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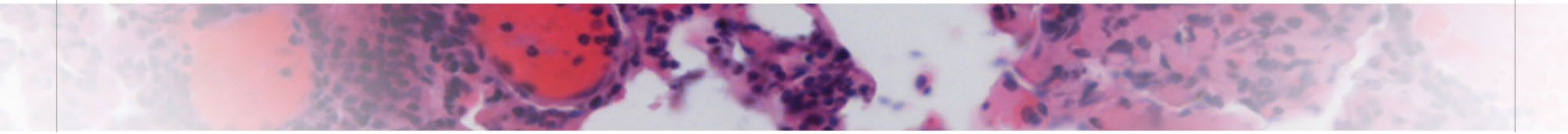

Preliminary Efficacy and Safety of the Bruton Tyrosine Kinase Degrader BGB-16673 in Patients With Relapsed or Refractory Waldenström Macroglobulinemia: Results From the Phase 1 CaDAnCe-101 Study

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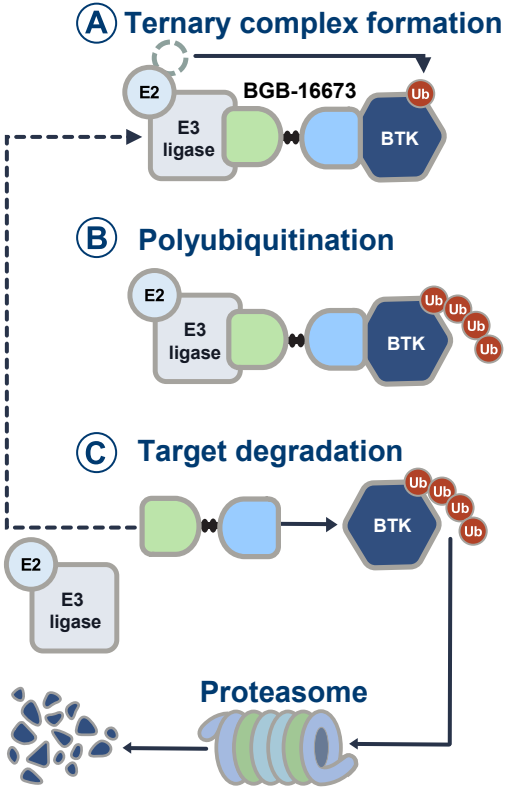
CaDAnCe-101

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.

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

- Histologically confirmed, meeting IWWM-7 criteria for treatment
- ≥2 prior therapies, including anti-CD20 monoclonal antibody and cBTK inhibitor (US and EU only)
- ECOG PS 0-2
- Adequate organ function

Key study objectives for part 1

- **Primary:** safety[c] and tolerability, MTD, and RP2D
- **Secondary:** PK, PD, and 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 meeting other criteria for treatment discontinuation. [c] Safety was assessed according to CTCAE v5.0; DLTs were assessed during the first 4 weeks of part 1a. [d] Responses were assessed per IWWM-6, modified Owen 2013 criteria after 4 weeks. cBTK, covalent BTK; GCB, germinal center B cell; RT, Richter transformation.

Baseline Patient Characteristics

Heavily pretreated with high rate of WM mutations

	Total (N=27)
Age, median (range), years	73.0 (56-81)
Male, n (%)	15 (55.6)
ECOG PS, n (%)	
0	14 (51.9)
1	12 (44.4)
2	1 (3.7)
Hemoglobin, median (range), g/dL	10.3 (6.0-13.5)
Neutrophils, median (range), 10^9/L	2.7 (0.21-7.43)
Platelets, median (range), 10^9/L	157 (14-455)
Mutation status, n/N with known status (%)[a]	
MYD88 mutation present	24/26 (92.3)
CXCR4 mutation present	12/25 (48.0)
BTK mutation present	11/25 (44.0)
TP53 mutation present	13/25 (52.0)

	Total (N=27)
IgM, median (range), g/L	37.4 (2.8-74.4)
No. of prior lines of therapy, median (range)	3.0 (2-11)
Prior therapy, n (%)	
cBTK inhibitor	27 (100)
Chemotherapy	25 (92.6)
Proteasome inhibitor	9 (33.3)
BCL2 inhibitor	5 (18.5)
ncBTK inhibitor[b]	4 (14.8)
Discontinued prior BTK inhibitor due to PD, n (%)	21 (77.8)

Data cutoff: September 2, 2024.

[a] Confirmed by central laboratory. [b] All 4 patients with ncBTK inhibitor exposure were exposed to a cBTK inhibitor.

cBTK, covalent BTK; IgM, immunoglobulin M; ncBTK, noncovalent BTK.

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

Well tolerated with no AEs leading to treatment discontinuation

- No DLTs[a]
- No cases of atrial fibrillation, hypertension, major hemorrhage,[b] febrile neutropenia, or pancreatitis
- One patient had IgM flare and/or rebound 1 week after starting treatment (went on to develop PR)

Patients, n (%)	Total (N=27)
Any TEAE	25 (92.6)
Any treatment-related	19 (70.4)
Grade ≥3	11 (40.7)
Treatment-related grade ≥3	7 (25.9)
Serious	7 (25.9)
Treatment-related serious	2 (7.4)
Leading to death[c]	1 (3.7)
Treatment-related leading to death	0
Leading to treatment discontinuation	0

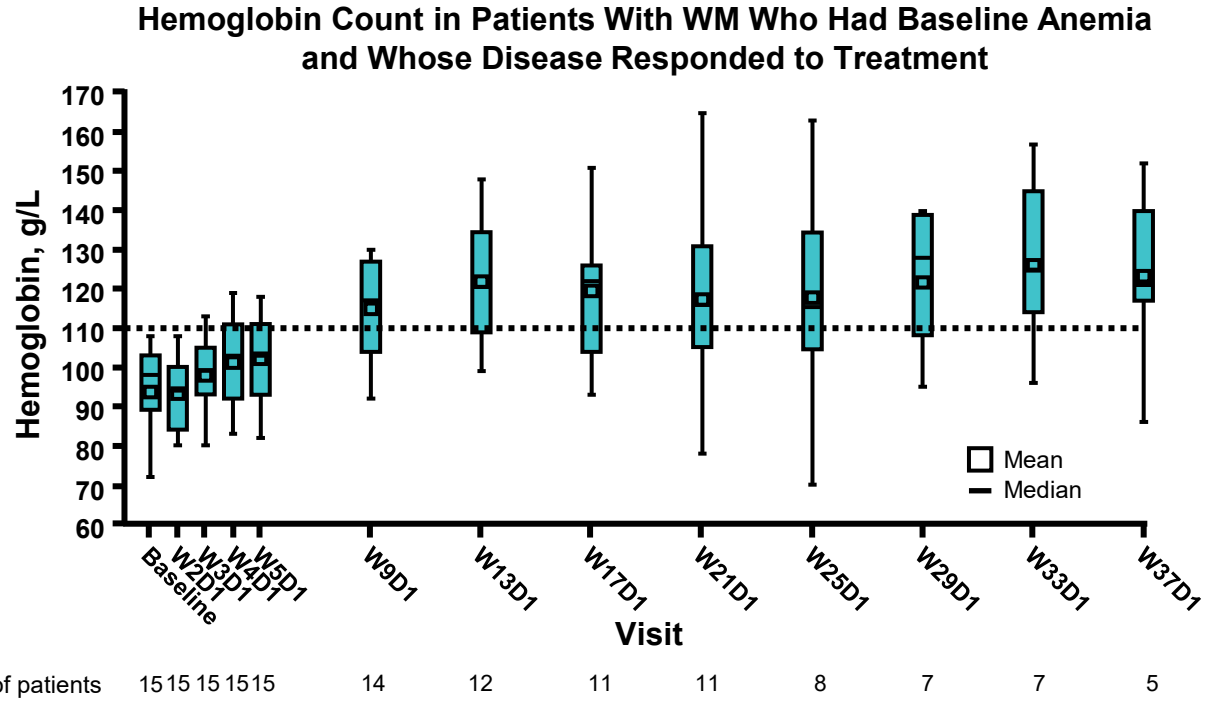
Patients, n (%)	Total (N=27)	
	All Grade	Grade ≥3
Neutropenia[d]	8 (29.6)	7 (25.9)
Diarrhea	7 (25.9)	0
Anemia	5 (18.5)	3 (11.1)
Contusion (bruising)	5 (18.5)	0
Rash	5 (18.5)	0
Thrombocytopenia[e]	5 (18.5)	2 (7.4)
Amylase increased	4 (14.8)	0
Dizziness	4 (14.8)	0
Pyrexia	4 (14.8)	1 (3.7)
Arthralgia	3 (11.1)	0
Constipation	3 (11.1)	0
COVID-19	3 (11.1)	0
Fall	3 (11.1)	0
Headache	3 (11.1)	0
Lipase increased	3 (11.1)	1 (3.7)
Muscle spasms	3 (11.1)	0
Petechiae	3 (11.1)	0
Upper respiratory tract infection	3 (11.1)	0

Data cutoff: September 2, 2024. Median follow-up: 5.0 months (range, 0.8-24.6+).

[a] DLTs were only assessed during the first 4 weeks of part 1a. [b] Grade ≥3, serious, or any central nervous system bleeding. [c] Septic shock (200-mg dose level), note in the context of PD. [d] Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [e] Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.

In Patients With Disease Response, There Was Rapid And Significant Improvement of Cytopenias

	Baseline	W9D1
Neutrophil count, median, 10^9/L	0.49	1.05
Hemoglobin level, median, g/L	98	117
Platelet count, median, 10^9/L	38	131.5



Overall Response Rate

High response rates across all risk groups

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

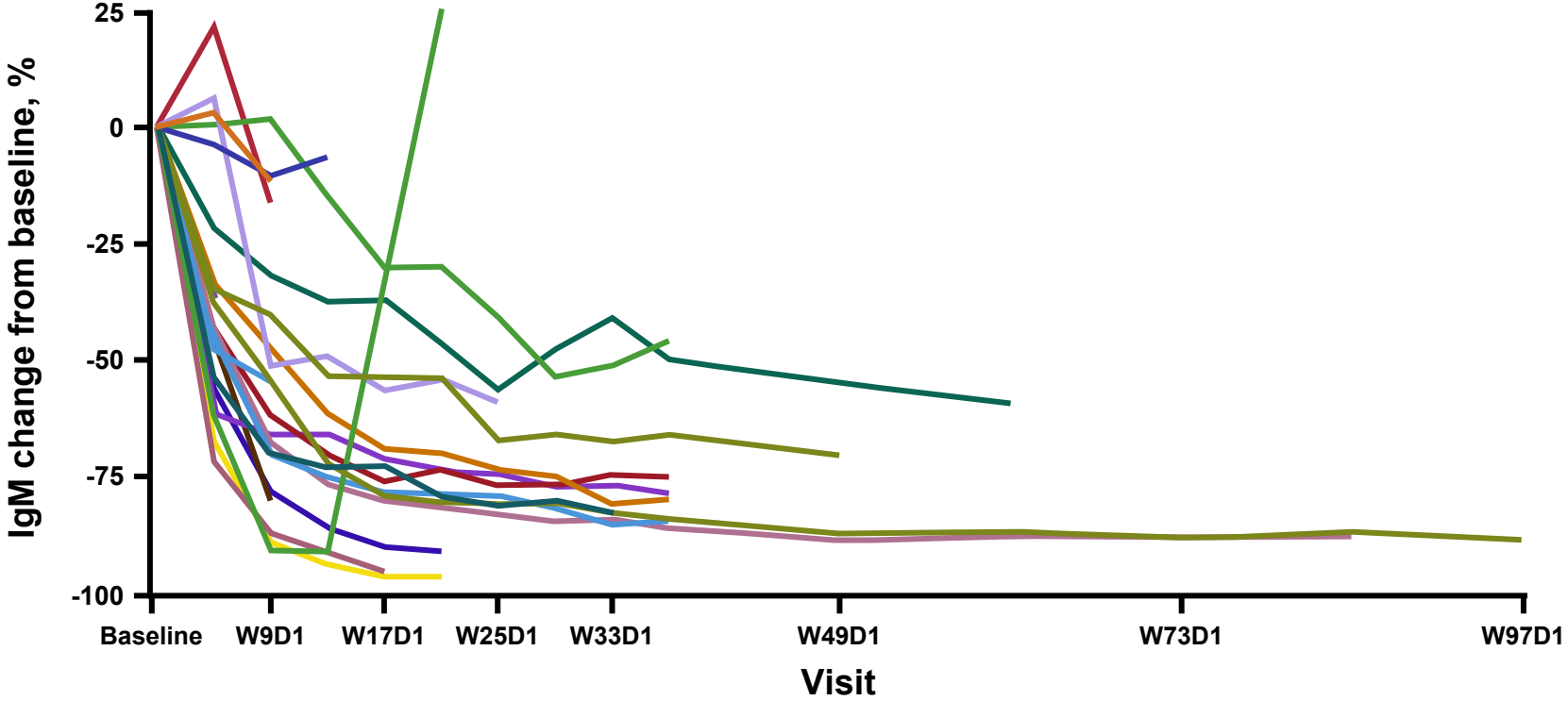
	Total[a] (N=27)
Best overall response, n (%)	
VGPR	7 (25.9)
PR	13 (48.1)
MR	2 (7.4)
SD	3 (11.1)
Not evaluable	1 (3.7)
Discontinued prior to first assessment	1 (3.7)
ORR, n (%)[b]	22 (81.5)
Major response rate, n (%)[c]	20 (74.1)
Disease control rate (DCR), n (%)[d]	25 (93.0)
Follow-up, median (range), 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] Efficacy-evaluable population. [b] Includes best overall response of MR or better. [c] Includes best overall response of PR or VGPR. [d] Includes best overall response of SD or better.
[e] In patients with a best overall response better than SD.
cBTK, covalent BTK; MR, minor response; ncBTK, noncovalent BTK; VGPR, very good partial response.

IgM Decreased in All Patients

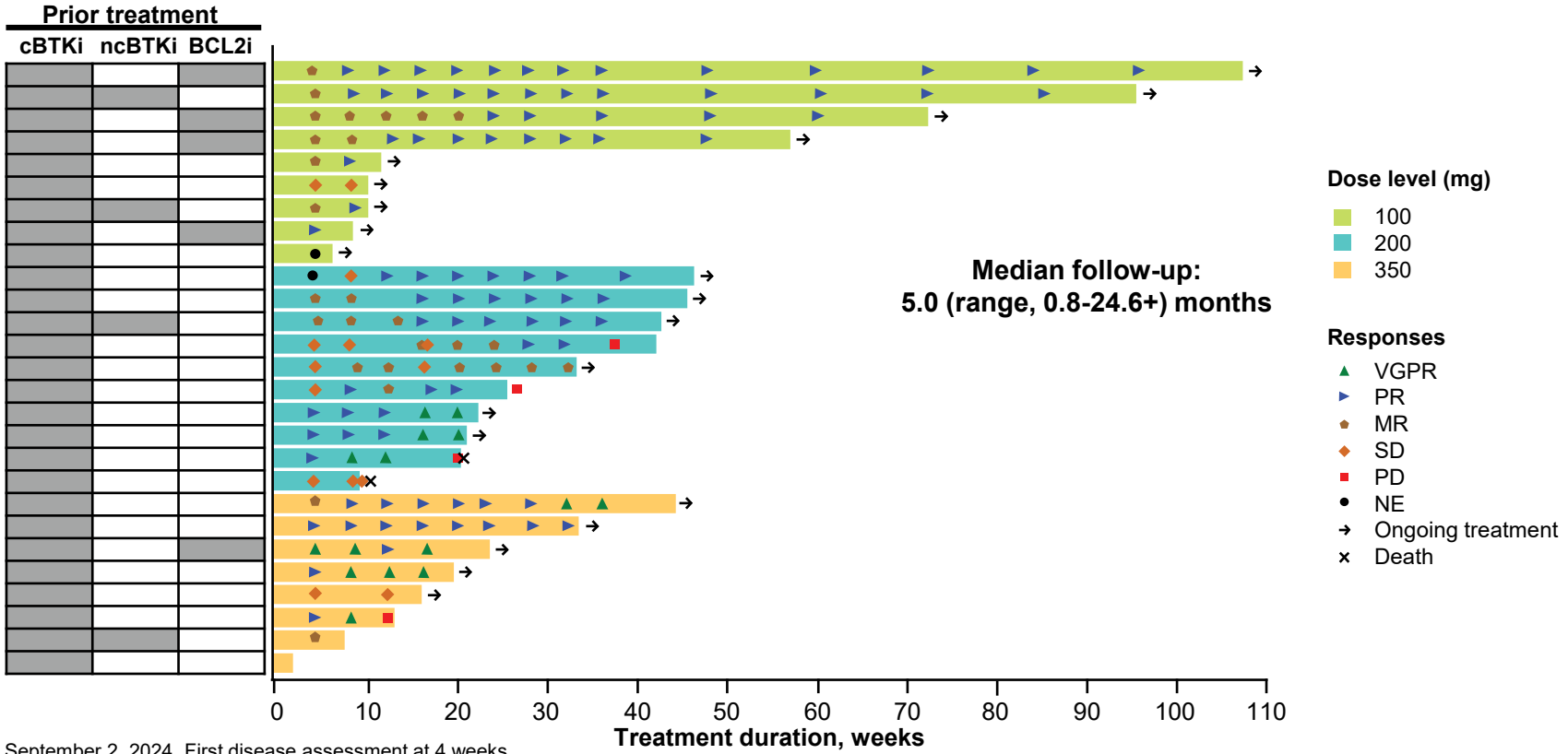
Rapid decline in IgM at all dose levels



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

Treatment Duration and Response

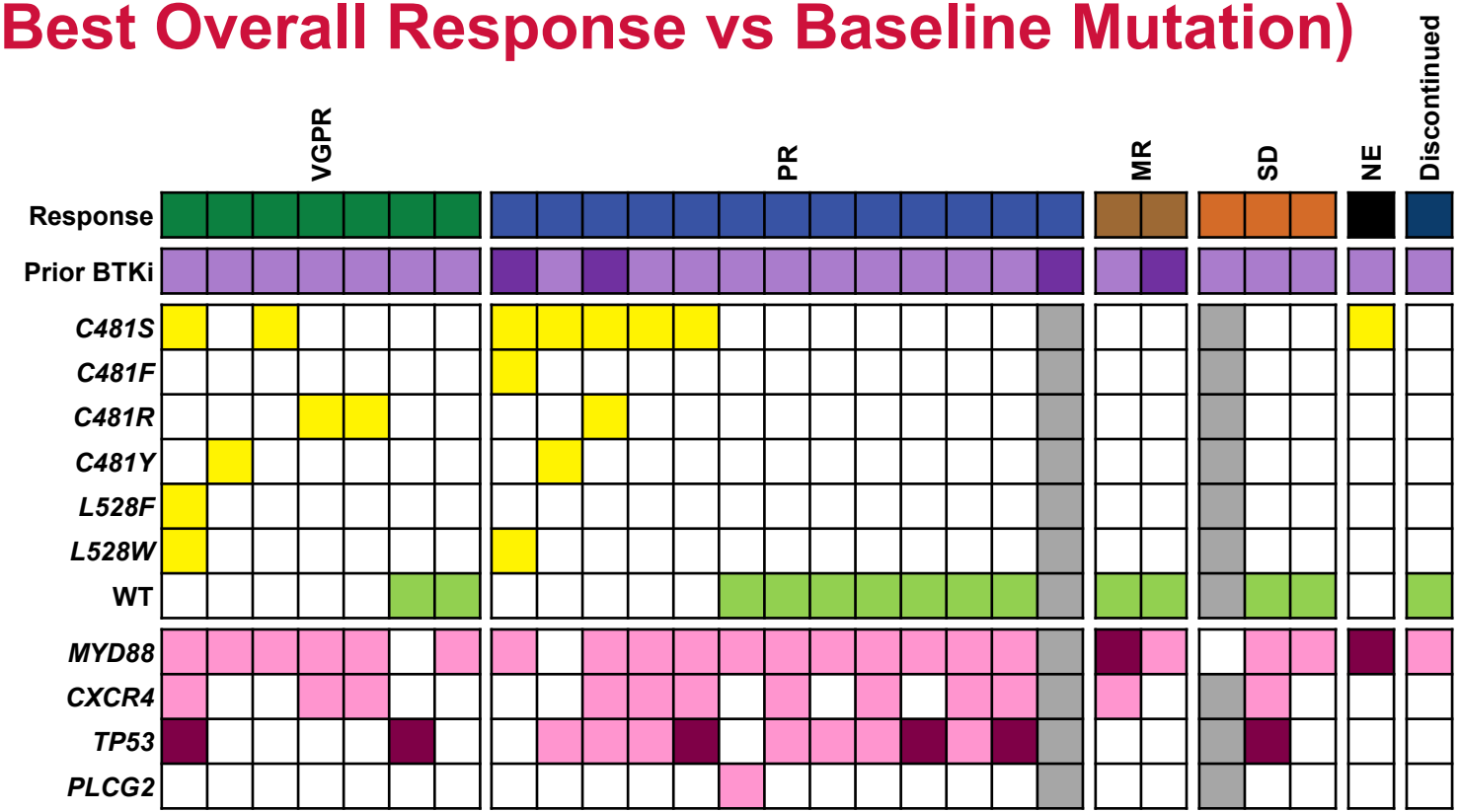
Deepening of responses at all dose levels



Data cutoff: September 2, 2024. First disease assessment at 4 weeks.

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

Responses Occurred Regardless of Specific Mutations (Best Overall Response vs Baseline Mutation)



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

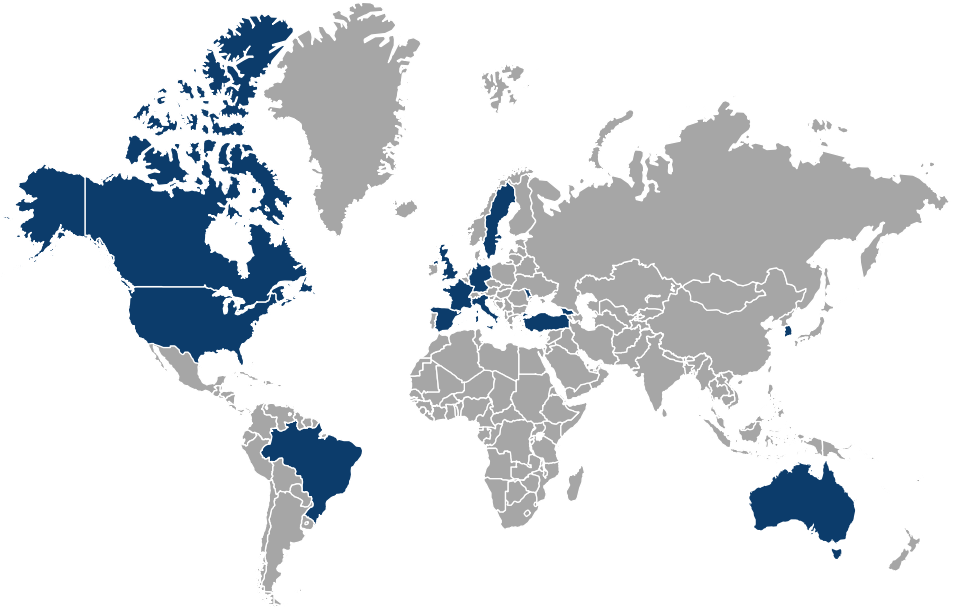
Conclusions

CaDAnCe-101

- In phase 1 of CaDAnCe-101, the BTK degrader BGB-16673 was well tolerated in heavily pretreated patients with R/R WM
  - No DLTs occurred; MTD was not reached
  - No atrial fibrillation or hypertension reported
- VGPR 25.9% (7/27 patients); ORR 81.5% (22/27); DCR 93.0% (25/27)
  - Rapid decline in IgM with median time to first response of 1.0 month
  - Rapid improvement in cytopenias seen in patients who experience disease response
  - Responses continue to deepen over time (median 5.0-month follow-up)
- Promising antitumor activity, including in patients with:
  - BTK inhibitor–resistant mutations
  - *TP53* and *CXCR4* mutations
  - Previous exposure to cBTK inhibitors, ncBTK inhibitors, and BCL2 inhibitors
- These data support further investigation of BGB-16673 clinical activity in patients with WM; enrollment in CaDAnCe-101 continues

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, and Brazil



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