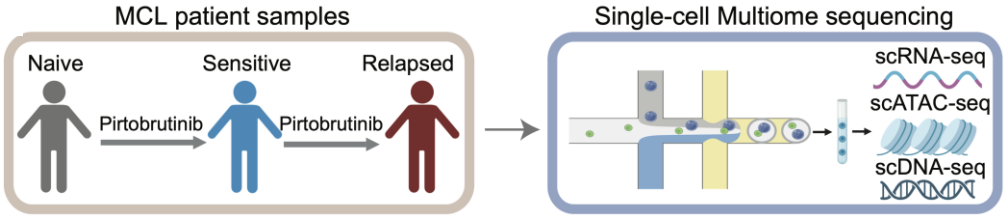
Integrated Single-Cell Multi-Omic Analysis of Longitudinal Patient Cohorts

Yan F, Liu Y, Wang M, et al.

American Journal of Hematology (2026)

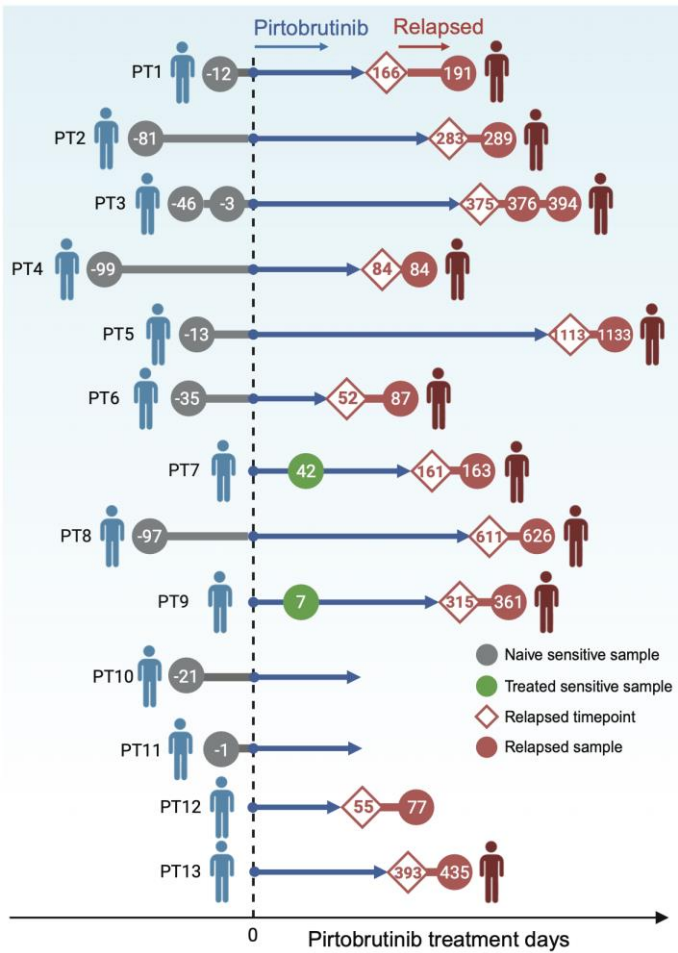
Single-Cell Resolution

The study analyzed **24 samples** from 13 MCL patients at **drug-sensitive** and **resistant** timepoints.

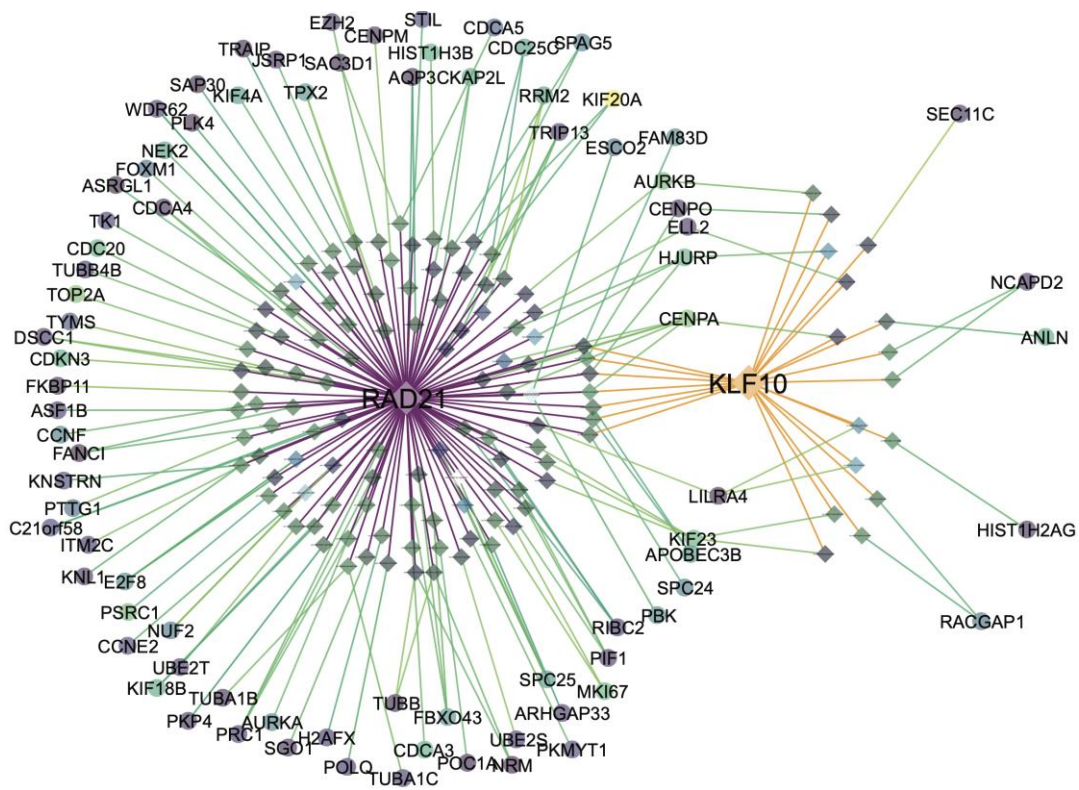


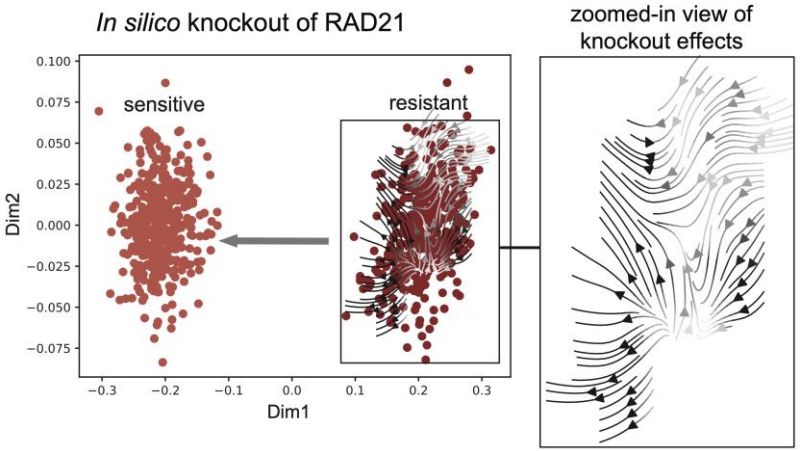
- **scRNA-seq:** Capturing 56,889 malignant B cells to map transcriptomic states and pathway activation.
- **scATAC-seq:** Assessing chromatin accessibility to reveal the underlying regulatory landscape.
- **scDNA-seq:** Reconstructing phylogenetic trees and identifying clonal chromosomal alterations (CNVs).

This integration allows for the correlation of **genetic changes** with upstream **epigenetic reprogramming** within the same tumor population.



A Master Regulatory Hub





Integration of scATAC-seq data identified **RAD21**, a core cohesin component, as a critical regulator of the resistant state.

- **Binding Landscape:** RAD21 binds to 987 resistance-specific DNA regions, directly regulating 816 genes.
- **Network Inference:** RAD21 coordinates programs associated with mitosis, chromosome segregation, and NF-κB signaling.
- **Targetability:** *In silico* perturbation models show that silencing RAD21 re-sensitizes cells to pirtobrutinib.

This suggests that cohesin complex dysregulation maintains the structural architecture required for pro-survival gene expression.

- **Single cell multi-omic approach:** In this study, we applied single-cell multi-omic profiling to longitudinal MCL patient samples to uncover dynamic changes associated with acquired PBN resistance.

- **Dual resistance routes:** Consistent with the emerging model of genetic and non-genetic resistance, we found that while some PBN-resistant tumors exhibited clear genomic alterations, others lacked detectable genetic changes.

- **A DTP-like population:** We also identified a population of stem-like malignant B cells that expanded during the resistant stage.

  These cells displayed metabolic reprogramming marked by impaired oxidative phosphorylation and increased EMT signatures, closely resembling the DTP phenotype described in our recently published study of PBN resistance.

Thank you!