Updated Efficacy & Safety of Bruton Tyrosine Kinase Degrader BGB-16673 in Patients With Relapsed/Refractory Waldenström Macroglobulinemia: Ongoing Phase 1 CaDAnCe-101 Results

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CaDAnCe-101

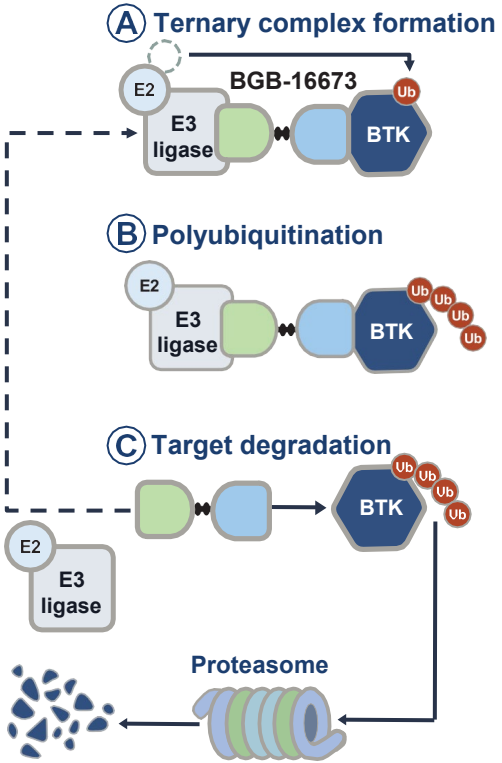
Presented at the International Conference on Malignant Lymphoma (ICML); June 17-21, 2025; Lugano, Switzerland
Data originally presented at EHA2025 Congress; June 12-15, 2025; Milan, Italy. Abstract S231

Disclosures for Anna Maria Frustaci

- **Honoraria, consulting, or advisory role:** AbbVie, BeOne Medicines Ltd, AstraZeneca, Janssen
- **Travel, accommodations, expenses:** AbbVie, BeOne Medicines Ltd, AstraZeneca

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 an orally available protein degrader that blocks BTK signaling by tagging BTK for degradation through the cell's proteasome pathway, leading to tumor regression[3]
- In preclinical models, BGB-16673 showed CNS penetration and degraded both wild-type and mutant BTK resistant to cBTK (C481S, C481F, C481Y, L528W, T474I) and ncBTK inhibitors (V416L, M437R, T474I, L528W)[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



BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CNS, central nervous system; ncBTK, noncovalent Bruton tyrosine kinase inhibitor; R/R, relapsed/refractory; ub, ubiquitin; WM, Waldenström macroglobulinemia.

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.

CaDAnCe-101: Phase 1/2, Open-Label, Dose-Escalation/Expansion Study in R/R B-Cell Malignancies

CaDAnCe-101 (BGB-16673-101, NCT05006716)

Key eligibility criteria for WM

- Met IWWM-7 criteria for treatment
- ≥2 prior therapies, includ. anti-CD20 monoclonal antibody & cBTK inhibitor (US & EU only)
- ECOG PS 0-2
- Adequate organ function

Key objectives: part 1

- **Primary:** safety[c] & tolerability, MTD, & RDFE
- **Secondary:** PK, PD, & preliminary antitumor activity[d]

Part 1: Monotherapy dose finding[a]

Part 1a: Dose escalation
Selected R/R B-cell malignancies
(MZL, FL, MCL, CLL/SLL, **WM**, DLBCL, RT)
n≤72
Oral, QD, 28-day cycle[b]
Doses: 50 mg, 100 mg, 200 mg, 350 mg, 500 mg, 600 mg

Part 1b: Safety expansion
Selected R/R B-cell malignancies
(MZL, MCL, CLL/SLL, **WM**)
n≤120

Part 1c: Additional safety expansion
Selected R/R B-cell malignancies
(MZL, **WM**, RT, DLBCL, FL)
n≤100

Part 1d: Additional safety expansion
R/R CLL/SLL
n≤30

Part 1e: Additional safety expansion
Selected R/R B-cell malignancies (Japan only)
(MZL, FL, MCL, CLL/SLL, WM)
n=6-9

Part 1f: Monotherapy safety expansion
Selected BTK inhibitor–naive B-cell malignancies
(MZL, MCL, CLL/SLL, WM, RT)
n≤40

Determination of BGB-16673 RDFE

Phase 2

- **Cohort 1**: Post BTK inhibitor, R/R CLL/SLL
- **Cohort 2**: Post BTK inhibitor, R/R MCL
- **Cohort 3**: Post BTK inhibitor, R/R WM
- **Cohort 4**: Post BTK inhibitor, R/R MZL
- **Cohort 5**: R/R FL
- **Cohort 6**: R/R non-GCB DLBCL
- **Cohort 7**: Post BTK inhibitor, R/R RT

[a]Data from gray portions of the figure are not included in this presentation. [b]Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. [c]Safety was assessed according to CTCAE v5.0. [d]Responses were assessed per IWWM-6, modified Owen 2013 criteria after 4 weeks.
BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CTCAE, Common Terminology Criteria for Adverse Events; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; GCB, germinal center B cell; IWWM, International Workshop on Waldenström Macroglobulinemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; QD, daily; PD, pharmacodynamics; PK, pharmacokinetics; RDFE, recommended dose for expansion; R/R, relapsed/refractory; RT, Richter transformation; WM, Waldenström macroglobulinemia.

Baseline Patient Characteristics

Heavily pretreated with high rate of poor risk features

	Total (N=36)
Age, median (range), years	72.0 (49-81)
Male, n (%)	22 (61.1)
ECOG PS, n (%)	
0	17 (47.2)
1	17 (47.2)
2	2 (5.6)
Hemoglobin, median (range), g/L	102 (60-146)
Hemoglobin ≤110 g/L, n/N with known status (%)	25/34 (73.5)
Neutrophils, median (range), 10^9/L	2.6 (0.2-7.4)
Neutrophils ≤1.5×10^9/L, n/N with known status (%)	11/33 (33.3)
Platelets, median (range), 10^9/L	153.5 (14.0-455.0)
IgM, median (range), g/L	35.1 (0.3-92.6)

	Total (N=36)
Mutation status, n/N with known status (%)[a]	
MYD88 mutation present	31/35 (88.6)
CXCR4 mutation present	19/35 (54.3)
BTK mutation present	11/31 (35.5)
TP53 mutation present	16/31 (51.6)
No. of prior lines of therapy, median (range)	3 (1-11)
Prior therapy, n (%)	
cBTK inhibitor	36 (100)
Anti-CD20 antibody	36 (100)
Chemotherapy	34 (94.4)
Proteasome inhibitor	11 (30.6)
BCL2 inhibitor	9 (25.0)
ncBTK inhibitor[b]	7 (19.4)
Discontinued prior BTK inhibitor due to PD, n (%)	30 (83.3)

Data cutoff: March 3, 2025.

[a]Confirmed by central laboratory. [b]All seven patients with ncBTK inhibitor exposure were also exposed to a cBTK inhibitor.

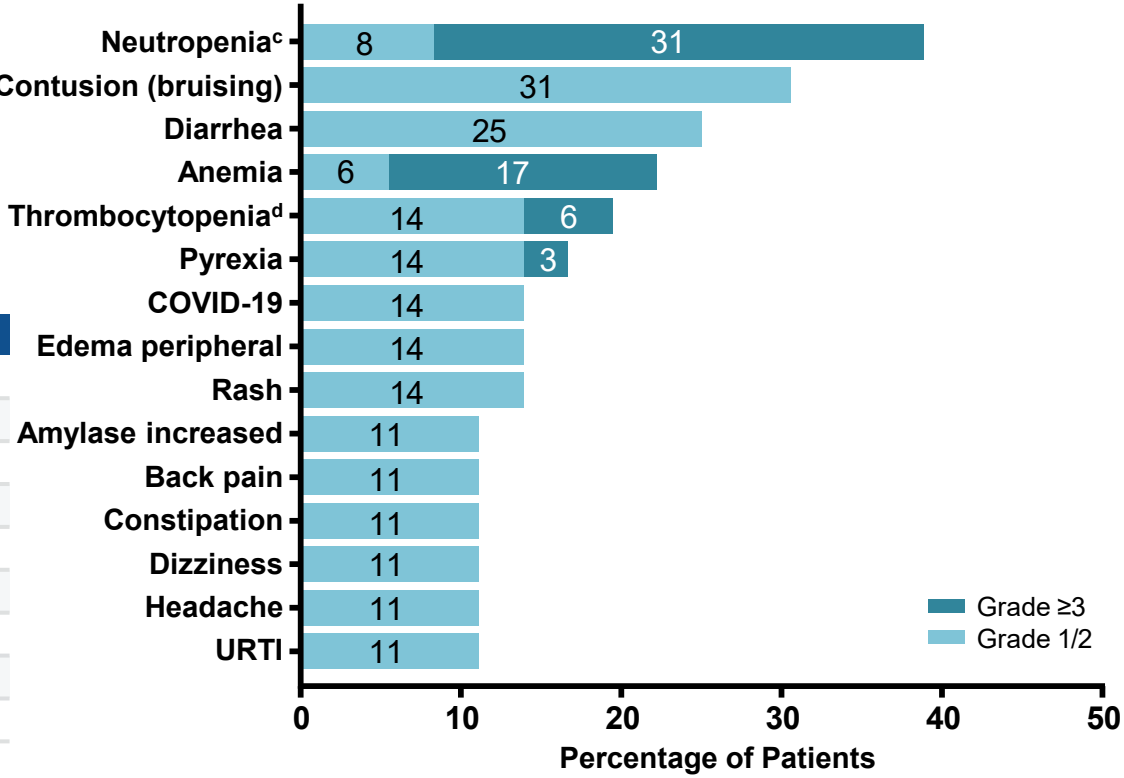
BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; cBTK, covalent BTK; ECOG PS, Eastern Cooperative Oncology Group performance status; IgM, immunoglobulin M; ncBTK, noncovalent BTK; PD, progressive disease; WM, Waldenström macroglobulinemia.

Safety Summary and All-Grade TEAEs in ≥10% of All Patients

Well tolerated with no treatment-related TEAEs leading to death

- Most common TEAEs were neutropenia in 39% and contusion (bruising) in 31% of patients
- No atrial fibrillation, major hemorrhage[a], febrile neutropenia, or pancreatitis

Patients, n (%)	Total (N=36)
Any TEAE	32 (88.9)
Any treatment-related	25 (69.4)
Grade ≥3	22 (61.1)
Treatment-related grade ≥3	14 (38.9)
Serious	12 (33.3)
Treatment-related serious	4 (11.1)
Leading to death[b]	1 (2.8)
Treatment-related leading to death	0
Leading to treatment discontinuation	2 (5.6)



Data cutoff: March 3, 2025. Median follow-up: 8.2 months (range, 0.6-30.6 months).

[a]Grade ≥3, serious, or any central nervous system bleeding. [b]Septic shock (200-mg dose level), note in the context of PD. [c]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [d]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

IgM, immunoglobulin M; PD, progressive disease; PR, partial response; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Overall Response Rate

High response rates across all risk groups

- Responses were observed at all dose levels and in patients with prior chemoimmunotherapy (25/30), cBTK inhibitor (27/32), or ncBTK inhibitor (4/4)

	Total (N=32)[a]
Best overall response, n (%)	
VGPR	10 (31.3)
PR	14 (43.8)
MR	3 (9.4)
SD	3 (9.4)
PD	1 (3.1)
Discontinued prior to first assessment	1 (3.1)
ORR, n (%)[b]	27 (84.4)
Major response rate, n (%)[c]	24 (75.0)
Time to first response, median (range), months[d]	1.0 (0.9-3.7)

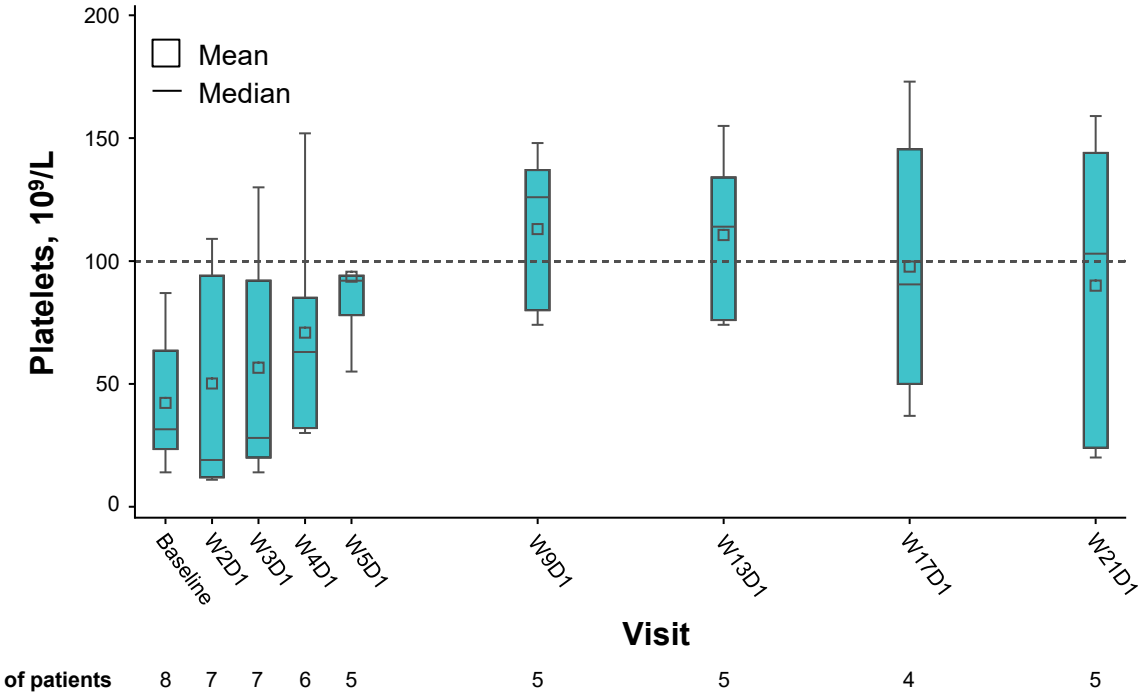
Mutation status, n/N tested (%)	ORR (N=32)[a]
BTK	
Mutated	11/11 (100)
Unmutated	15/19 (78.9)
Unknown	1/2 (50.0)
MYD88	
Mutated	25/28 (89.3)
Unmutated	2/3 (66.7)
Unknown	0/1 (0)
CXCR4	
Mutated	16/17 (94.1)
Unmutated	11/14 (78.6)
Unknown	0/1 (0)
TP53	
Mutated	15/15 (100)
Unmutated	11/15 (73.3)
Unknown	1/2 (50.0)

[a]Efficacy-evaluable population; 4 patients were too early in treatment course to be response-evaluable. [b]Includes best overall response of MR or better. [c]Includes best overall response of PR or VGPR.
[d]In patients with a best overall response better than SD.
BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; MR, minor response; ncBTK, noncovalent Bruton tyrosine kinase; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Rapid and Significant Cytopenia Improvement Was Observed in Patients With Treatment Response

	Baseline	W9D1
Neutrophil count, median, 10^9/L	0.9	1.1
Hemoglobin level, median, g/L	98.0	114.0
Platelet count, median, 10^9/L	39.5	126.0

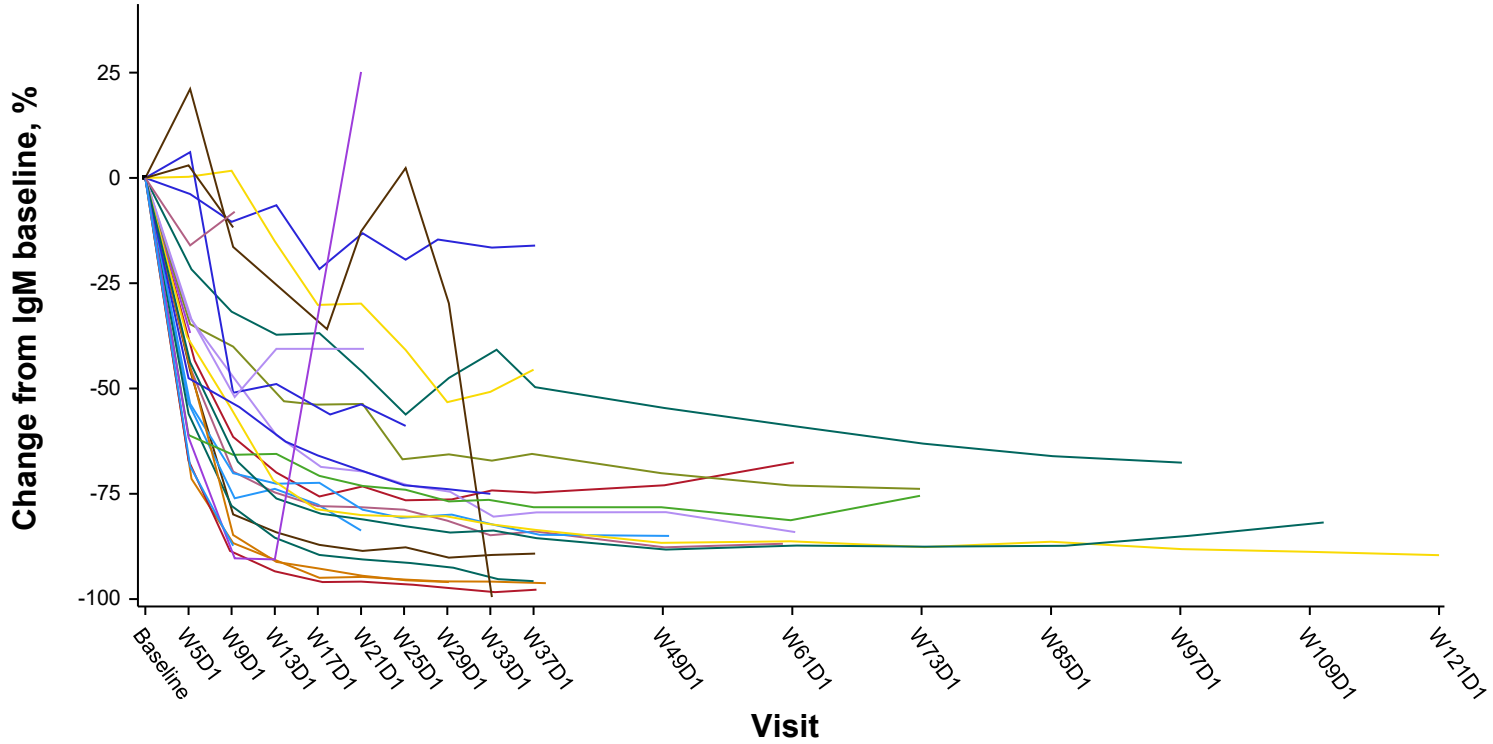
Platelet Count in Patients With WM Who Had Baseline Thrombocytopenia and Whose Disease Responded to Treatment



D, day; W, week; WM, Waldenström macroglobulinemia.

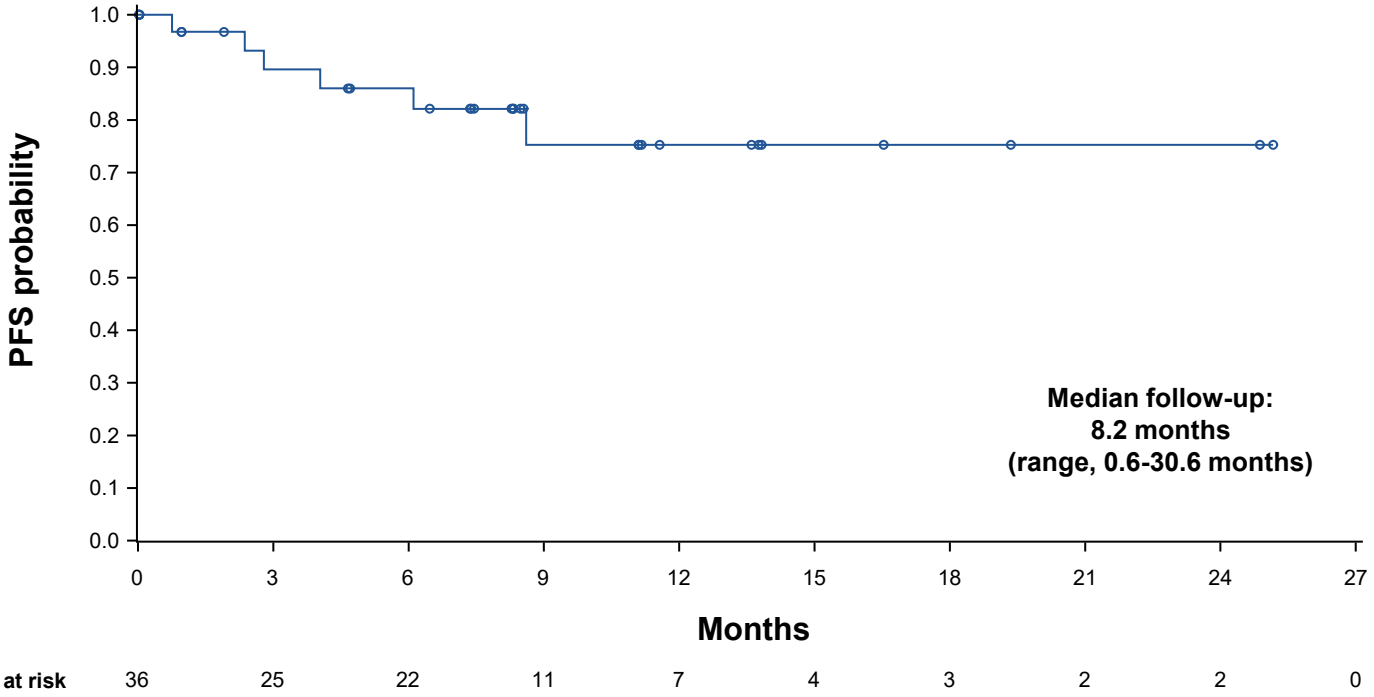
IgM Decreased in All Patients

Rapid and sustained decrease in IgM in most patients



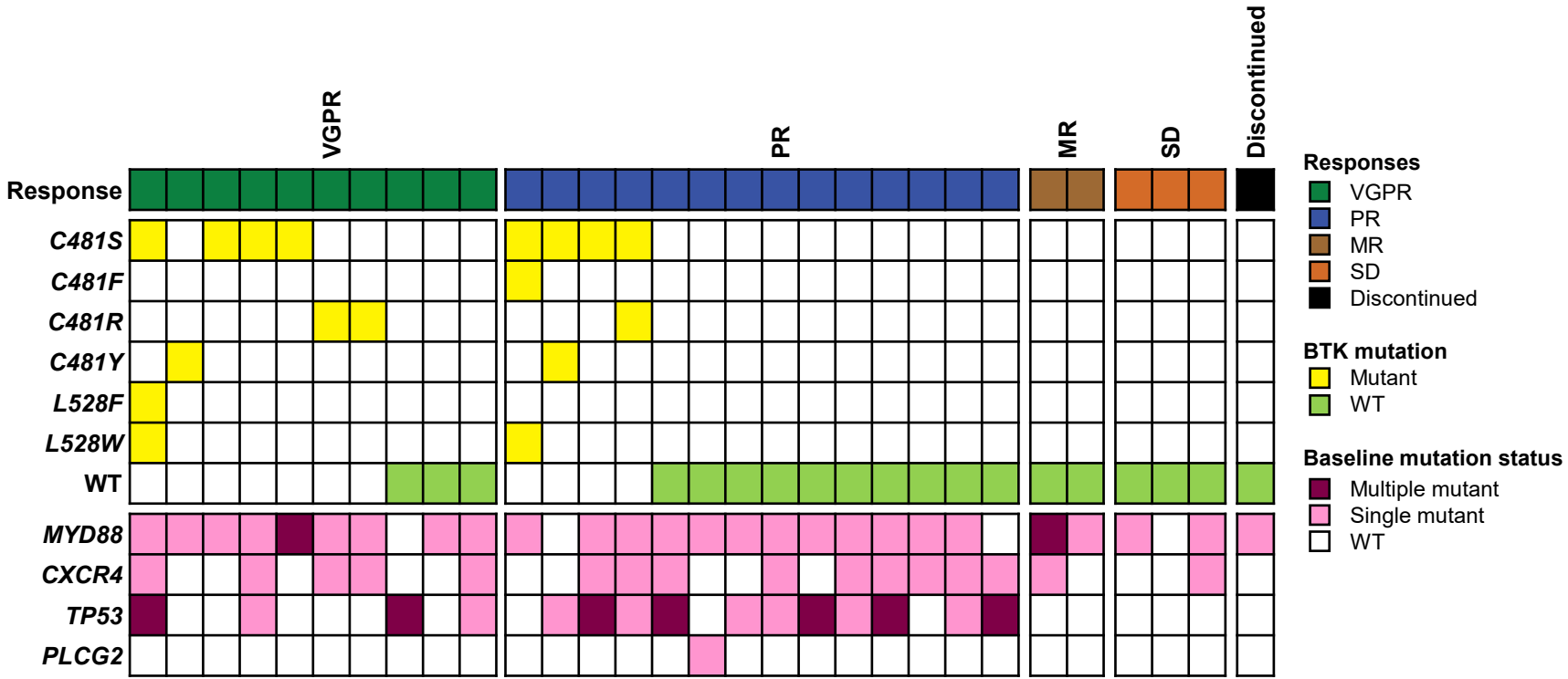
Patient with rapid IgM increase had *BTK, MYD88, CXCR4*, and *TP53* mutations at baseline, paused treatment for 2-3 weeks due to COVID-19 infection, and developed rapid progression shortly after restarting treatment.
D, day; IgM, immunoglobulin M; W, week.

Median PFS Was Not Reached



PFS, progression-free survival.

Responses Occurred Regardless of Baseline Mutations (Best Overall Response vs Baseline Mutation)[a]



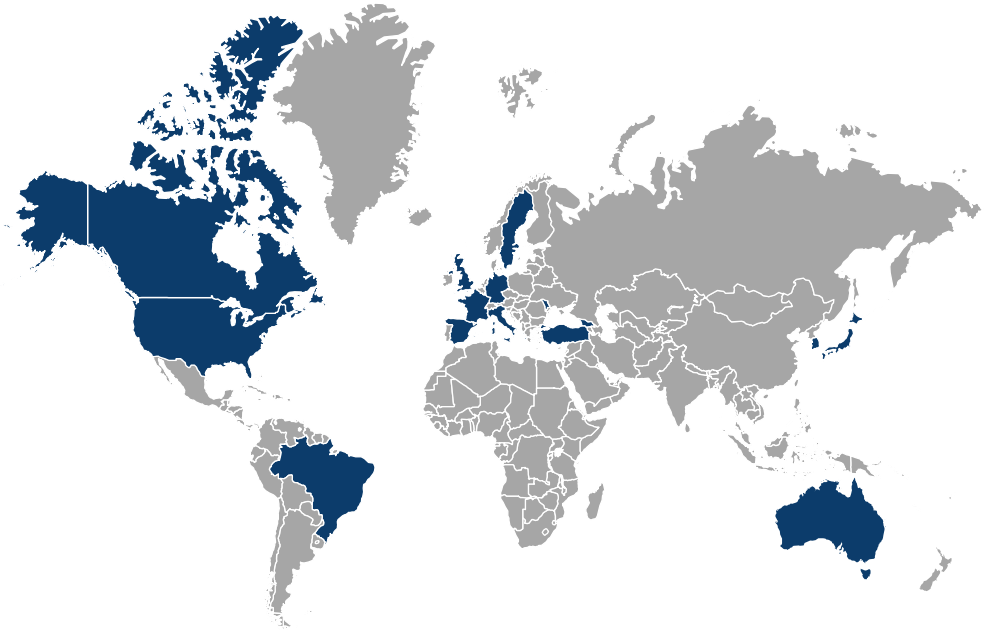
[a]Genomic mutations were centrally assessed by targeted next-generation sequencing.
BTKi, Bruton tyrosine kinase inhibitor; MR, minor response; NE, not evaluable; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild type.

Conclusions

- In phase 1 of CaDAnCe-101, the BTK degrader **BGB-16673** was **well tolerated** in **heavily pretreated** patients with R/R **WM**
  - Only two patients discontinued treatment due to TEAEs
- Promising **antitumor activity** was observed, including in patients with **BTK inhibitor–resistant mutations**, ***TP53*** **and** ***CXCR4*** **mutations**, and those **previously exposed to chemoimmunotherapy, cBTK inhibitors, and ncBTK inhibitors**
  - VGPR 31.3% (10/32); ORR 84.4% (27/32)
  - Rapid decline in IgM, with median time to first response of 1.0 month
  - Rapid improvement in cytopenias seen in responding patients
  - Responses continue to deepen (median follow-up, 8.2 months)
- Based on the totality of data available, **BGB-16673** is being evaluated in an **ongoing phase 2** study in **R/R WM**

CaDAnCe-101 Study Sites (Recruiting)

- Enrollment for CaDAnCe-101 phase 1 and phase 2 is ongoing at >100 study sites across the US, Canada, the UK, France, Georgia, Germany, Italy, Moldova, Spain, Sweden, Turkey, Australia, South Korea, Brazil, and Japan



Acknowledgments

- The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers
- This study was sponsored by BeOne Medicines Ltd
- Medical writing was provided by Brittany Gifford, PharmD, of Nucleus Global, an Inizio company, and supported by BeOne Medicines

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