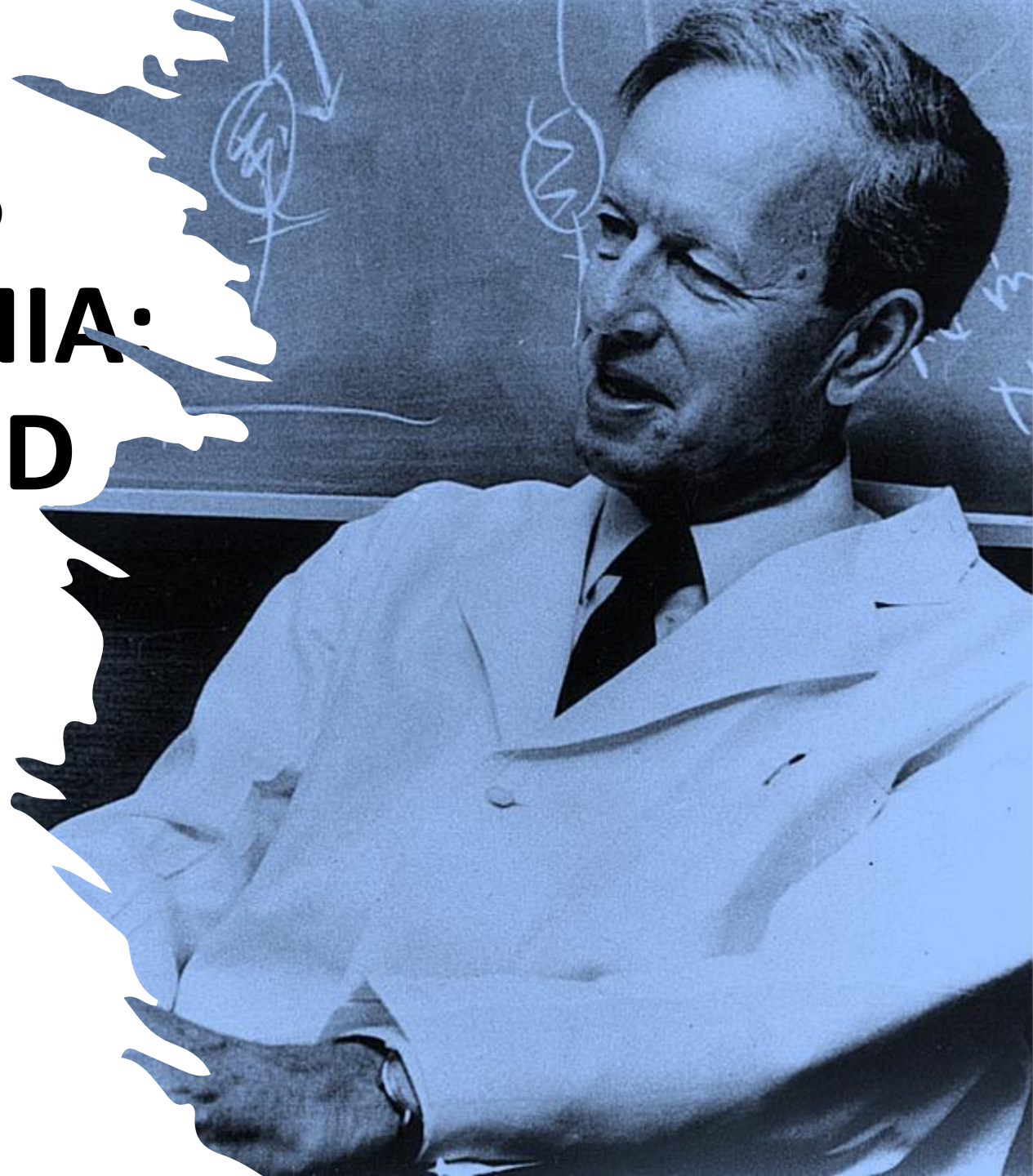
# WALDENSTROM'S MACROGLOBULINEMIA: TODAY AND BEYOND 2025



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# DISCLOSURES

| Abbvie/Pharmacyclics | Research Support |
|---|---|
| Beigene | Research Support, Consulting |
| Eli Lilly | Research Support |
| Johnson and Johnson | Research Support, Consulting |
| Ono Pharmaceuticals | Consulting |


# 12TH INTERNATIONAL WORKSHOP ON WM, PRAGUE 2024

# MYD88 DIRECTED PRO-SURVIVAL SIGNALING IN WM

The NEW ENGLAND JOURNAL of MEDICINE

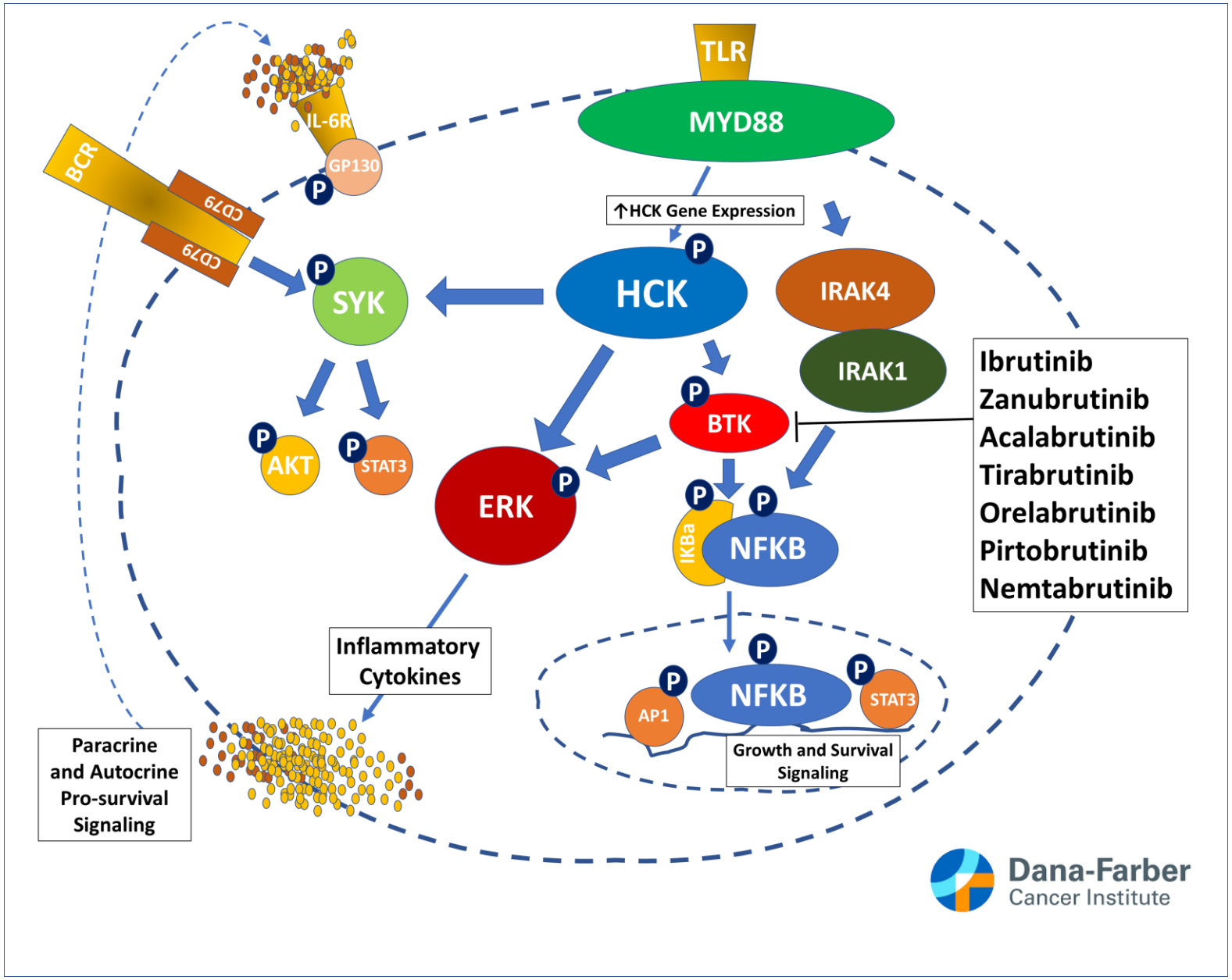
ORIGINAL ARTICLE

## MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifter, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.

**MYD88 mutations occur in 95-97% WM Patients**

Treon, et al. N Engl J Med. 2012;367(9):826-833.
Yang, et al. Blood. 2013;122(7):1222-1232.
Hodge, et al. Blood. 2014;123(7):1055-1058.
Yang, et al. Blood. 2016;127(25):3237-3252.
Chen, et al. Blood. 2018;131(18):2047-2059.
Liu, et al. Blood Adv. 2020;4(1):141-153.
Munshi, et al. Blood Cancer J. 2020;10:12.
Munshi, et al. Blood Adv. 2022.



# BTK-INHIBITOR TRIALS IN WM

| Study | Cohort | Agent (s) | N= | Time to Major Resp. | ORR/Major RR | ≥VGPR | PFS |
|---|---|---|---|---|---|---|---|
| **Pivotal Study** | R/R | Ibrutinib | 63 | 2 mo. | 91% / 79% | 30% | 54% @ 60 mo. |
| **INNOVATE Arm C** | R/R | Ibrutinib | 31 | 2 mo. | 87% / 77% | 29% | 40% @ 60 mo. |
| **Phase 2** | TN | Ibrutinib | 30 | 1.9 mo. | 100% / 87% | 30% | 76% @ 48 mo. |
| **INNOVATE Arms A. B** | TN, R/R | Ibrutinib Rituximab | 150 | 3 mo. | 92% / 76% | 31% | 68% @ 54 mo. |
| **(MYD88$^{WT}$)** | | | | | | | |
| **Phase 2** | TN, R/R | Acalabrutinib | 106 | N/A | 94% / 81% | 39% | 84% TN / 52% R/R (@ 66 mo.) |
| **Phase 2** | TN, R/R | Tirabrutinib | 27 | 1.9 TN 2.1 R/R | 96% / 93% | 33% | 93% @ 24 mo. |
| **Phase 2** | R/R | Pirtobrutinib | 80 | N/A | 81% / 67% (prior cBTKi) 88% / 88% (cBTKi naïve) | 24% (prior cBTKi) 29% (cBTKi naïve) | 57% @ 18 mo. (for prior cBTKi) N/A for cBTKi naïve. |

*Median ORR: 93%; Major RR: 81%; ≥VGPR: 30%; PFS 76% @ 4 yrs*

# CXCR4 MUTATIONS ARE COMMON IN WM AND IMPACT DISEASE PRESENTATION AND TREATMENT RESPONSE.

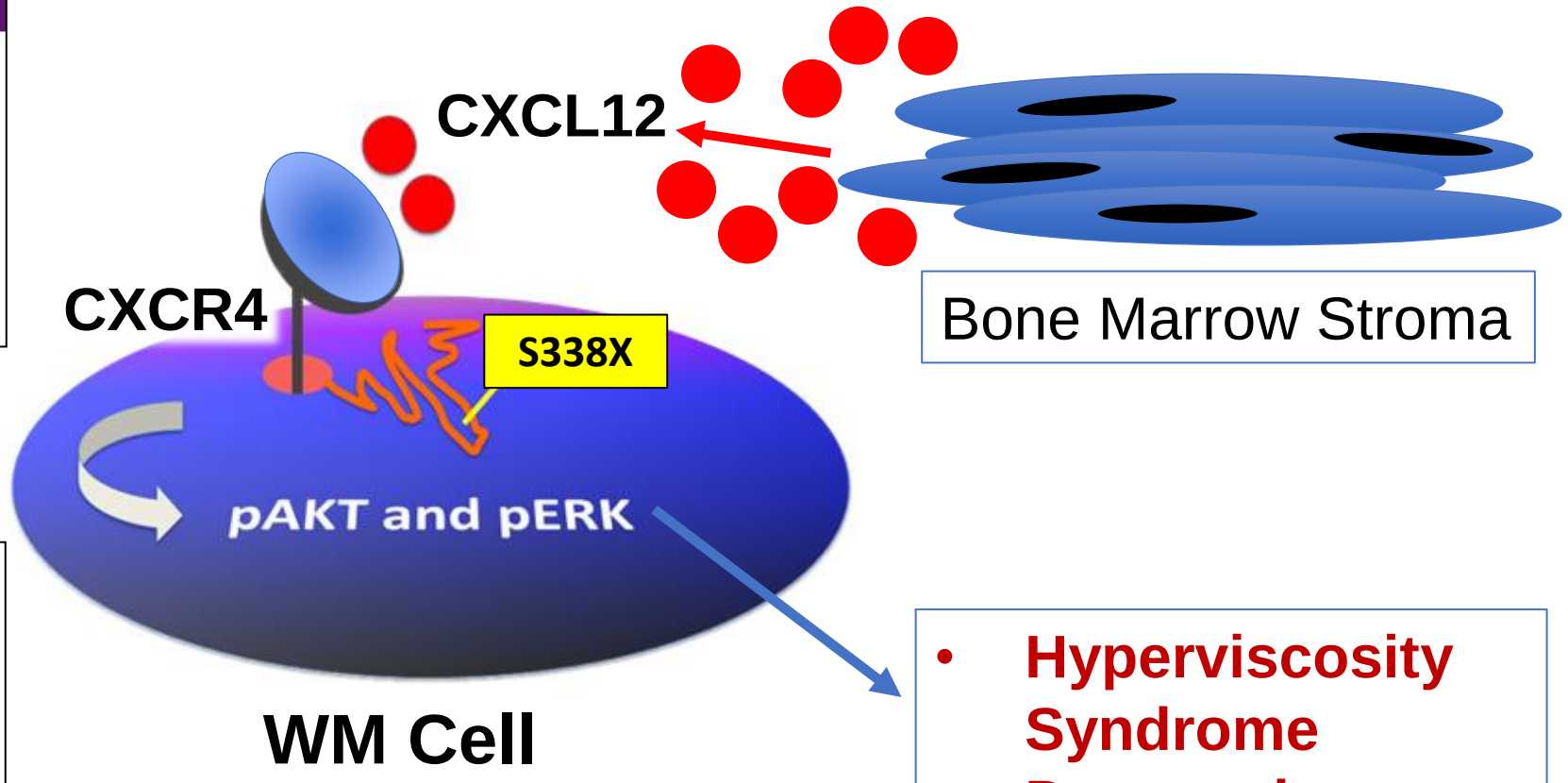
**Plenary Paper**

LYMPHOID NEOPLASIA

**The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis**

Zachary R. Hunter,[1,2] Lian Xu,[1] Guang Yang,[1] Yangsheng Zhou,[1] Xia Liu,[1] Yang Cao,[1] Robert J. Manning,[1] Christina Tripsas,[1] Christopher J. Patterson,[1] Patricia Sheehy,[1] and Steven P. Treon[1,3]

[1]Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [2]Department of Pathology and Laboratory Medicine, Boston University School of Graduate Medical Sciences, Boston, MA; and [3]Harvard Medical School, Boston, MA




- 30-40% of WM patients are CXCR4 mutated.
- >40 different CXCR4 mutations described, most common is S338X.

- Hyperviscosity Syndrome
- Drug resistance

Hunter et al, Blood 2013; Treon et al, Blood 2014; Roccarro et al, Blood 2014; Cao et al, Leukemia 2014.

Dana-Farber Cancer Institute

# CXCR4 IMPACT ON BTK-INHIBITOR OUTCOMES IN WM

| Study | Patient Population | Agent (s) | Time to Major Response (CXCR$^{Mut\ vs.\ WT}$) | Major Response Rate (CXCR$^{Mut\ vs.\ WT}$) | ≥VGPR (CXCR$^{Mut\ vs.\ WT}$) | PFS (CXCR$^{Mut\ vs.\ WT}$) |
|---|---|---|---|---|---|---|
| **Pivotal Study** | R/R | Ibrutinib | 4.7 vs.1.8 mo. | 68% vs. 97% | 9% vs. 47% | 38% vs. 70% (@ 60 mo.) |
| **ASPEN Cohort 1** | TN, R/R | Ibrutinib | 6.6 vs. 2.8 mos. | 65% vs. 82% | 10% vs. 24% | 49% vs. 75% (@ 42 mo.) |
| | TN, R/R | Zanubrutinib | 3.4 vs. 2.8 mos. | 70% vs. 82% | 18% vs. 34% | 73% vs. 81% (@ 42 mo.) |

*$CXCR4^{Mut}$ vs $CXCR4^{WT}$*

*Median Time to Major Response: (4.2 vs. 1.9 mos)*

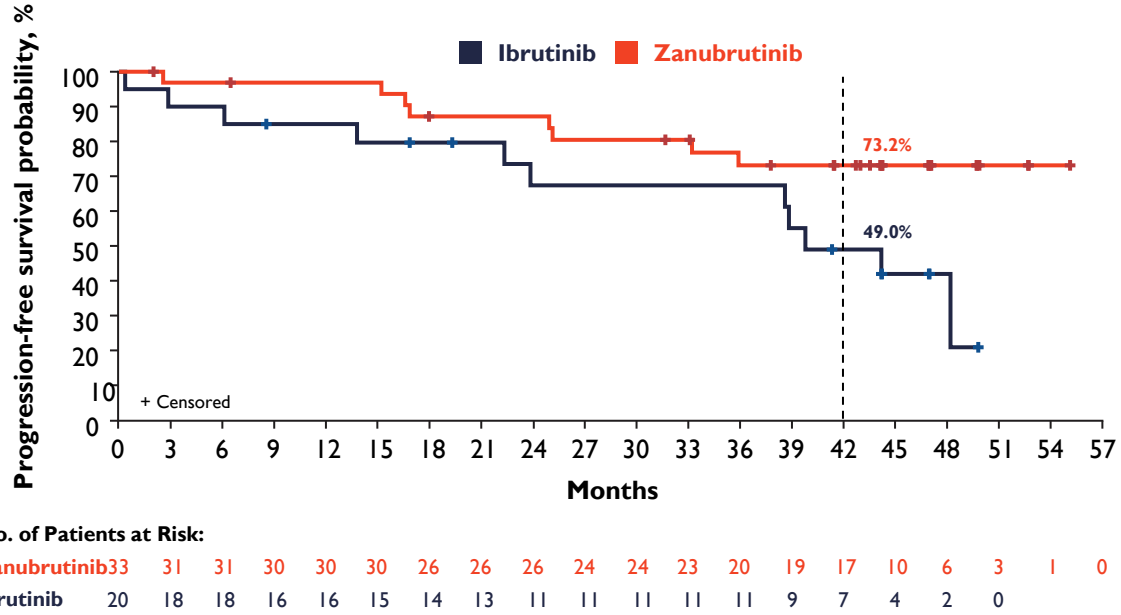
*Median Major RR: 71% vs. 87%*

*Median ≥VGPR: 14% vs. 41%*

*PFS: 59% vs. 75% @4 years*

# PROGRESSION-FREE SURVIVAL IN PATIENTS WITH *CXCR4*$^{MUT}$ AND RESPONSE ASSESSMENT BY CXCR4 STATUS

## ASPEN – Long-term follow-up




| | Zanubrutinib | Ibrutinib |
|---|---|---|
| **Events, n (%)** | 8 (24.2) | 11 (55.0) |
| **HR (95% CI)** | 0.50 (0.20, 1.29) | |

| | *CXCR4*$^{MUT}$ | | *CXCR4*$^{WT}$ | |
|---|---|---|---|---|
| | **Ibrutinib (n=20)** | **Zanubrutinib (n=33)** | **Ibrutinib (n=72)** | **Zanubrutinib (n=65)** |
| **VGPR or better** | 2 (10.0) | **7 (21.2)** | 22 (30.6) | **29 (44.6)** |
| **Major response** | 13 (65.0) | **26 (78.8)** | 61 (84.7) | 54 (83.1) |
| **Overall response** | 19 (95.0) | 30 (90.9) | 68 (94.4) | 63 (96.9) |
| **Time to major response, median (months)** | 6.6 | 3.4 | 2.8 | 2.8 |
| **Time to VGPR, median (months)** | 31.3 | 11.1 | 11.3 | 6.5 |

- In patients with *CXCR4*$^{MUT}$ by NGS, zanubrutinib demonstrated deeper and faster responses, as well as favorable PFS, compared with ibrutinib

**Dimopoulos et al, IWWM-12, 2024**

# ADVERSE EVENTS OF INTEREST (COHORT 1)

## ASPEN – Long-term follow-up

| AEs,[a] n (%) | All grades | | Grade ≥3 | |
|---|---|---|---|---|
| | Ibrutinib (n=98) | Zanubrutinib (n=101) | Ibrutinib (n=98) | Zanubrutinib (n=101) |
| **Infection** | 78 (79.6) | 80 (79.2) | **27 (27.6)** | 22 (21.8) |
| Bleeding | 61 (62.2) | 56 (55.4) | 10 (10.2) | 9 (8.9) |
| **Diarrhea** | **34 (34.7)** | 23 (22.8) | 2 (2.0) | 3 (3.0) |
| **Hypertension*** | **25 (25.5)** | 15 (14.9) | **20 (20.4)*** | 10 (9.9) |
| **Atrial fibrillation/flutter*** | **23 (23.5)*** | 8 (7.9) | **8 (8.2)*** | 2 (2.0) |
| **Anemia** | 22 (22.4) | 18 (17.8) | 6 (6.1) | **12 (11.9)** |
| **Neutropenia*[b]** | 20 (20.4) | **35 (34.7)*** | 10 (10.2) | **24 (23.8)*** |
| Thrombocytopenia | 17 (17.3) | 17 (16.8) | 6 (6.1) | 11 (10.9) |
| Second primary malignancy/ Non-Skin Cancers | 17 (17.3)/ 6 (6.1) | 17 (16.8)/ 6 (5.9) | 3 (3.1)/ 3 (3.1) | 6 (5.9)/ 4 (4.0) |

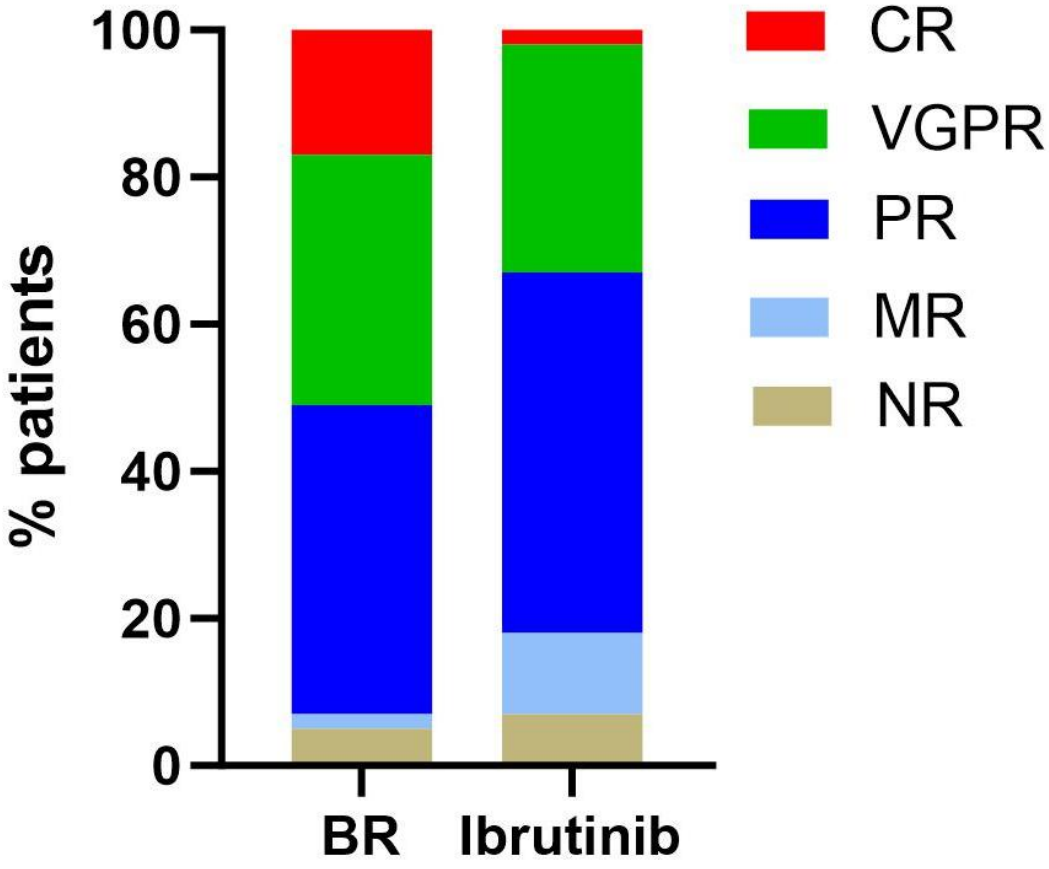
**Dimopoulos et al, IWWM-12, 2024**

**Bold text** indicates rate of AEs with ≥10% (all grades) or ≥5% (grade ≥3) difference between arms.
Data cutoff: October 31, 2021.
*Descriptive purposes only, 1-sided P<0.025 in rate difference in all grades and/or grade ≥3. [a]AE categories (grouped terms) of preferred terms by Medical Dictionary for Regulatory Activities v24.0. [b]Including preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.
AE=adverse event.
Dimopoulos MA et al. JCO 2023 DOI: 10.1200/JCO.22.02830


Do we give BTK-inhibitors or chemo-immunotherapy to treatment-naïve patients?

# COMPARATIVE EFFICACY OF BENDAMUSTINE-RITUXIMAB AND IBRUTINIB IN TREATMENT-NAÏVE WM (INTERNATIONAL RETROSPECTIVE STUDY)

| Variable | BR (n=123) | Ibrutinib (n=123) | p-value |
|---|---|---|---|
| Follow-up, median, 95%CI, y | 6.0 (5.1-6.6) | 6.0 (5.4-6.6) | 0.89 |
| Age, median, range, y | 68 (40-86) | 68 (39-86) | 0.9 |
| IPSS, % | | | |
| Low | 11 | 17 | 0.63 |
| Intermediate | 33 | 33 | |
| High | 56 | 48 | |
| Cycles, median (range) | 6 (1-6)<br>>4 cycles, 79% | 54 (1-114) | |
| Overall response rate, % | 95 | 93 | 0.47 |
| Major response rate, % | 93 | 82 | **0.014** |
| Complete response, % | 17 | 2 | **<0.001** |
| ≥VGPR, % | 50 | 33 | **0.008** |

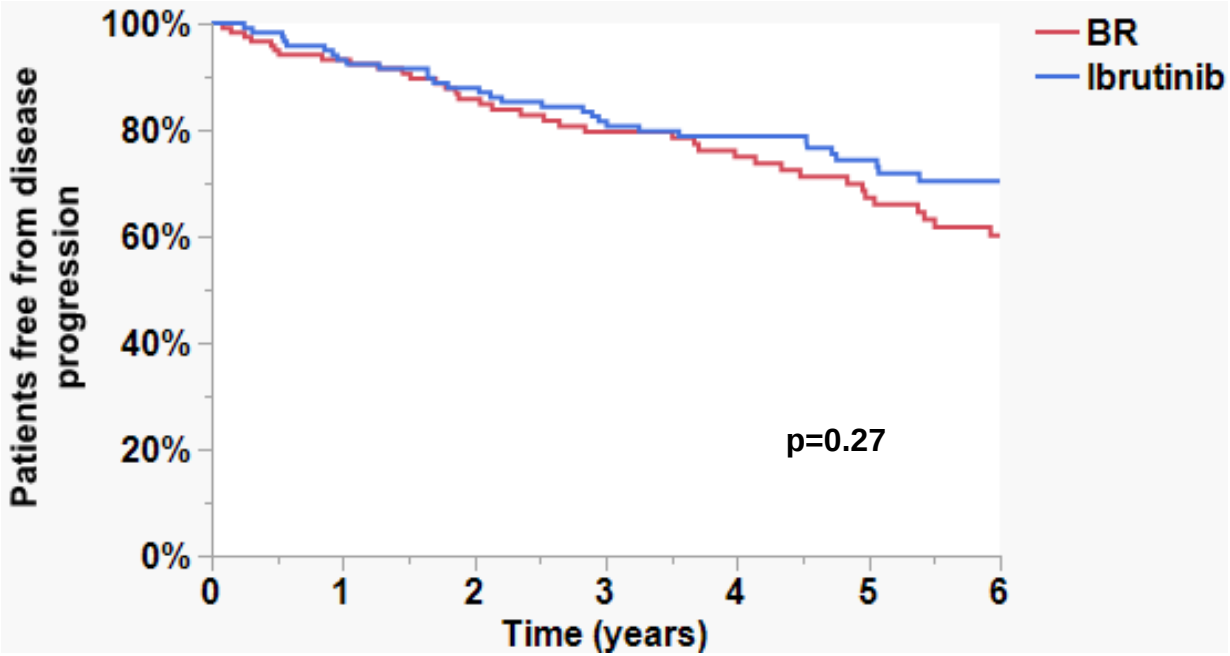



**Abeykoon et al, IWWM-12, 2024**

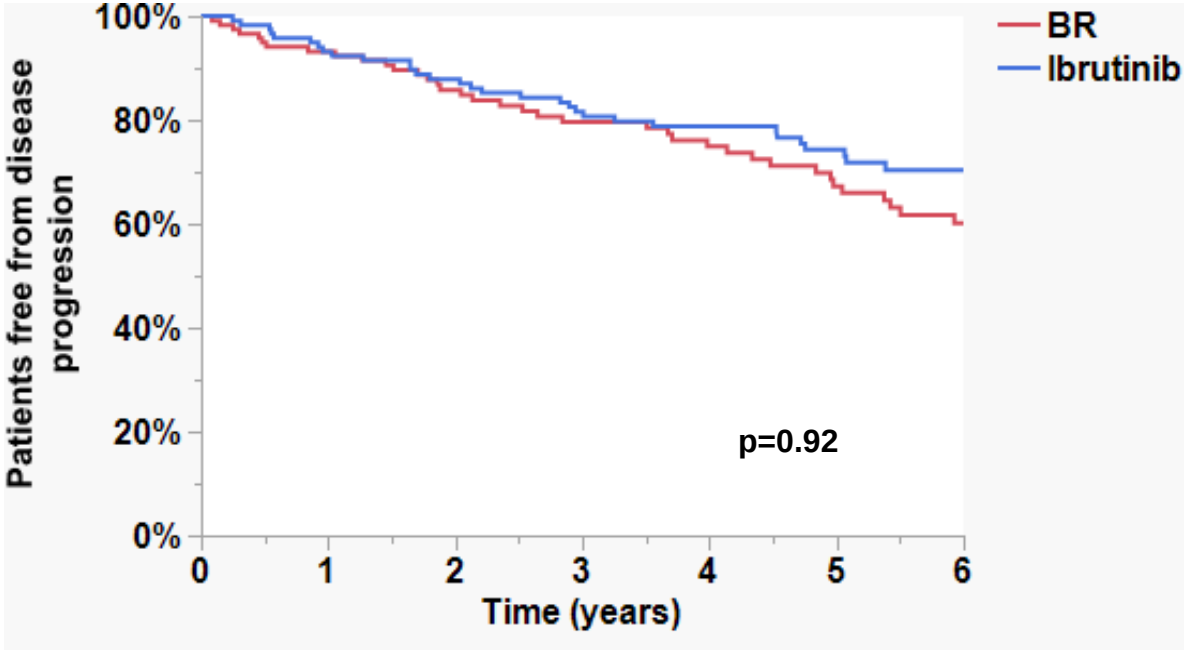
IPSS: International Prognostic Scoring System; VGPR: very good partial response; MR: minor response; NR: no response

# BENDA-R VS. IBRUTINIB: TIME-TO-EVENT ANALYSES

## Progression Free Survival




## Overall Survival




| Variable | BR (n=123) | Ibrutinib (n=123) | p-value |
|---|---|---|---|
| 6-year PFS, % | 58 | 70 | 0.27 |
| 6-year OS, % | 80.5 | 84 | 0.92 |

Abeykoon et al, IWWM-12, 2024

FRENCH INNOVATIVE
LEUKEMIA ORGANIZATION


# BENDAMUSTINE AND RITUXIMAB (BR) IN WALDENSTROM MACROGLOBULINEMIA (WM): LONG-TERM RESULTS

## A STUDY ON BEHALF OF THE FRENCH INNOVATIVE LEUKEMIA ORGANIZATION (FILO)

***Eveillard JR, Chaoui D, Cavalieri D, Dartigeas C, Willems L, Le Calloch R, Roos-Weil D, Merabet F, Roussel X, Bareau B, Tricot S, Dupuis J, Poulain S, Laribi K, Leblond V***

MÉDECINE SORBONNE UNIVERSITÉ

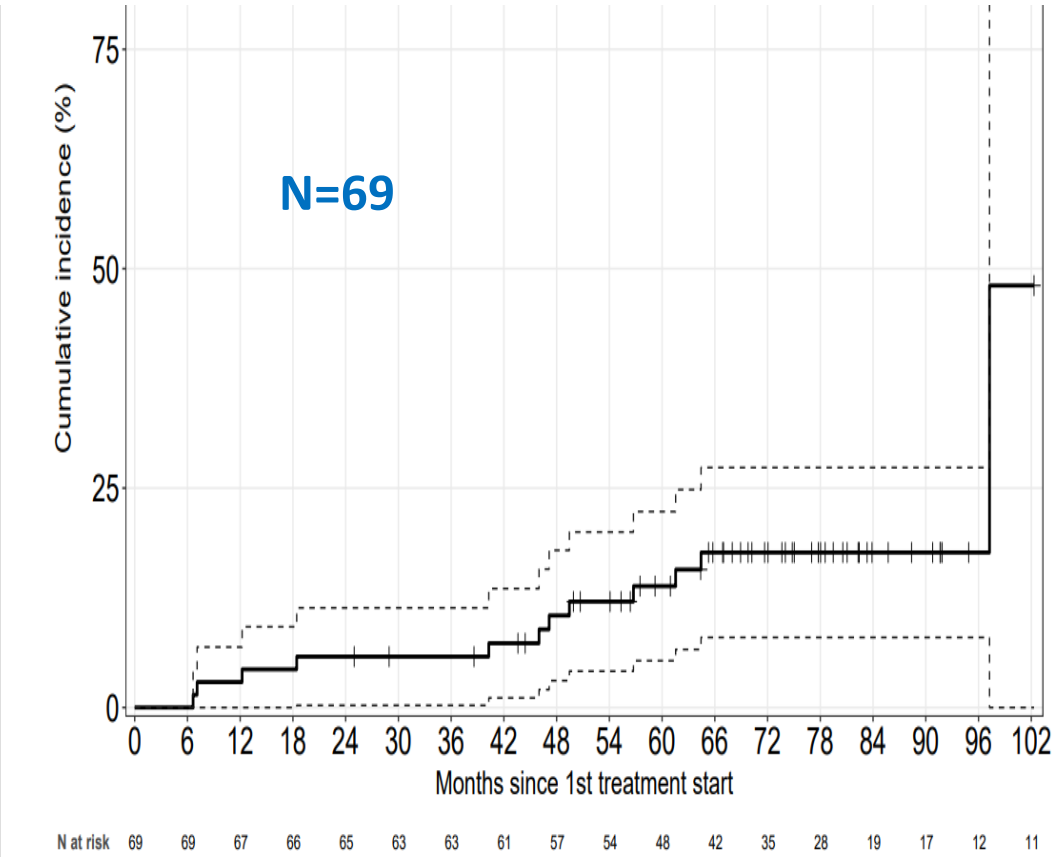
**Leblond et al, IWWM-12, 2024**

# FILO STUDY: LATE-ONSET TOXICITIES

| Type of Cytopenia | N | % | Duration (months) median (range) |
|---|---|---|---|
| Neutropenia | 26 | 38% | 9m (3-24) |
| Anemia | 17 | 25% | 6m (3-36) |
| Thrombocytopenia | 11 | 16% | 9m (3-36) |

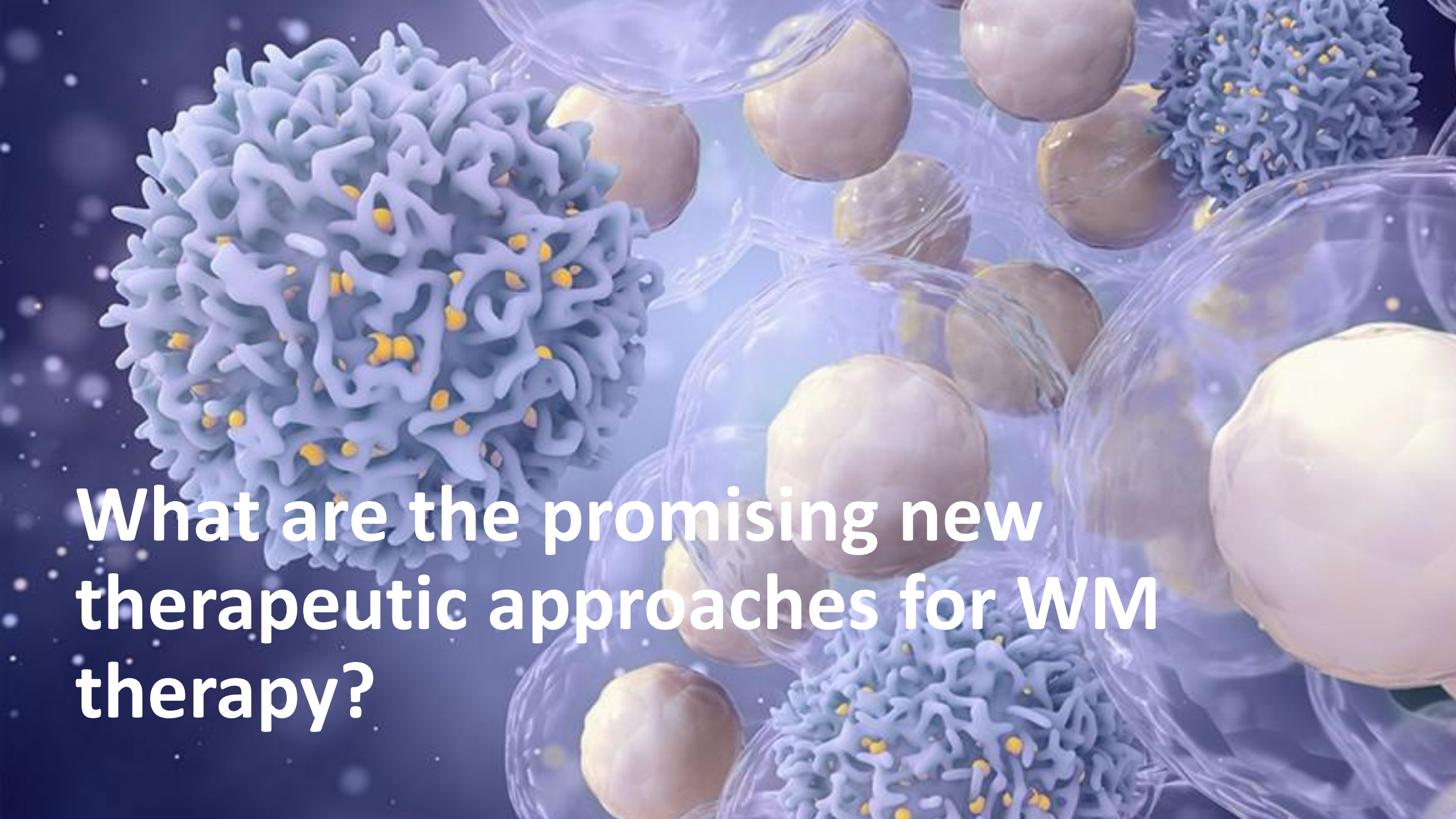
- Long–lasting cytopenia occurred in 35 patients ( 51%)

- **Second malignancies: 12 patients**
  - 9 solid tumors ( 2 pancreas , 2 gastric, 1 colic, 1 oesophagus 1 lung, 1 skin, 1 breast)
  - 3 myelodysplastic syndromes with 2 AML




Cumulative incidence of second malignancies of 17.66% [7.99-27.64] at 66 months.

**Leblond et al, IWWM-12, 2024**



# What are the promising new therapeutic approaches for WM therapy?

# A Multi-Center, Open-Label, Single-Arm Phase II Trial of *Bendamustine, Rituximab and the Next Generation BTK Inhibitor Acalabrutinib* in Treatment Naïve WM - BRAWM

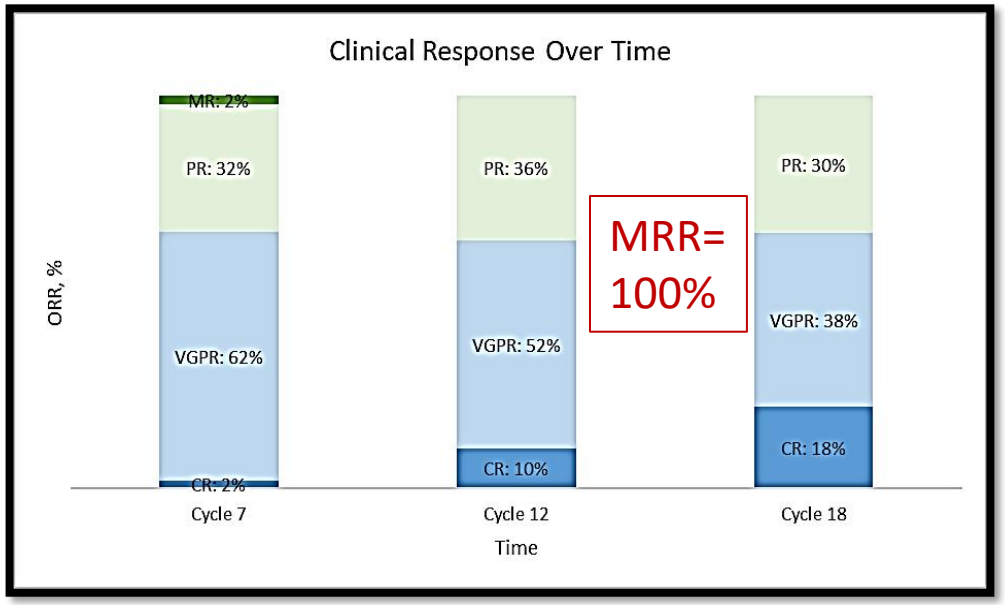

**N=63**

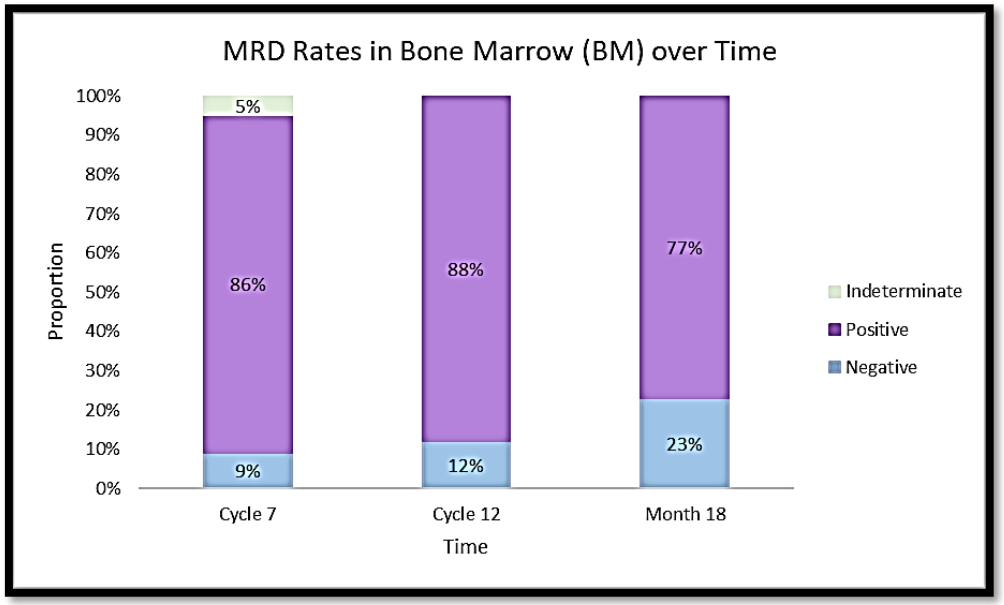
**Berenstein et al, IWWM-12, 2024**

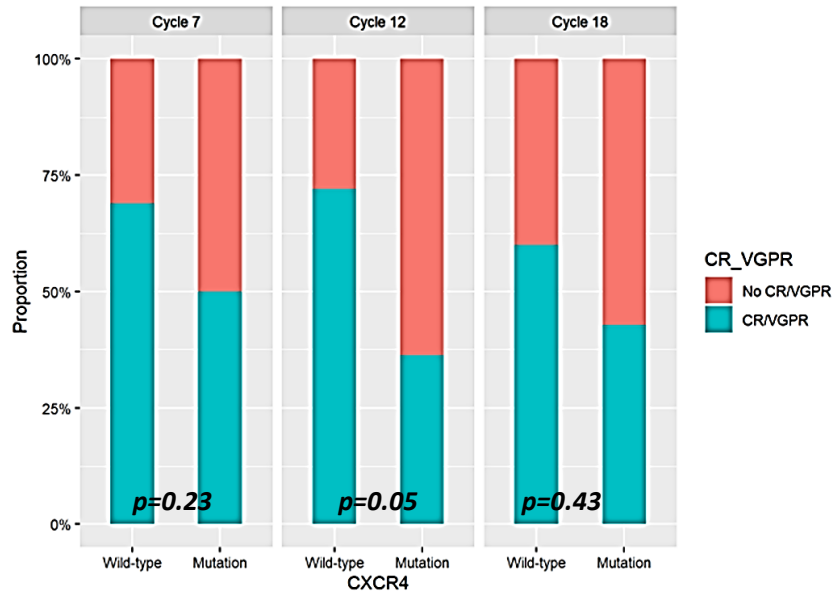
ClinicalTrials.gov Identifier: NCT04624906

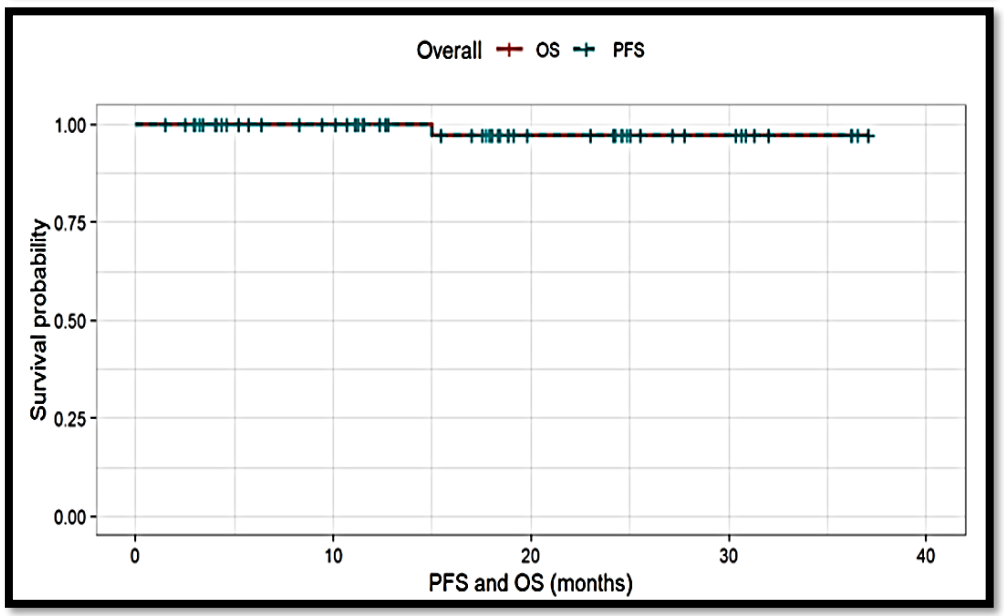
Sunnybrook RESEARCH INSTITUTE

# BENDAMUSTINE, RITUXIMAB AND ACALABRUTINIB FOR TREATMENT NAÏVE WM

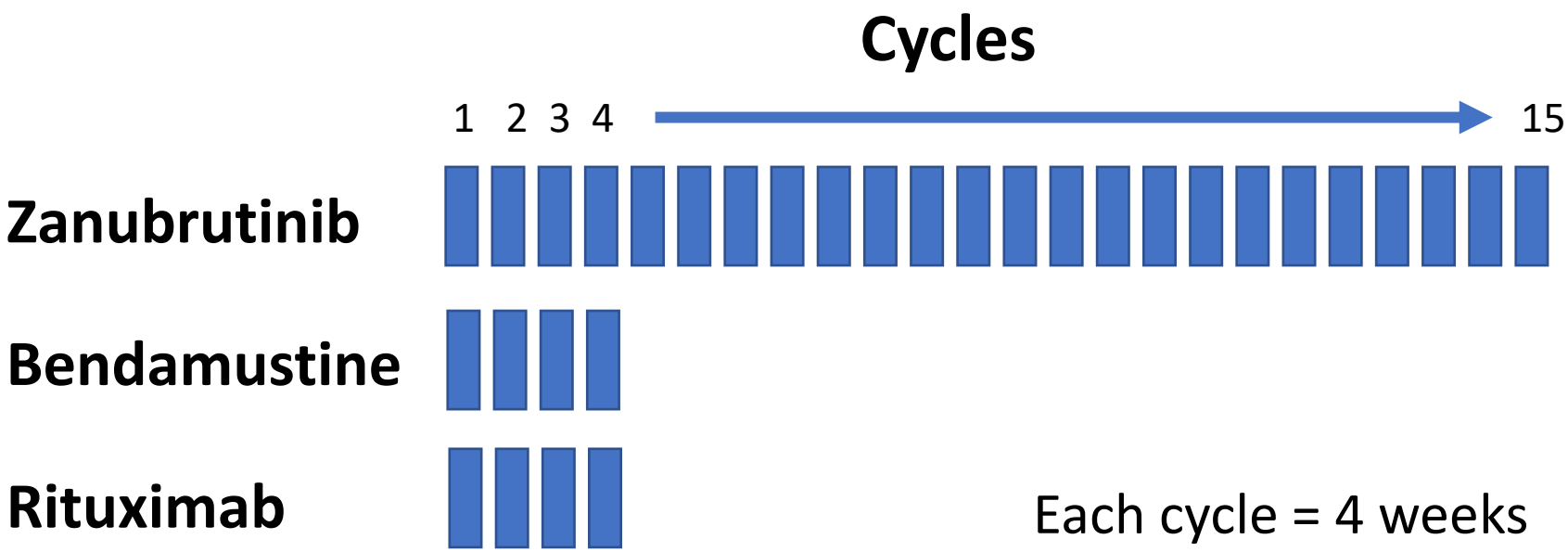


# ZANUBRUTINIB, BENDAMUSTINE AND RITUXIMAB IN TREATMENT NAÏVE WM (ZEBRA TRIAL)



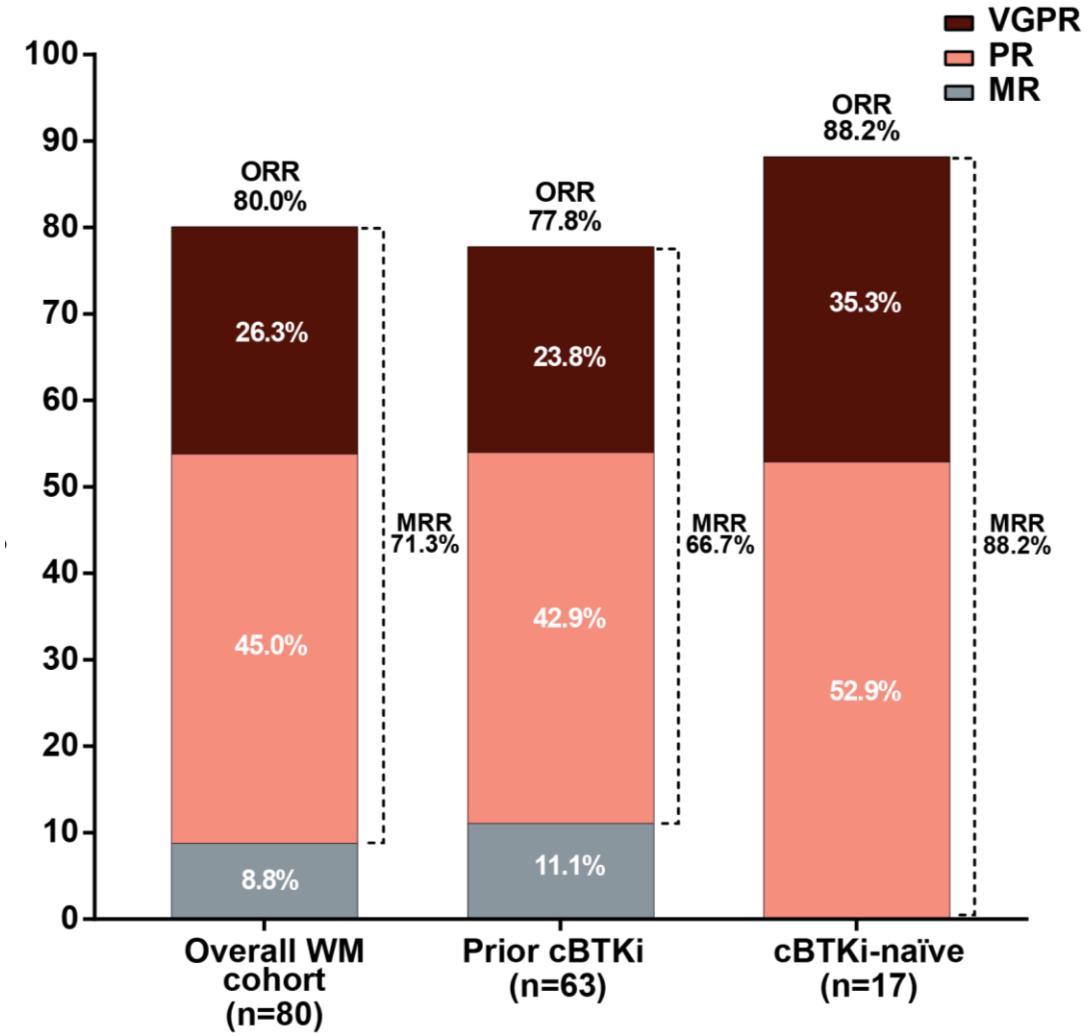

Each cycle = 4 weeks

MASSACHUSETTS GENERAL HOSPITAL

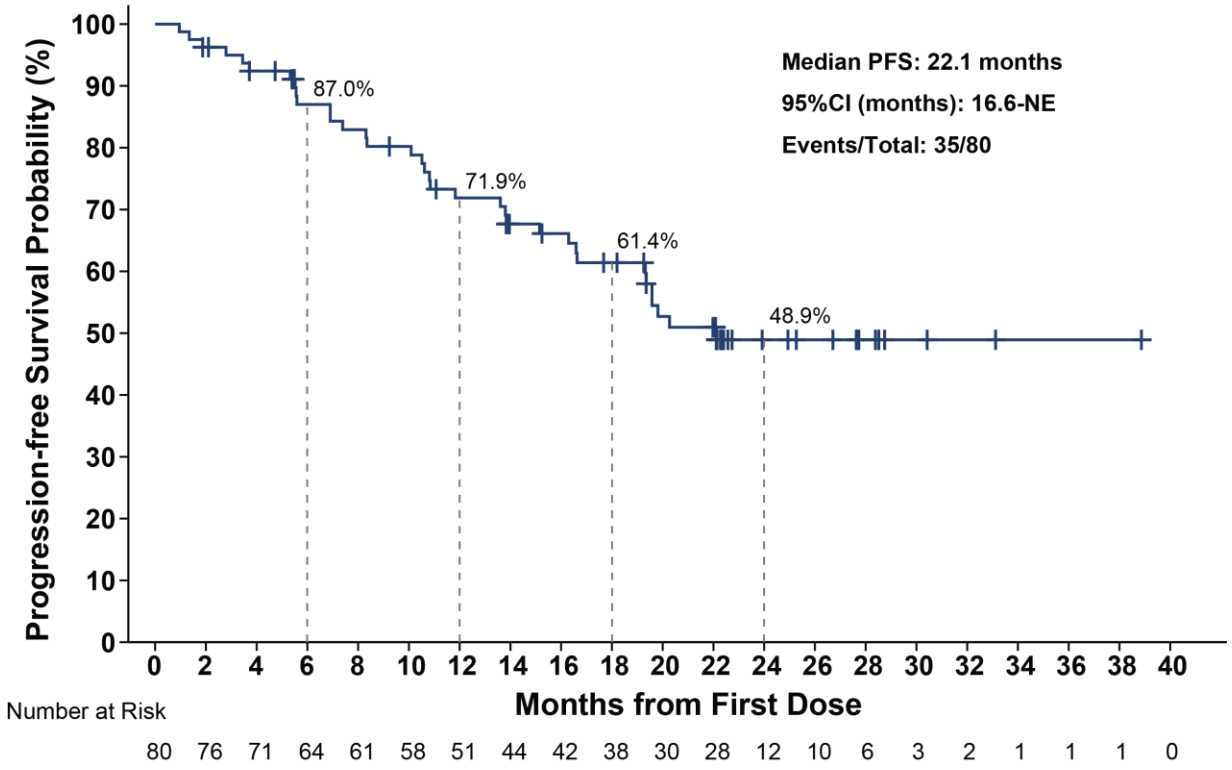
Dana-Farber Cancer Institute

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

# NON-COVALENT BTK-I PIRTOBRUTINIB IN RELAPSED/REFRACTORY WM PATIENTS




## Progression-Free Survival



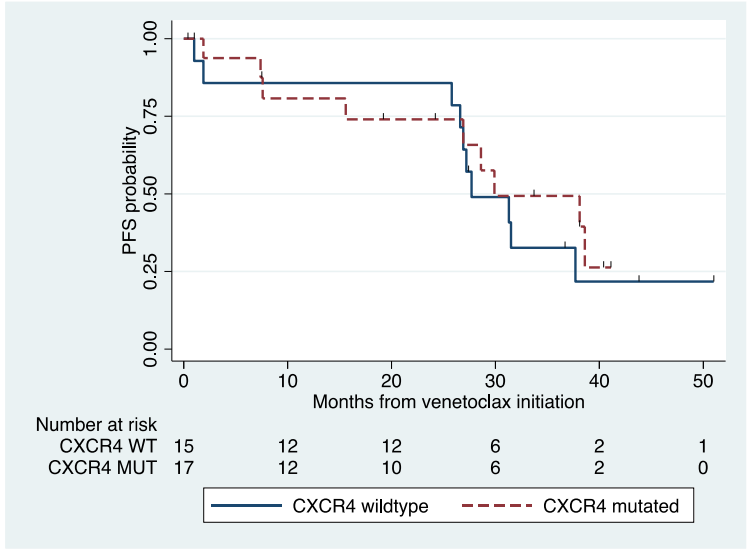

- The median follow-up was 22 months (IQR, 19.3–26.7)
- The PFS rate at 18 months was 61.4% (95%CI, 49.1-71.6)

Palomba et al, IWWM-12, 2024

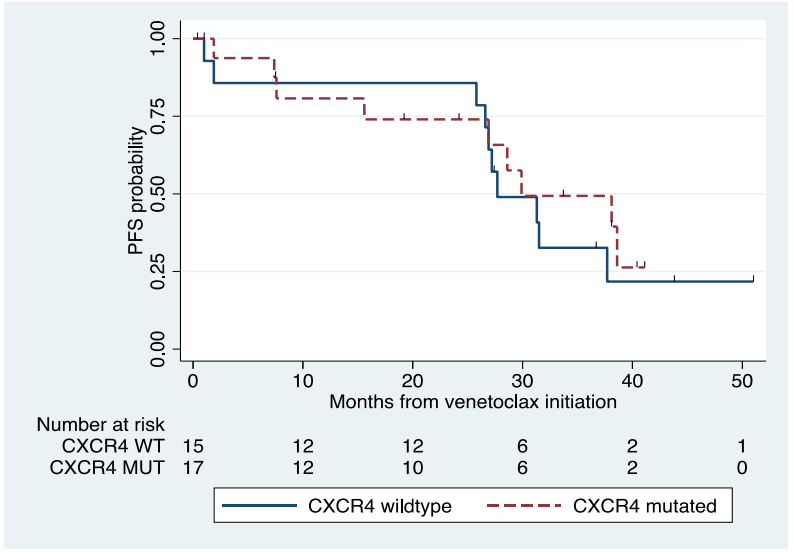
# VENETOCLAX FOR PREVIOUSLY TREATED WM

Dose escalation to 800 mg/day, 2 years treatment

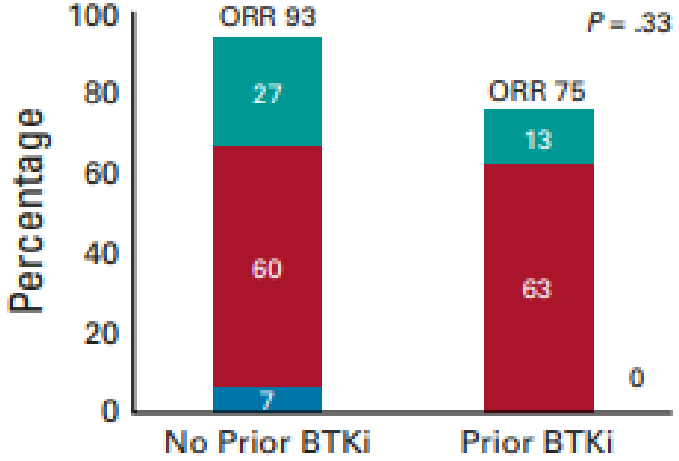
**ORR 84%; Major RR 81%**
**Median PFS: 30 mos.**
**Not impacted by CXCR4 mutation status.**
**Grade ≥3 neutropenia: 45%**

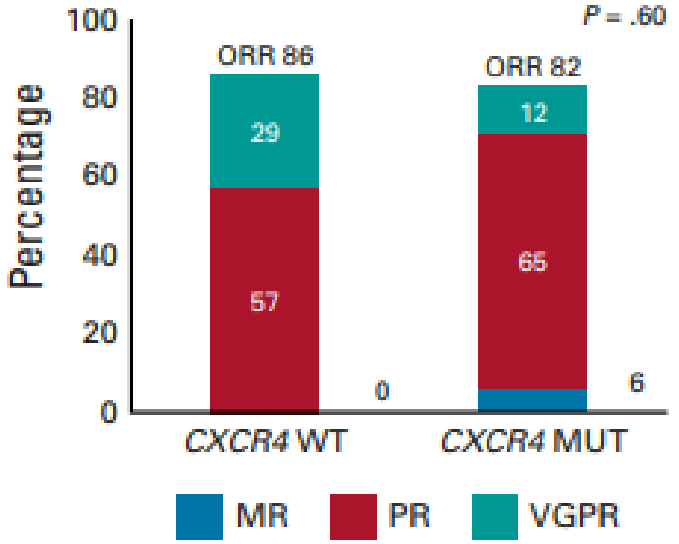



**PFS for All Pts**



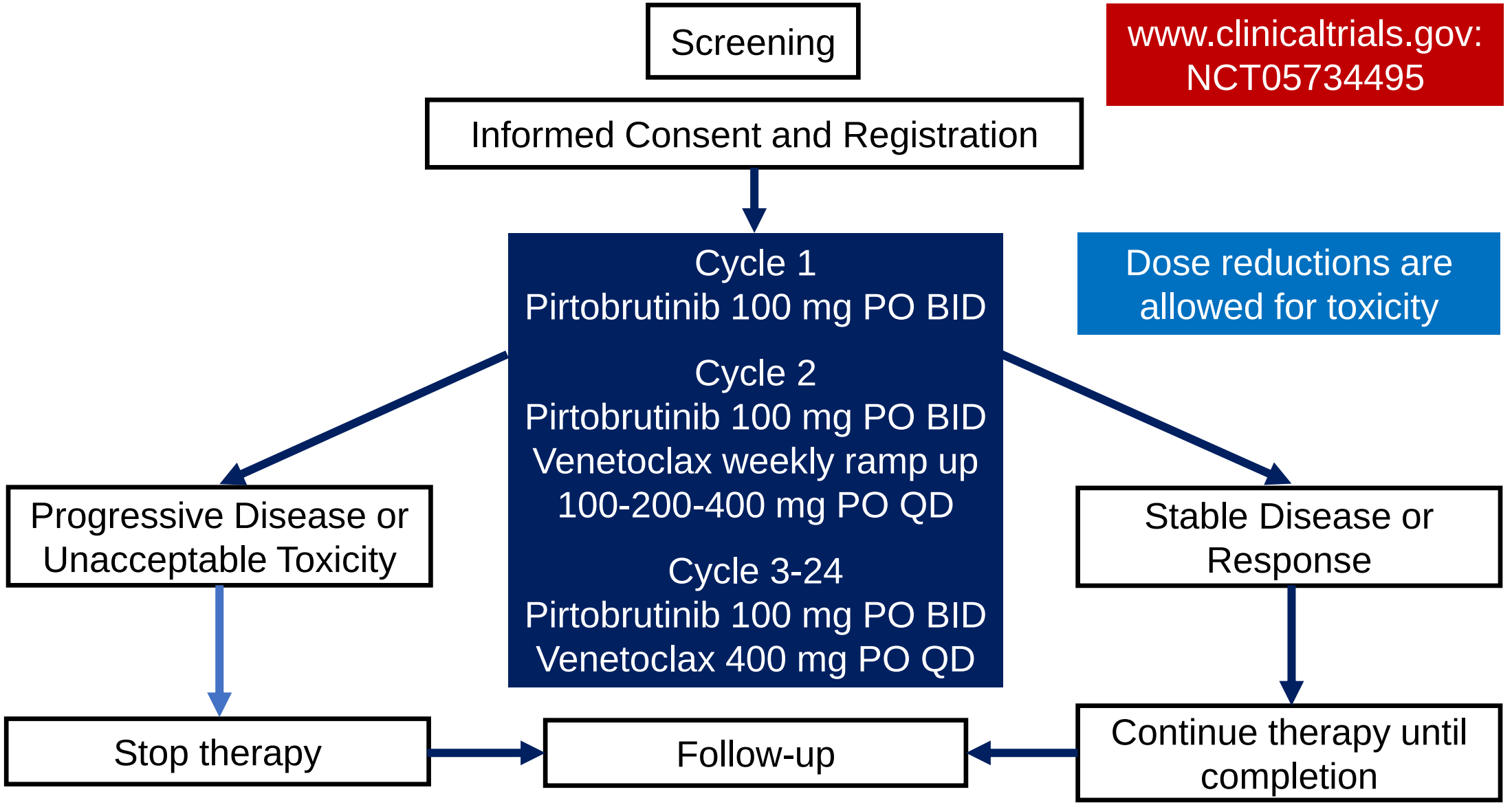

**PFS by CXCR4 Mut Status**



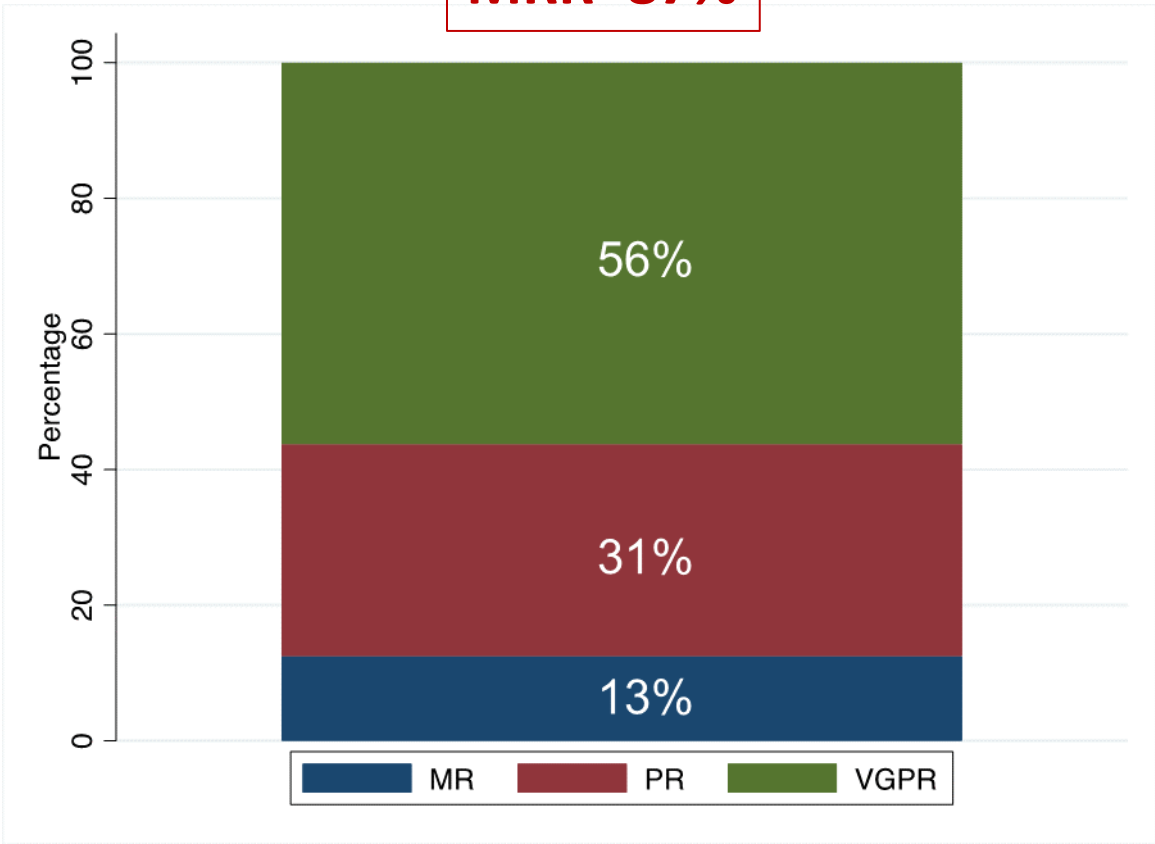

Castillo et al, JCO 2021

# PHASE II STUDY OF PIRTOBRUTINIB PLUS VENETOCLAX IN PREVIOUSLY TREATED WM



# PIRTOBRUTINIB AND VENETOCLAX IN RELAPSED/REFRACTORY WM PATIENTS

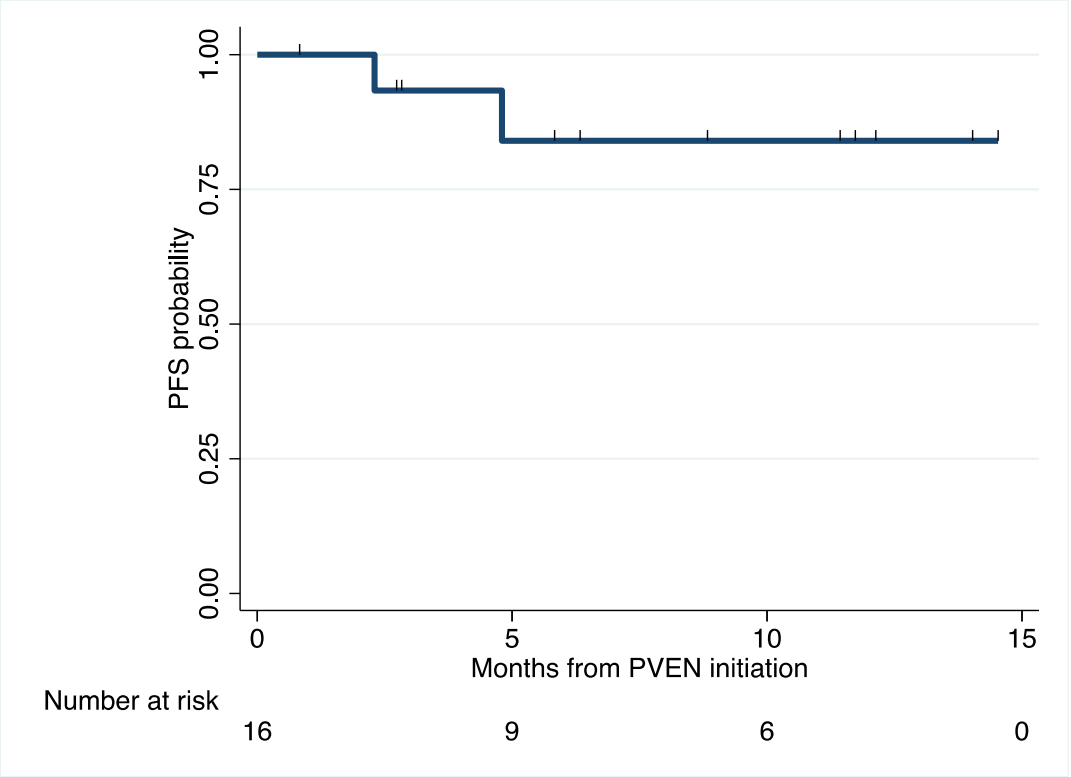
**MRR=87%**




**Major RR by CXCR4 WT vs. Mut: 90% vs. 83%**
**Major RR by prior BTK-I Exp vs. Non-Exp: 86% vs. 89%**

**N=16**

## Progression-Free Survival

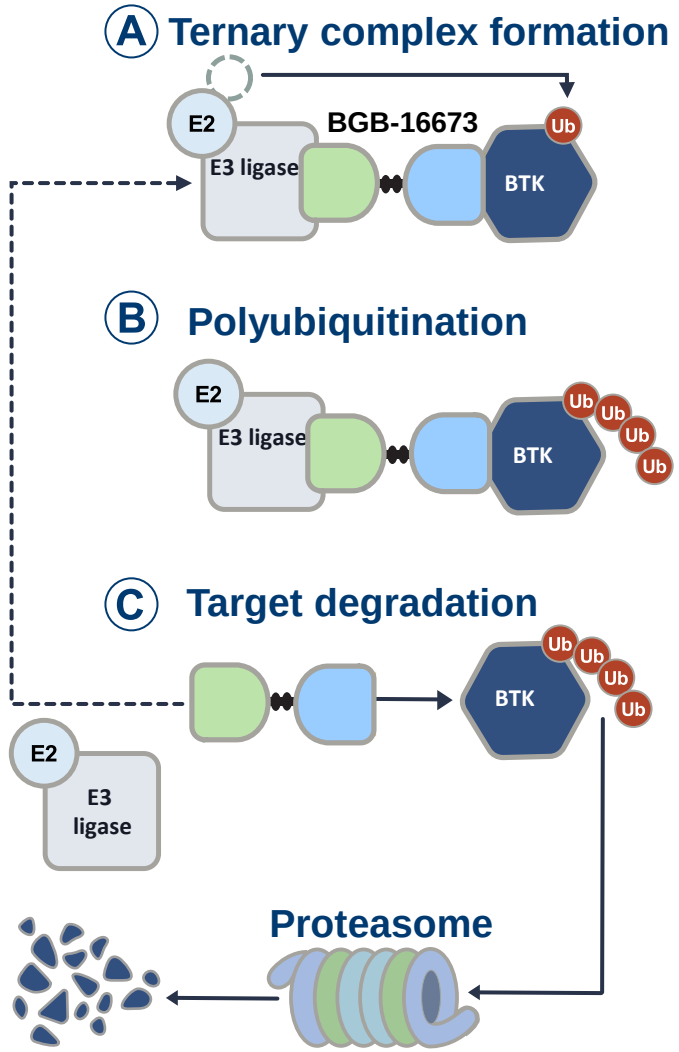



- **The median follow-up was 6 months (95% CI, 3-12)**
- **The PFS rate at 6 months 84% (95% CI 49-96%)**

**Castillo et al, IWWM-12, 2024**

# BGB-16673: A CHIMERIC DEGRADATION ACTIVATING COMPOUND (CDAC)

- BTK inhibitors are effective in WM but are associated with toxicities and/or resistance development[1,2]
- BGB-16673 is a bivalent CNS-penetrating small molecule that induces BTK degradation by binding specifically to BTK and the E3 ligase[3]
- In preclinical models, BGB-16673 degraded both wild-type and mutant BTK resistant to cBTK (C481S, C481F, C481Y, L528W, T474I) and ncBTK inhibitors (V416L, M437R, T474I, L528W), leading to tumor suppression[3,4]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue[5]
- Here, updated safety and efficacy results are presented in patients with R/R WM in phase 1 of CaDAnCe-101




cBTK, covalent BTK; CNS, central nervous system; ncBTK, noncovalent BTK; ub, ubiquitin.

1. Castillo JJ, et al. *Lancet Haematol*. 2020;7(11):e827-e837; 2. Ntanasis-Stathopoulos I, et al. *Ther Adv Hematol.* 2021;12:2040620721989586;
3. Feng X, et al. EHA 2023. Abstract P1239; 4. Wang H, et al. EHA 2023. Abstract P1219; 5. Seymour JF, et al. ASH 2023. Abstract 4401.

# OVERALL RESPONSES FOR BGB-16673 IN R/R WM

- Responses were observed at the lowest dose (100 mg; 7/9) and in patients with prior cBTK inhibitor (22/27) or ncBTK inhibitor (4/4)

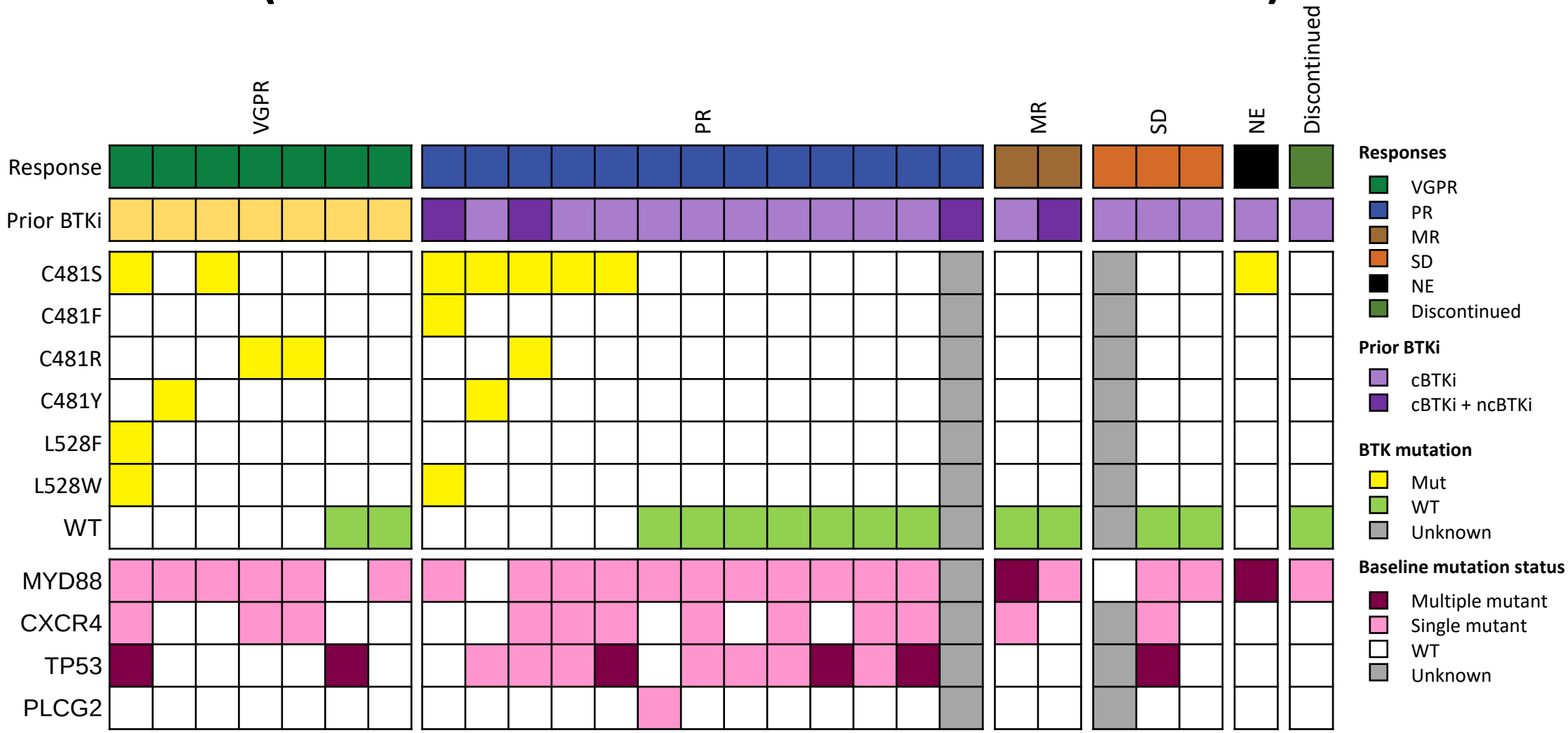
| | Total[a] (N=27) |
|---|---|
| **Best overall response, n (%)** | |
| VGPR | 7 (25.9) |
| PR | 13 (48.1) |
| MR | 2 (7.4) |
| SD | 3 (11.1) |
| Not evaluable | 1 (3.7) |
| Discontinued prior to first assessment | 1 (3.7) |
| **ORR, n (%)[b]** | **22 (81.5)** |
| **Major response rate, n (%)[c]** | **20 (74.1)** |
| **DCR, n (%)[d]** | 25 (93.0) |
| **Follow-up, median (range), months** | 5.0 (0.8-24.6) |
| **Time to first response, median (range), months[e]** | 1.0 (0.9-3.7) |

| Mutation status, n/N tested (%) | Total[a] (N=27) |
|---|---|
| ***BTK*** | |
| Mutated | 10/11 (90.9) |
| Unmutated | 11/14 (78.6) |
| Unknown | 1/2 (50.0) |
| ***MYD88*** | |
| Mutated | 20/24 (83.3) |
| Unmutated | 1/2 (50.0) |
| Unknown | 1/1 (100) |
| ***CXCR4*** | |
| Mutated | 11/12 (91.7) |
| Unmutated | 10/13 (76.9) |
| Unknown | 1/2 (50.0) |
| ***TP53*** | |
| Mutated | 12/13 (92.3) |
| Unmutated | 9/12 (75.0) |
| Unknown | 1/2 (50.0) |

a
e best overall response of SD or better.
cBTK, covalent BTK; DCR, disease control rate; MR, minor response; ncBTK, noncovalent BTK; VGPR, very good partial response.

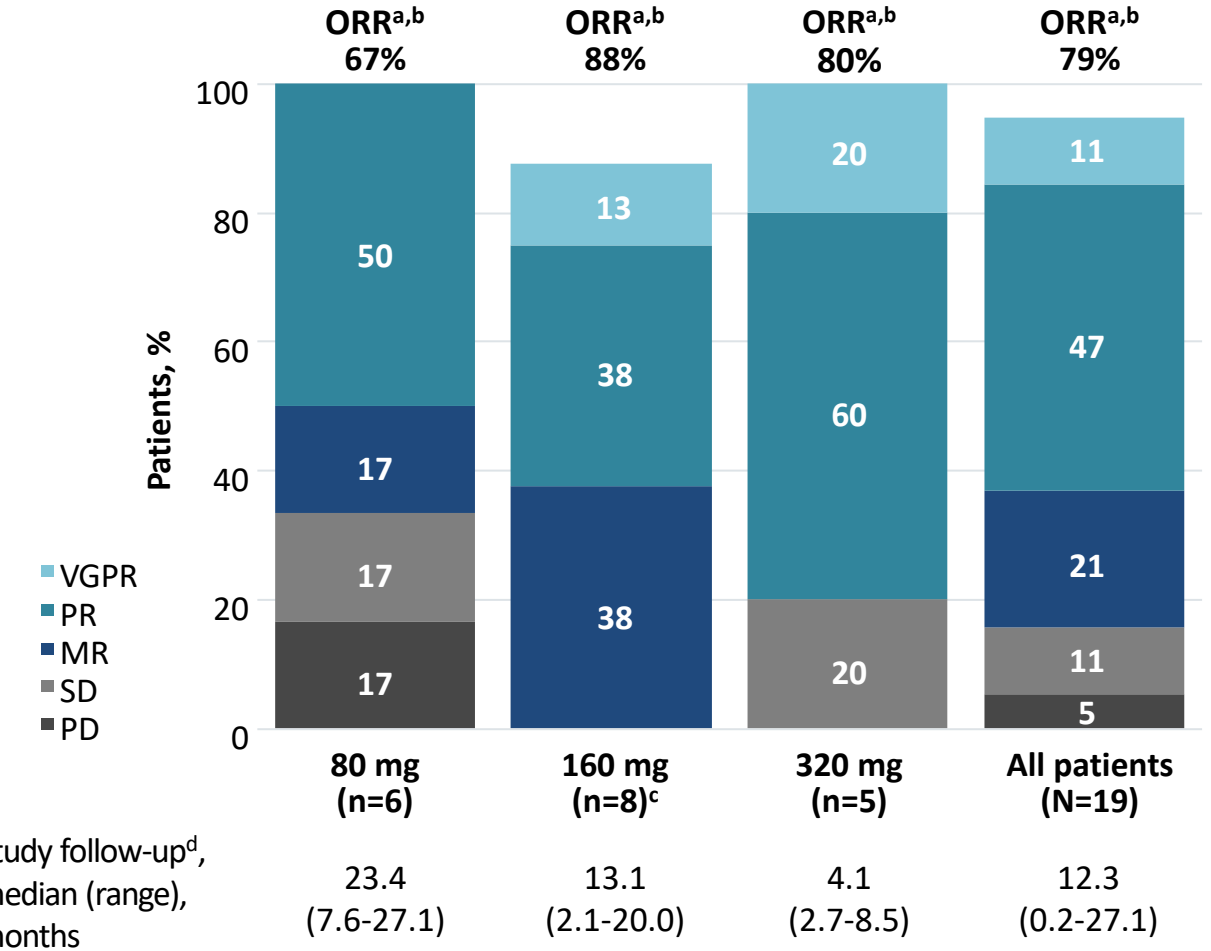
**Seymour et al, IWWM-12, 2024**

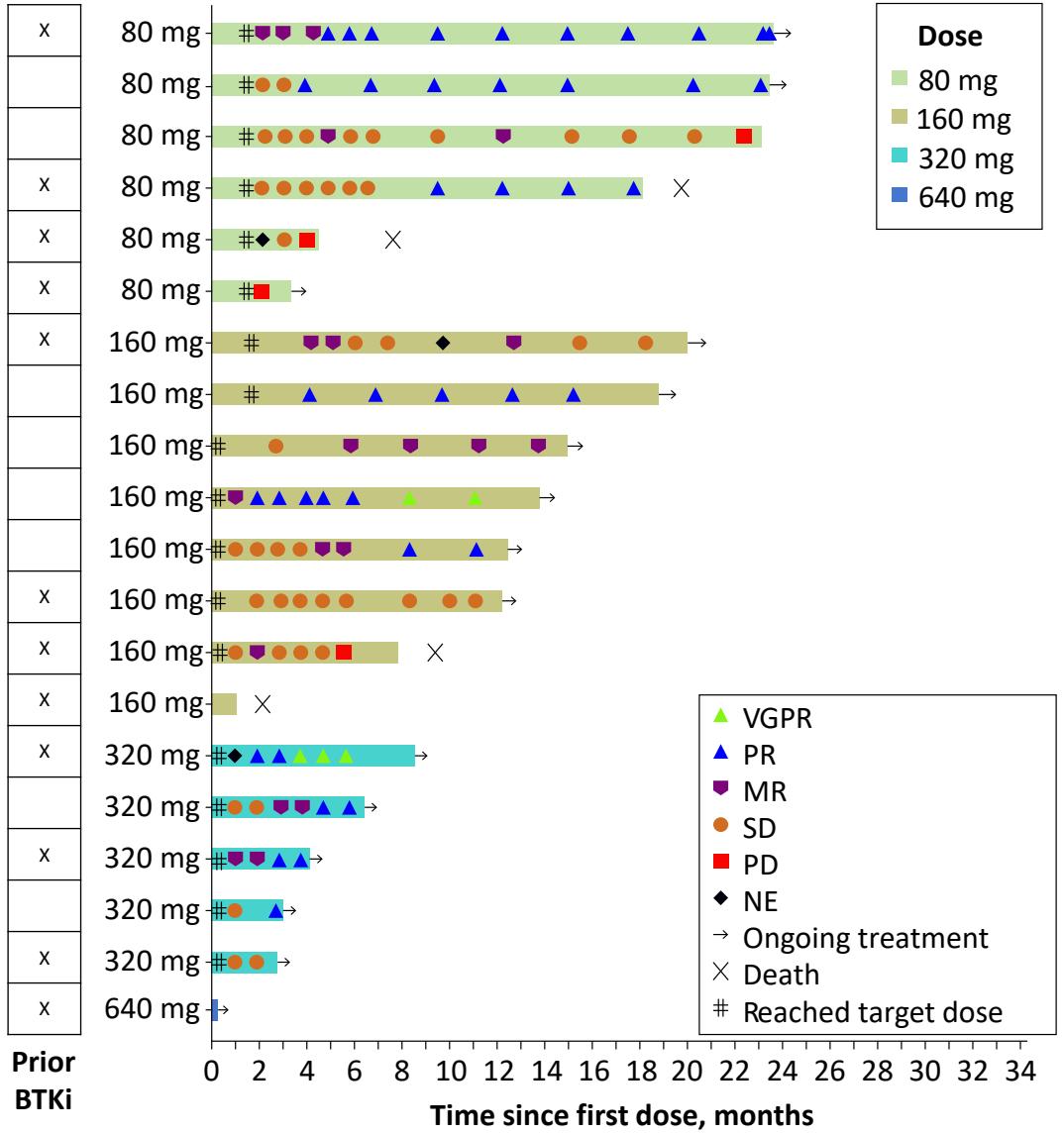
# BGB-16673 RESPONSES OCCURRED REGARDLESS OF SPECIFIC MUTATIONS (RESPONSE VS BASELINE MUTATION PROFILE)



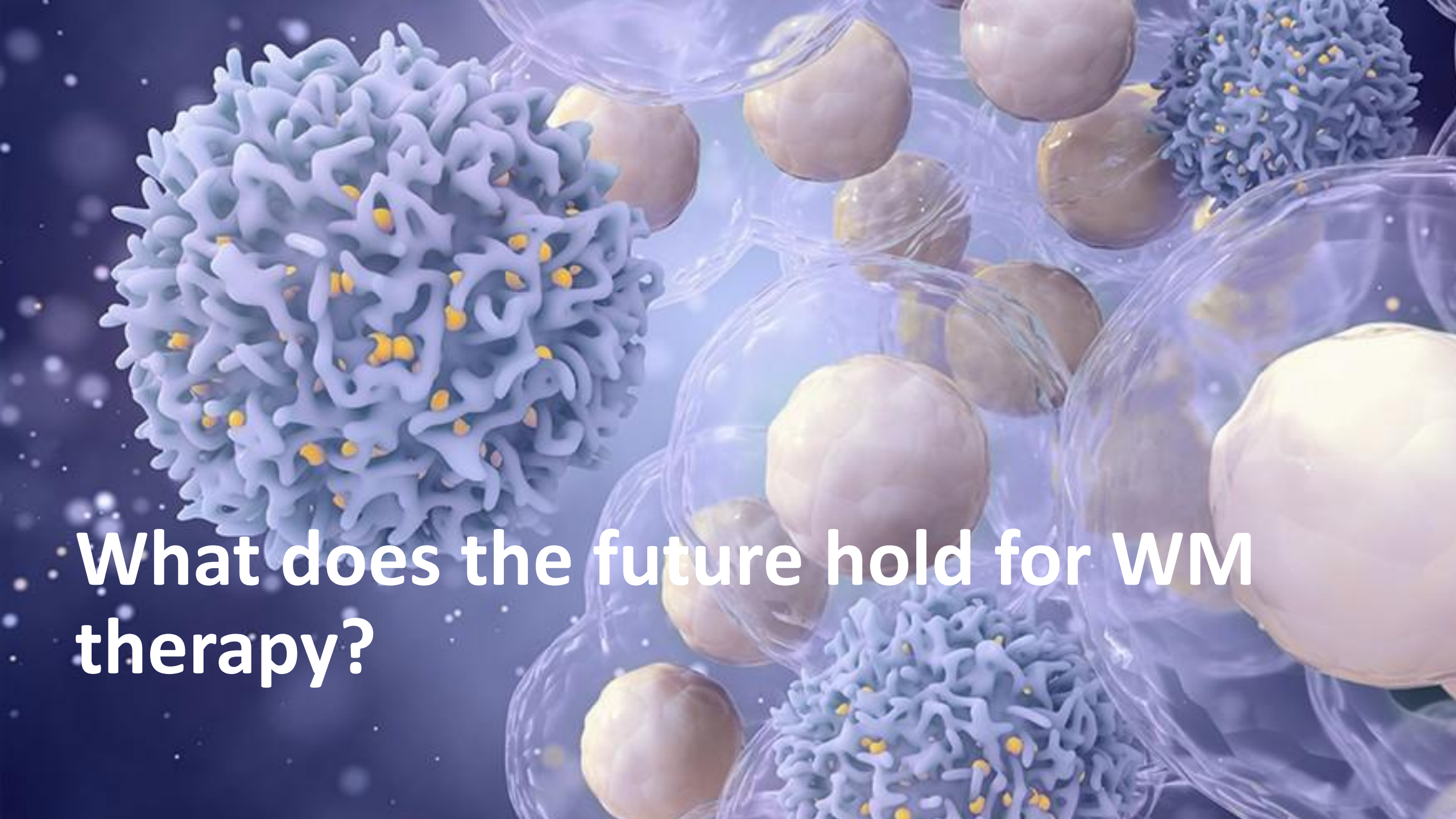

cBTKi, covalent BTK inhibitor; MR, minor response; ncBTKi, noncovalent BTK inhibitor; NE, not evaluable; VGPR, very good partial response; WT, wild type.

# PHASE 1 STUDY OF THE NOVEL BCL2 INHIBITOR SONROTOCLAX (BGB-11417) IN R/R WM



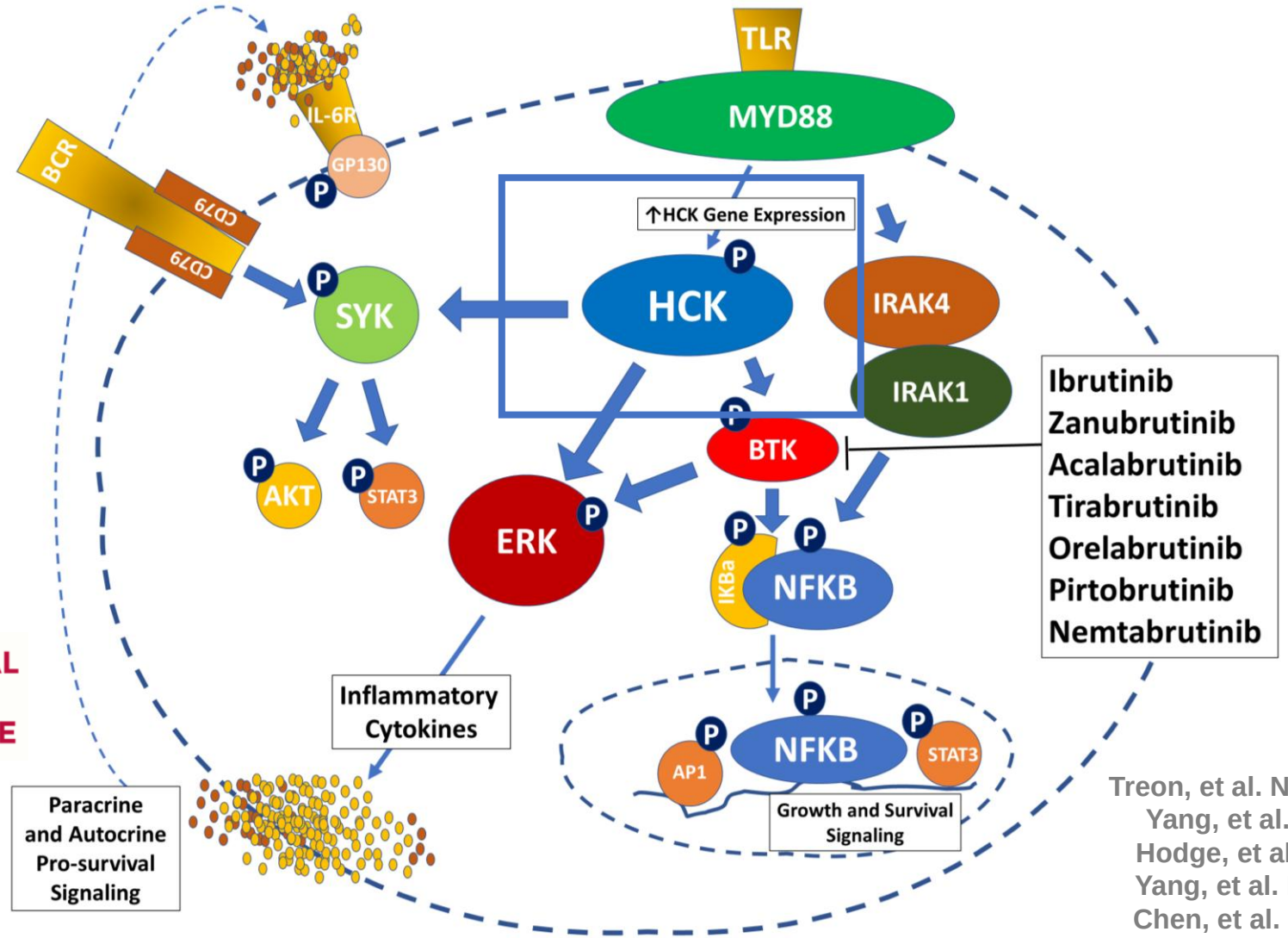




**Garcia-Sanz et al, IWWM-12, 2024**



# What does the future hold for WM therapy?

# MYD88 DIRECTED PRO-SURVIVAL SIGNALING IN WM





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Munshi, et al. Blood Cancer J. 2020;10:12.
Munshi, et al. Blood Adv. 2022.

# DEVELOPMENT OF THE DUAL HCK/BTK KINASE INHIBITOR KIN-8194

blood® Regular Article

LYMPHOID NEOPLASIA

## The HCK/BTK inhibitor KIN-8194 is active in MYD88-driven lymphomas and overcomes mutated BTK$^{Cys481}$ ibrutinib resistance

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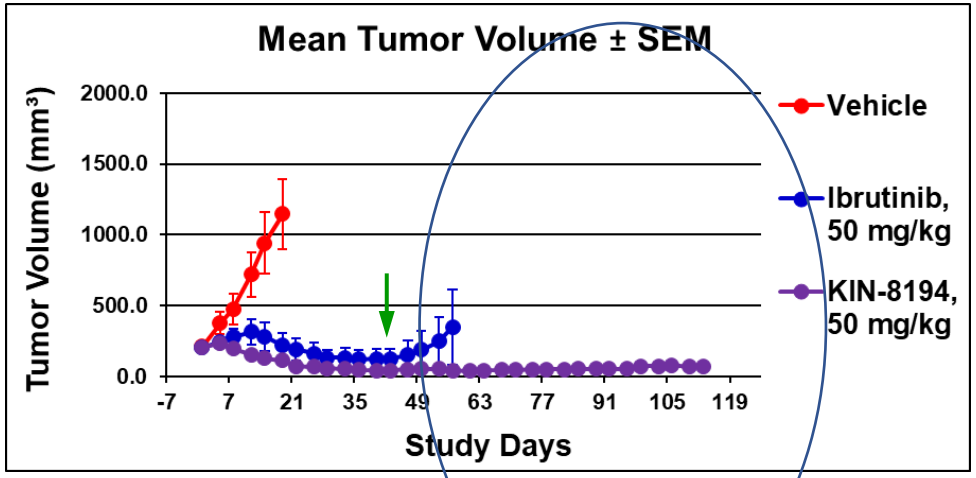
**KEY POINTS**

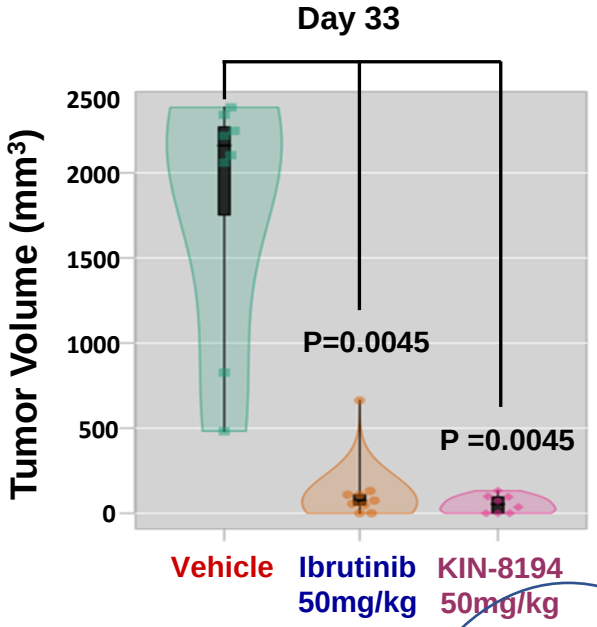
- KIN-8194 is a highly potent dual HCK and BTK inhibitor with superior antitumor activity over ibrutinib in MYD88-mutated B-cell lymphomas.
- KIN-8194 overcomes ibrutinib resistance with a survival benefit in TMD-8 ABC DLBCL xenografted mice and synergizes with venetoclax.

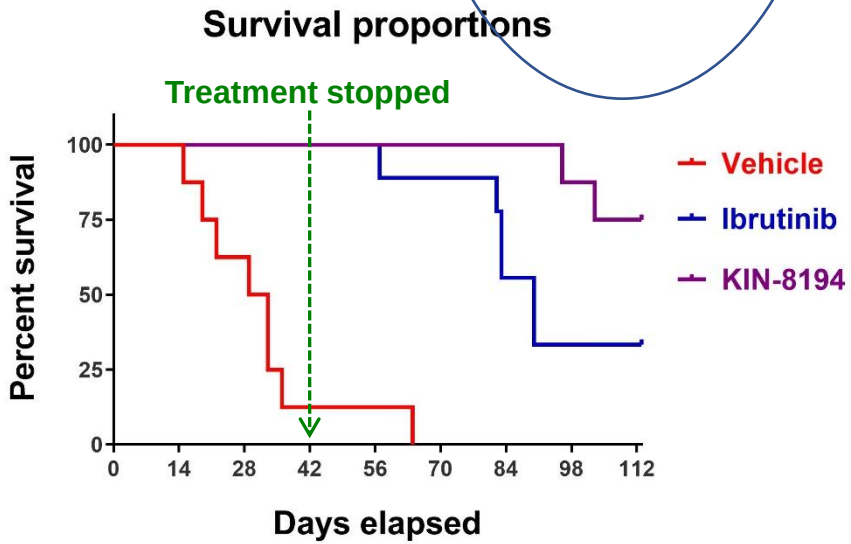
**Activating mutations in MYD88 promote malignant cell growth and survival through hematopoietic cell kinase (HCK)–mediated activation of Bruton tyrosine kinase (BTK). Ibrutinib binds to BTK$^{Cys481}$ and is active in B-cell malignancies driven by mutated MYD88. Mutations in BTK$^{Cys481}$, particularly BTK$^{Cys481Ser}$, are common in patients with acquired ibrutinib resistance. We therefore performed an extensive medicinal chemistry campaign and identified KIN-8194 as a novel dual inhibitor of HCK and BTK. KIN-8194 showed potent and selective in vitro killing of MYD88-mutated lymphoma cells, including ibrutinib-resistant BTK$^{Cys481Ser}$–expressing cells. KIN-8194 demonstrated excellent bioavailability and pharmacokinetic parameters, with good tolerance in rodent models at pharmacologically achievable and active doses. Pharmacodynamic studies showed sustained inhibition of HCK and BTK for 24 hours after single oral administration of KIN-8194 in an MYD88-mutated TMD-8 activated B-cell diffuse large B-cell lymphoma (ABC DLBCL) and BCWM.1 Waldenström macroglobulinemia (WM) xenografted mice with wild-type BTK (BTK$^{WT}$)– or BTK$^{Cys481Ser}$-expressing tumors. KIN-8194 showed superior survival benefit over ibrutinib in both BTK$^{WT}$- and BTK$^{Cys481Ser}$-expressing TMD-8 DLBCL xenografted mice, including sustained complete responses of >12 weeks off treatment in mice with BTK$^{WT}$-expressing TMD-8 tumors. The BCL_2 inhibitor venetoclax enhanced the antitumor activity of KIN-8194 in BTK$^{WT}$- and BTK$^{Cys481Ser}$-expressing MYD88-mutated lymphoma cells and markedly reduced tumor growth and prolonged survival in mice with BTK$^{Cys481Ser}$-expressing TMD-8 tumors treated with both drugs. The findings highlight the feasibility of targeting HCK, a key driver of mutated MYD88 pro-survival signaling, and provide a framework for the advancement of KIN-8194 for human studies in B-cell malignancies driven by HCK and BTK.**

| Kinases | Enzymatic IC50 (nM) | Kinase group | Kinase family |
|---|---|---|---|
| HCK | <0.495 | TK | SRC |
| BLK | <0.495 | TK | SRC |
| BTK | 0.915 | TK | TEC |
| LYN | 1.150 | TK | SRC |
| FRK | 1.400 | TK | SRC |
| ACK (TNK2) | 7.780 | TK | ACK |
| CSK | 16.100 | TK | CSK |
| ErbB2 | 52.600 | TK | EPH |
| ABL | 98.600 | TK | ABL |

# KIN-8194 EFFICACY STUDIES IN BTK WILD-TYPE TMD8 XENOGRAFTED MICE




| Median Survival | Vehicle | Ibrutinib (50mg/kg) | KIN-8194 (50mg/kg) |
|---|---|---|---|
| (days) | 31 | 90 | Undefined |

**Log-rank (Mantel-Cox) test, P<0.0001**

Yang et al, Blood 2021

# SCREENING APPROACH FOR BTK/HCK PROTACS

**Potency:**
BTK & HCK enzyme assays
**Cell based** (BCWM.1, TMD8)
**Efficacy**: cell viability, apoptosis
**Degradation**: BTK/HCK protein levels

**Selectivity**:
KINOMEScan
Proteomics

**In vivo studies**
**PK**: IV & PO dosing in mice
**PK/PD:** mouse xenograft model using TMD8 wt and BTK $^{C481S}$ mutant

**Dual BTK and HCK binders combined with virial linkers and E3 ligase binders.**

**~120 PROTACs synthesized and evaluated**

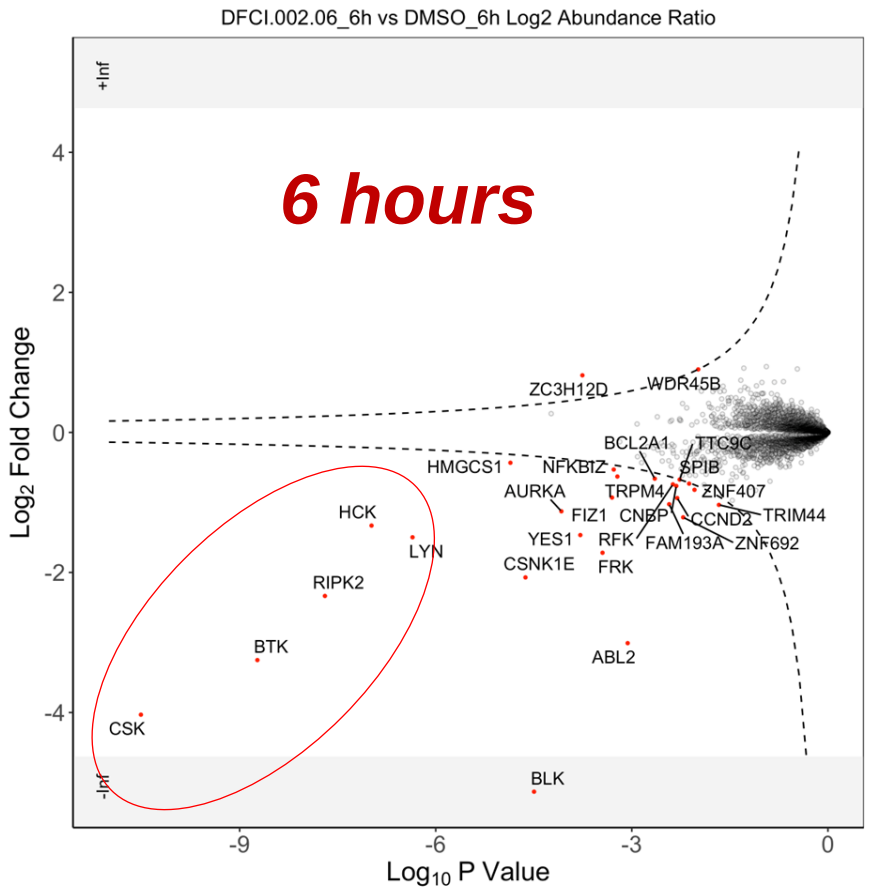
**Current lead** → **DFCI-002-06**
**MW 794**

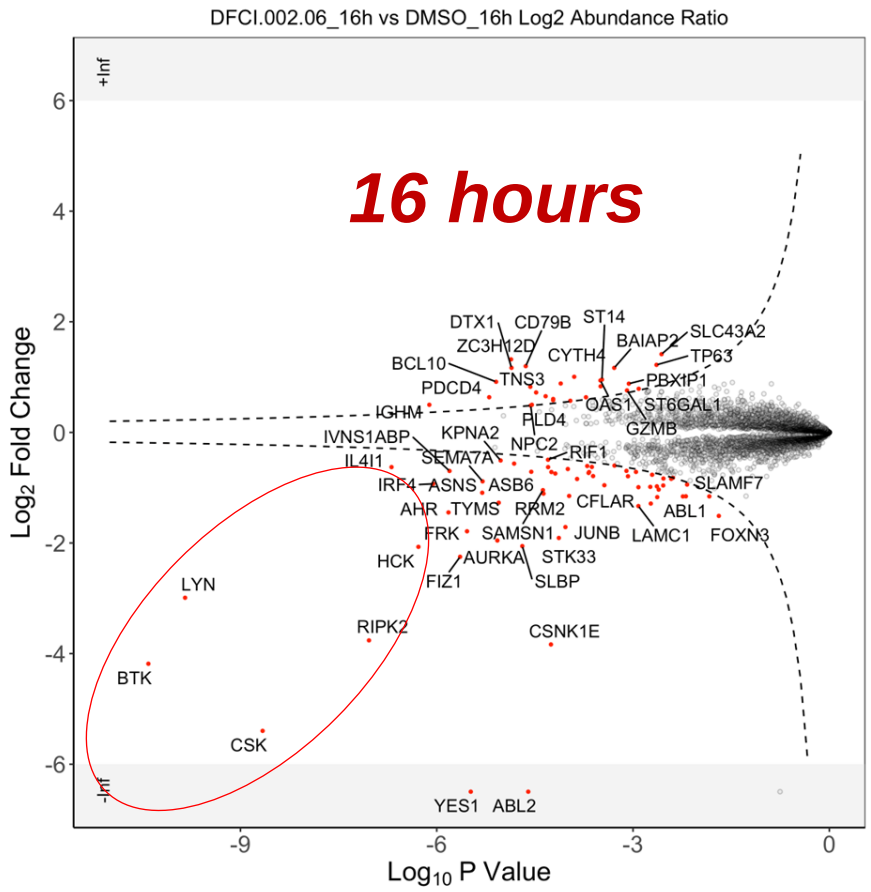
**John Hatcher, PhD**

**Sara Buhrlage, PhD**

**Jinhua Wang, PhD**

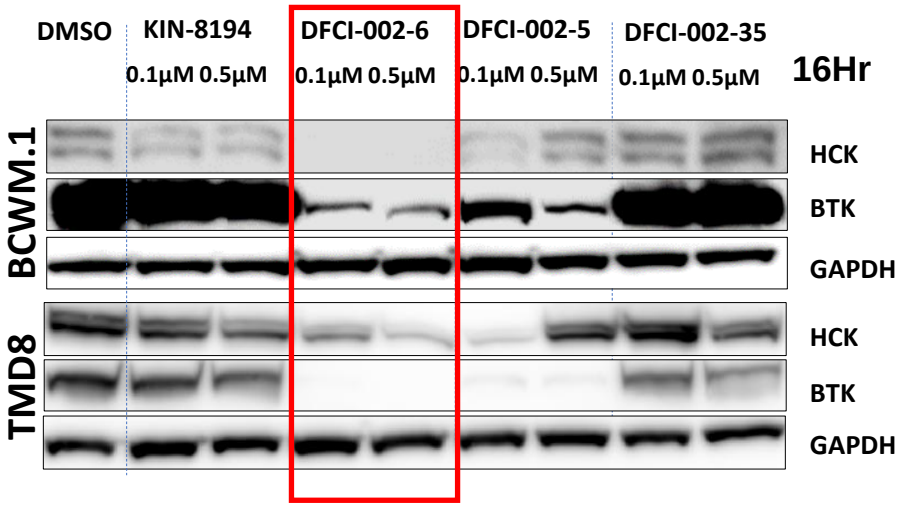
# DFCI-002-06 PROTEOMICS EVALUATION IN TMD8 CELLS

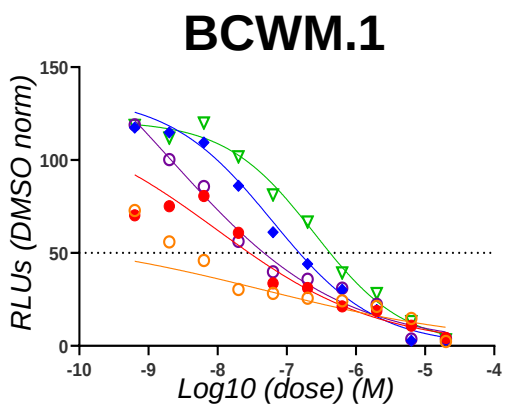


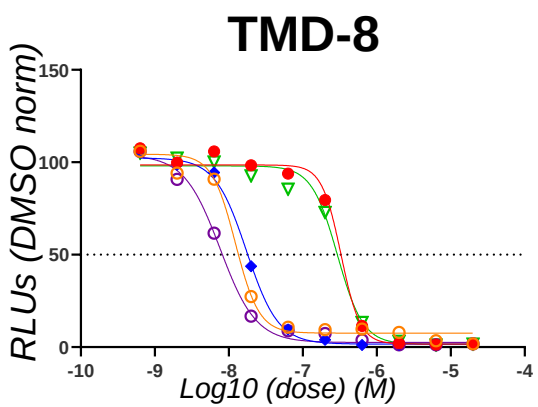




- **Proteomics testing of DFCI-002-06 at a concentration of 1µM in Molt4 cells shows HCK and BTK degradation and excellent selectivity.**
- **Only 3 off-targets show moderate degradation (LYN, RIPK2 and CSK).**

# ACTIVITY OF DFCI-002-06 IN BTK WT MYD88-MUTATED CELLS



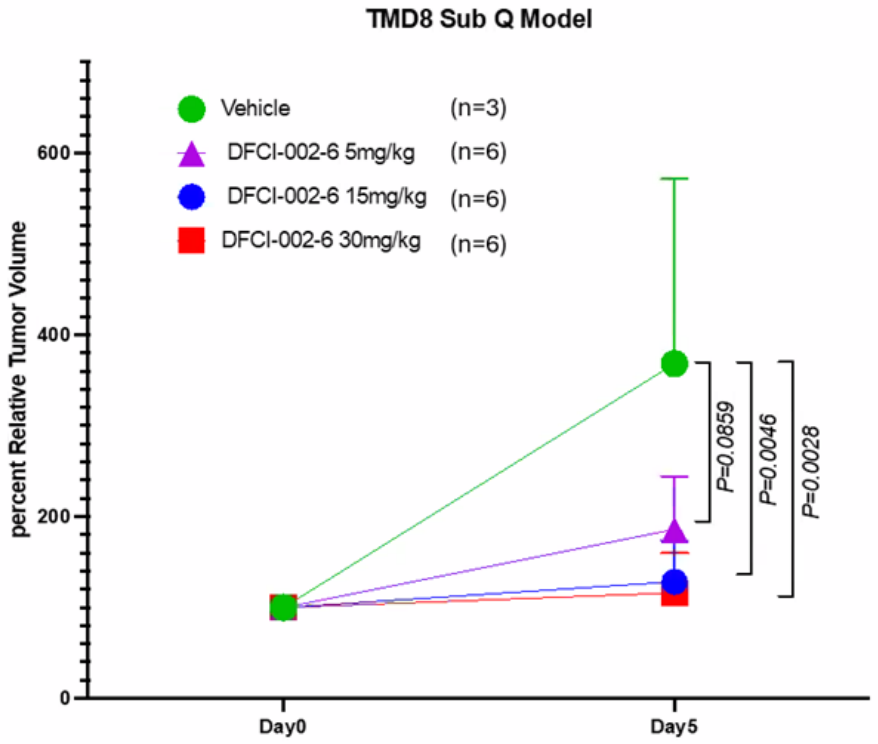



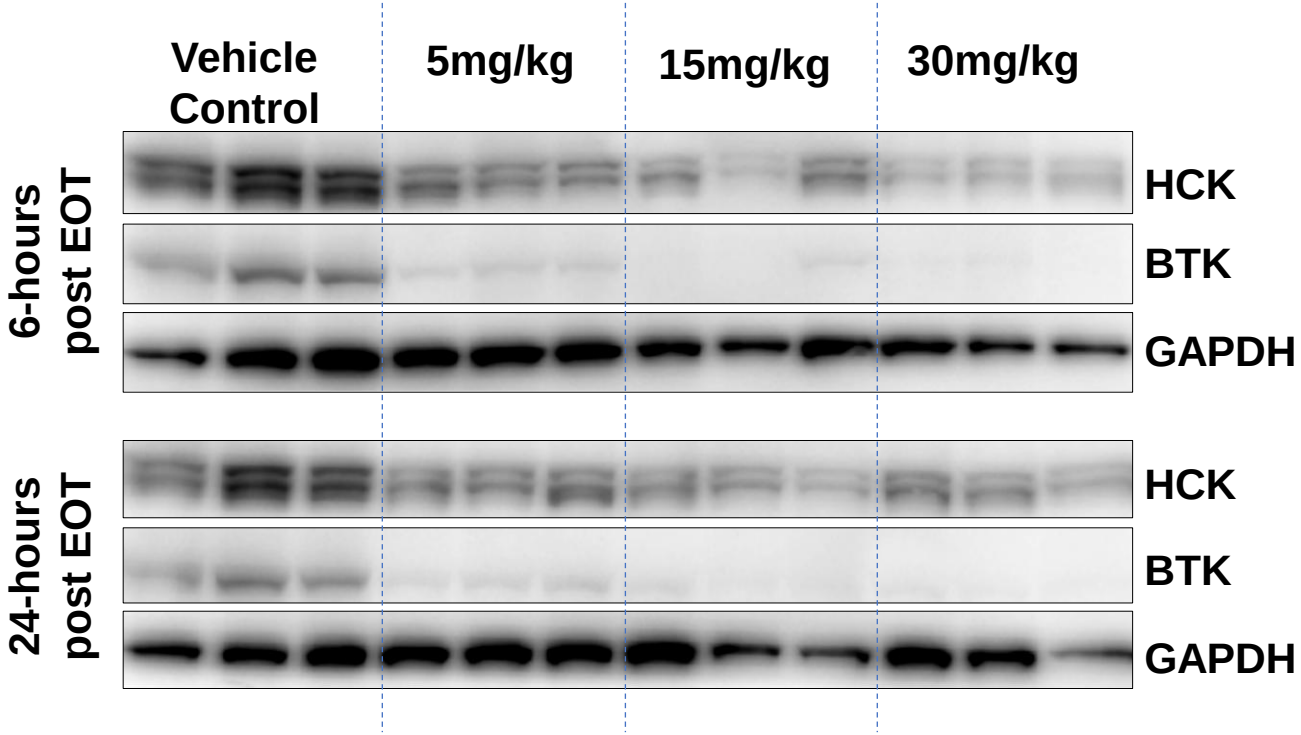




| | $EC_{50}$(nM) BCWM.1 | $EC_{50}$(nM) TMD8 | $IC_{50}$(nM) BTK (enzyme) | $IC_{50}$(nM) HCK (enzyme) |
|---|---|---|---|---|
| **KIN-8194** | 47 | 12 | 0.92 | <0.49 |
| **DFCI-002-4** | 10 | 329 | 2.8 | 1.4 |
| **DFCI-002-5** | 62 | 17 | 0.62 | <0.49 |
| **DFCI-002-6** | 2 | 8 | 0.52 | <0.49 |
| **DFCI-002-35 (Negative Ct)** | 250 | 294 | 0.88 | <0.49 |

Liu et al, ASH 2024

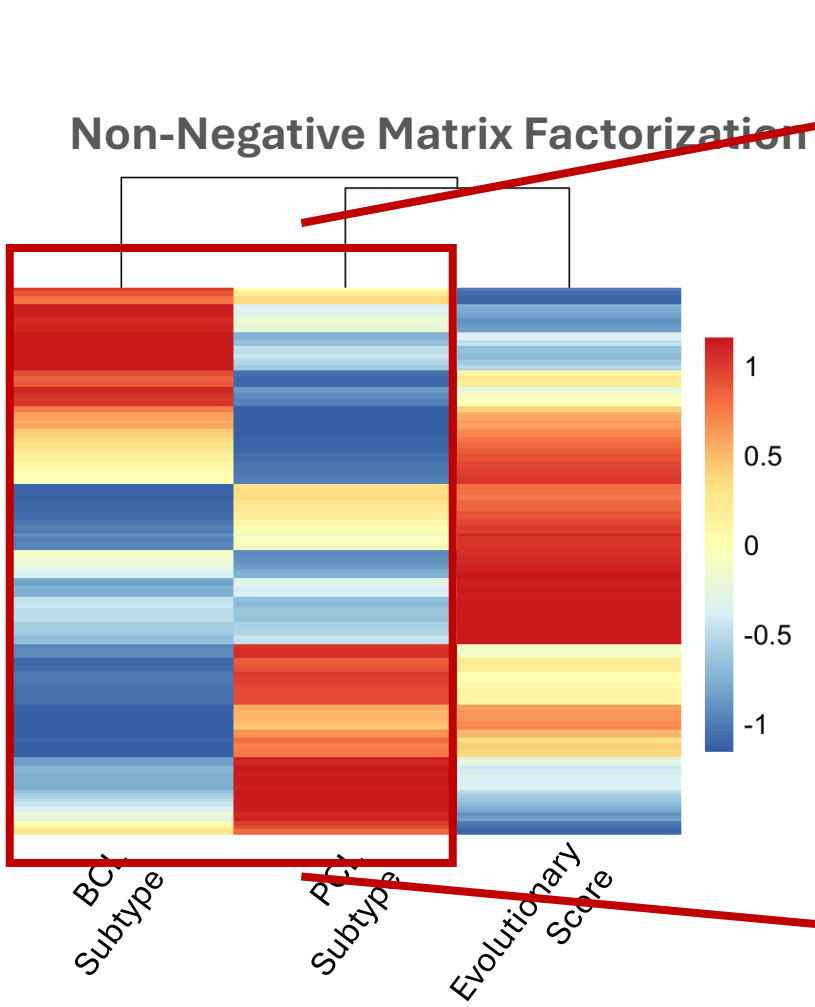
# ACTIVITY OF DFCI-002-06 IN TMD8 BTK WT XENOGRAFTED MURINE MODEL

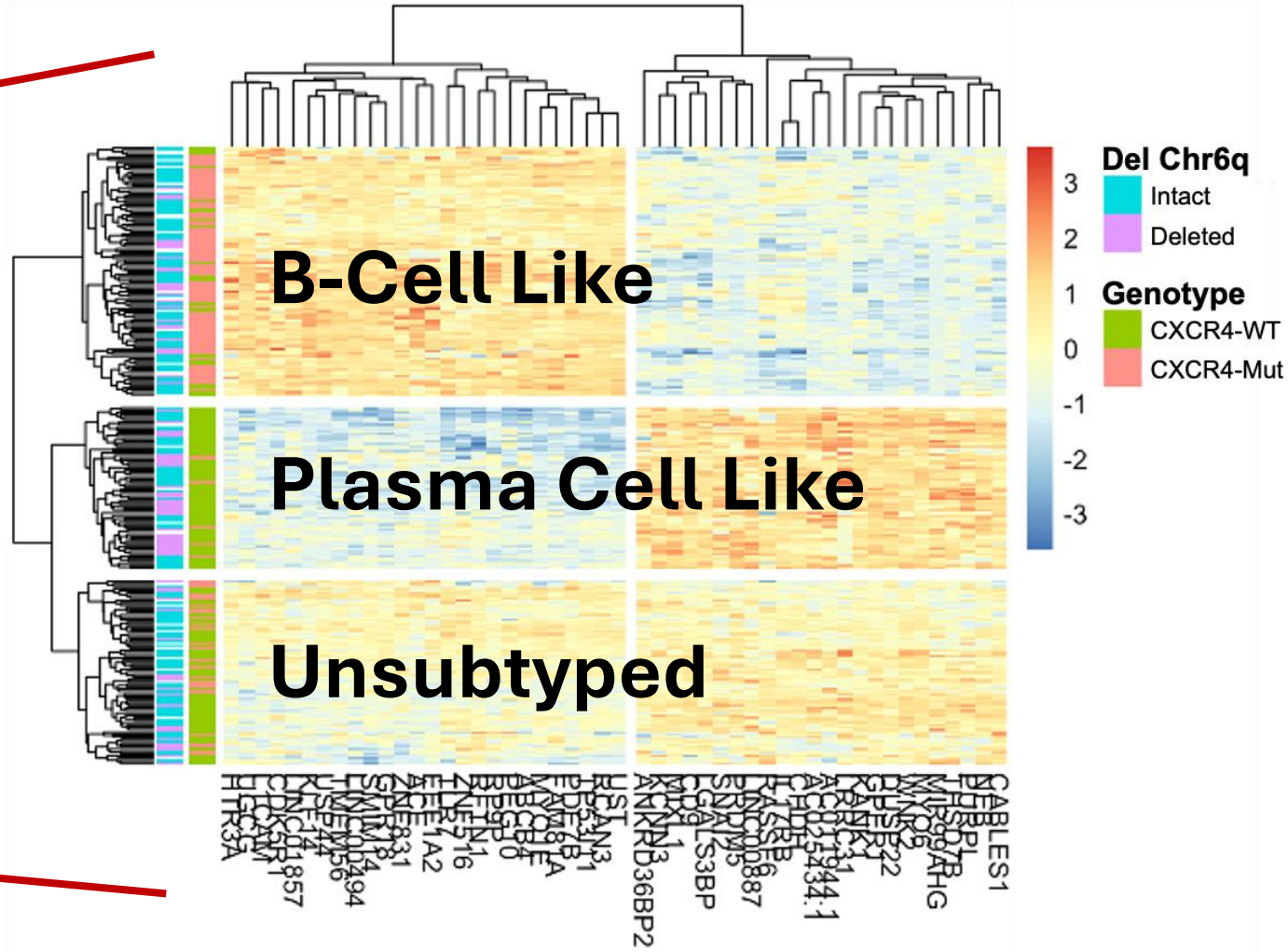



- DFCI-002-06 shows potent tumor growth suppression in mice xenografted with TMD8 cells following PO dose of 15mpk and 30mpk.
- Tissue analysis revealed potent degradation of both BTK and HCK 6hr and 24hr after the last dose.

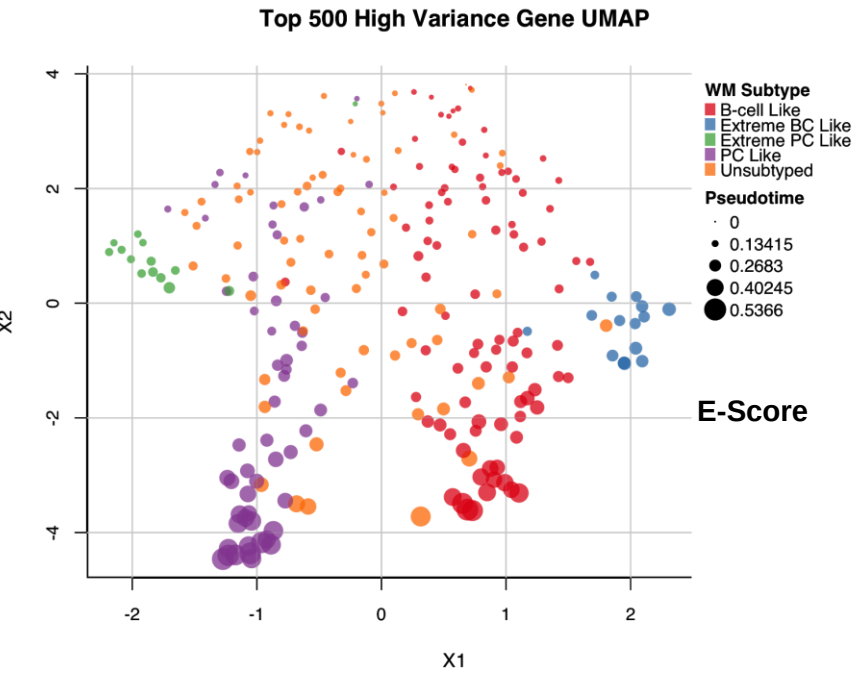
# 300 PROJECT: Modeling WM by Combining Multi-Omics and Pseudotime derived Tumor Evolution.




*Input: Top 1,000 high variance genes*

# SUBTYPES OF MYD88 MUTATED WM ARE ASSOCIATED WITH DISTINCT CLINICAL AND GENOMIC CHARACTERISTICS




## UNSUBTYPED (77/249; 31%)

- Concentrated in early pseudo-time values. Consistent with Smoldering WM. Appears to evolve into **BCL** or **PCL** over time.
- Intermediate expression of subtype associated genes

## B-CELL LIKE (BCL; 104/249; 42%)

- Subtype associated gene expression regressed to HD levels
- Mutations: **CXCR4 (80% vs. 7%); CD79B (9% vs. 3%);** Amp Chr18q (16% vs. 2%).
- Immunophenotype: CD5 (18% vs. 6%).

## PLASMA CELL LIKE (PCL; 68/249; 27%)

- Subtype associated gene expression becomes more extreme relative to HD levels
- Mutations: NOTCH1 (9.5% vs. 1.1%); EP300 (18% vs. 5%); Amp Chr6p (18% vs. 3%); Del **Chr6q (46% vs 28%); Del Chr17p (10% vs. 0%).**
- Immunophenotype: CD10 (12% vs. 1%);
- Clinical Presentation: Higher BM Involvement (70% vs. 40%);

*Note: Comparisons represent differences between the mature subtypes BCL/PCL*


# 13th International Workshop on Waldenstrom's Macroglobulinemia

## October 13-17, 2026

Ranjana Advani, Steve Ansell, Prashant Kapoor, Chairs

Palm Springs, California

http://waldenstromsworkshop.org