

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

**Anna Maria Frustaci,<sup>1</sup> John F. Seymour,<sup>2</sup> Chan Y. Cheah,<sup>3-5</sup> Ricardo D. Parrondo,<sup>6</sup> John N. Allan,<sup>7</sup> Judith Trotman,<sup>8</sup> Mazyar Shadman,<sup>9,10</sup> Ranjana Advani,<sup>11</sup> Herbert Eradat,<sup>12</sup> Pier Luigi Zinzani,<sup>13</sup> Masa Lasica,<sup>14</sup> Emmanuelle Tchernonog,<sup>15</sup> Steven P. Treon,<sup>16</sup> Linlin Xu,<sup>17</sup> Kunthel By,<sup>17</sup> Shannon Fabre,<sup>17</sup> Motohisa Takai,<sup>17</sup> Amit Agarwal,<sup>17</sup> Constantine S. Tam<sup>18</sup>**

<sup>1</sup>ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; <sup>2</sup>Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia; <sup>3</sup>Sir Charles Gairdner Hospital, Nedlands, WA, Australia; <sup>4</sup>Medical School, University of Western Australia, Crawley, WA, Australia; <sup>5</sup>Linear Clinical Research, Nedlands, WA, Australia; <sup>6</sup>Mayo Clinic - Jacksonville, Jacksonville, FL, USA; <sup>7</sup>Weill Cornell Medicine, New York, NY, USA; <sup>8</sup>Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; <sup>9</sup>Fred Hutchinson Cancer Center, Seattle, WA, USA; <sup>10</sup>University of Washington, Seattle, WA, USA; <sup>11</sup>Stanford Cancer Institute, Stanford, CA, USA; <sup>12</sup>David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; <sup>13</sup>Institute of Hematology "Seràgnoli", University of Bologna, Bologna, Italy; <sup>14</sup>St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; <sup>15</sup>CHRU Montpellier - Hôpital St Eloi, Montpellier, France; <sup>16</sup>Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; <sup>17</sup>BeOne Medicines Ltd, San Carlos, CA, USA; <sup>18</sup>Alfred Hospital and Monash University, Melbourne, VIC, Australia



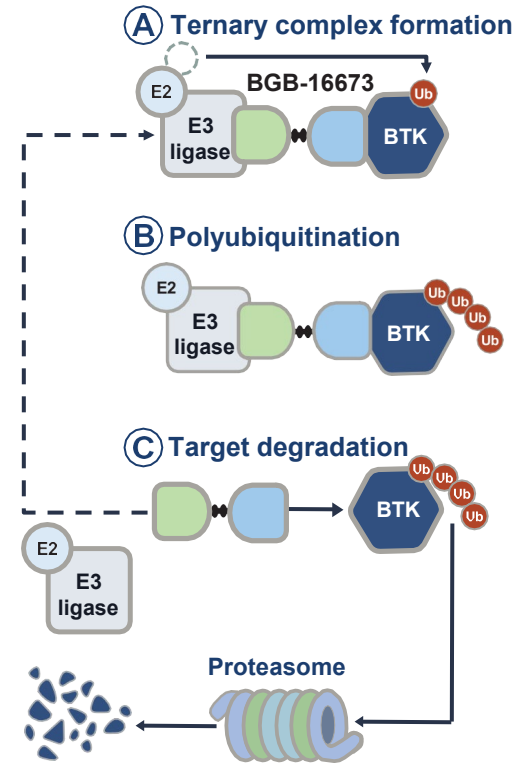
## Disclosures for Anna Maria Frustaci

---

- **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<sup>1,2</sup>
- 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<sup>3</sup>
- 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)<sup>3,4</sup>
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue<sup>5</sup>
- 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<sup>c</sup> & tolerability, MTD, & RDFE
  - **Secondary:** PK, PD, & preliminary antitumor activity<sup>d</sup>

## Part 1: Monotherapy dose finding<sup>a</sup>

**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<sup>b</sup>**  
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

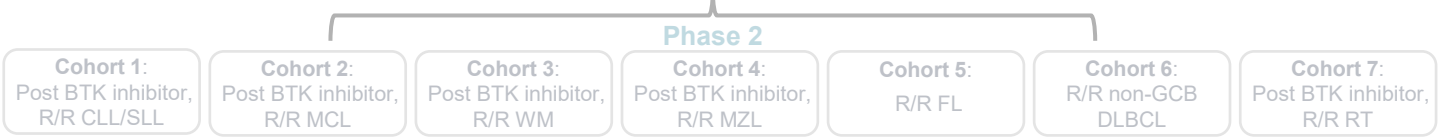
**Part 1e: Additional safety expansion**

**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**



<sup>a</sup>Data from gray portions of the figure are not included in this presentation. <sup>b</sup>Treatment was administered until progression, intolerance, or other criteria were met for treatment discontinuation. <sup>c</sup>Safety was assessed according to CTCAE v5.0. <sup>d</sup>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)
<b>Age, median (range), years</b>	72.0 (49-81)
<b>Male, n (%)</b>	22 (61.1)
<b>ECOG PS, n (%)</b>	
0	17 (47.2)
1	17 (47.2)
2	2 (5.6)
<b>Hemoglobin, median (range), g/L</b>	102 (60-146)
Hemoglobin $\leq$ 110 g/L, n/N with known status (%)	25/34 (73.5)
<b>Neutrophils, median (range), <math>10^9/L</math></b>	2.6 (0.2-7.4)
Neutrophils $\leq$ 1.5 $\times$ 10 <sup>9</sup> /L, n/N with known status (%)	11/33 (33.3)
<b>Platelets, median (range), <math>10^9/L</math></b>	153.5 (14.0-455.0)
<b>IgM, median (range), g/L</b>	35.1 (0.3-92.6)

	Total (N=36)
<b>Mutation status, n/N with known status (%)<sup>a</sup></b>	
<i>MYD88</i> mutation present	31/35 (88.6)
<i>CXCR4</i> mutation present	19/35 (54.3)
<i>BTK</i> mutation present	11/31 (35.5)
<i>TP53</i> mutation present	16/31 (51.6)
<b>No. of prior lines of therapy, median (range)</b>	3 (1-11)
<b>Prior therapy, n (%)</b>	
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 <sup>b</sup>	7 (19.4)
<b>Discontinued prior BTK inhibitor due to PD, n (%)</b>	30 (83.3)

Data cutoff: March 3, 2025.

<sup>a</sup>Confirmed by central laboratory. <sup>b</sup>All seven patients with ncBTK inhibitor exposure were also exposed to a cBTK inhibitor.

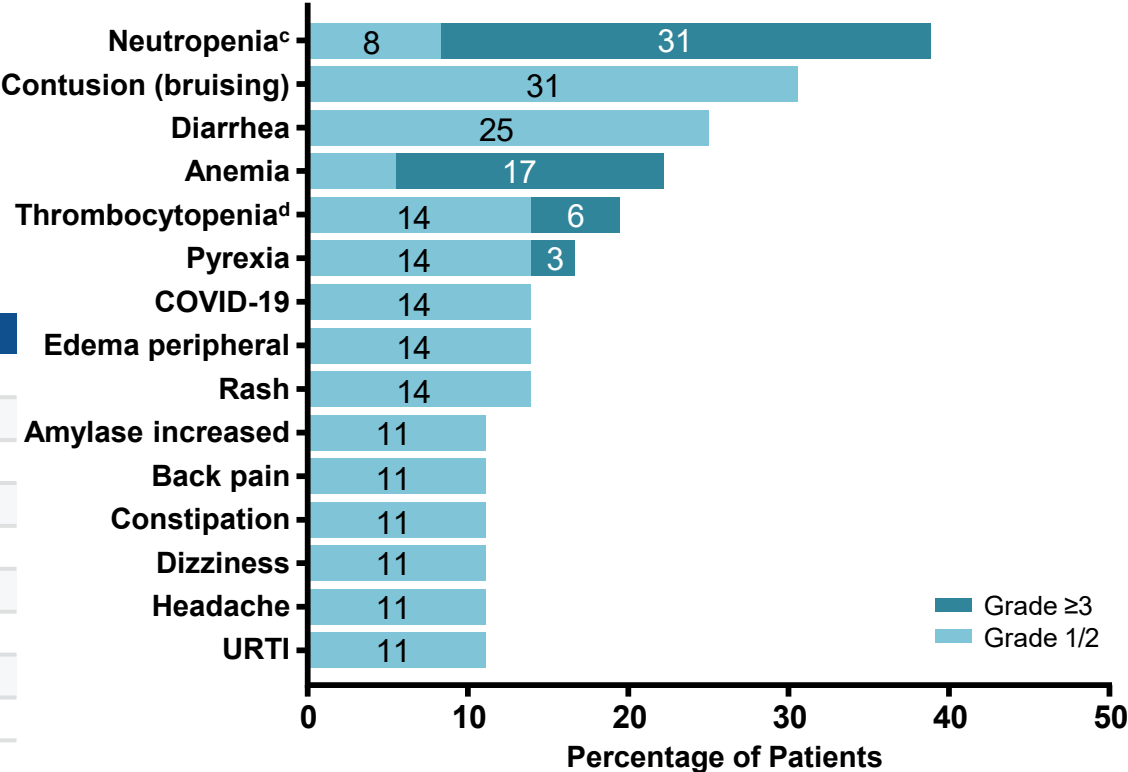
BCL2, B-cell lymphoma 2; BTK, Bruton tyrosine kinase; cBTK, covalent BTK; ECOG PS, Eastern Cooperative Oncology Group performance status; IgM, immunoglobulin M; ncBTK, noncovalent BTK; PD, progressive disease; WM, Waldenström macroglobulinemia.

# 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<sup>a</sup>, febrile neutropenia, or pancreatitis

Patients, n (%)	Total (N=36)
<b>Any TEAE</b>	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 <sup>b</sup>	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).

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

<sup>d</sup>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) <sup>a</sup>
<b>Best overall response, n (%)</b>	
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)
<b>ORR, n (%)<sup>b</sup></b>	<b>27 (84.4)</b>
<b>Major response rate, n (%)<sup>c</sup></b>	<b>24 (75.0)</b>
<b>Time to first response, median (range), months<sup>d</sup></b>	<b>1.0 (0.9-3.7)</b>

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

<sup>a</sup>Efficacy-evaluable population; 4 patients were too early in treatment course to be response-evaluable. <sup>b</sup>Includes best overall response of MR or better. <sup>c</sup>Includes best overall response of PR or VGPR.

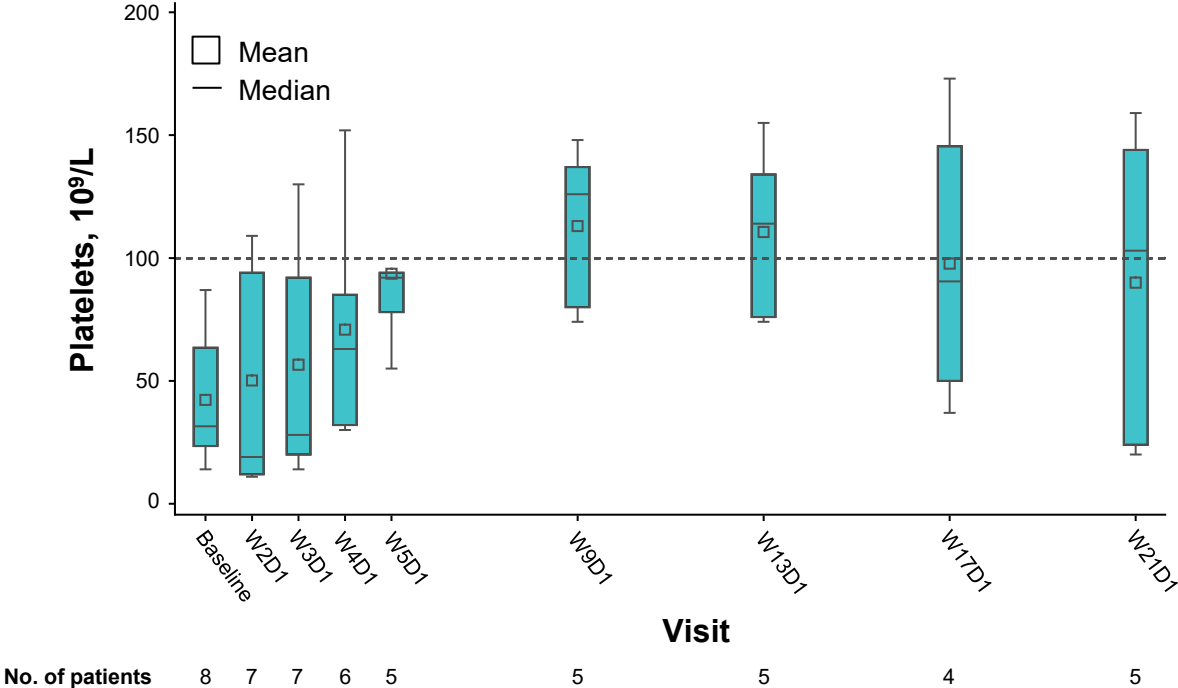
<sup>d</sup>In patients with a best overall response better than SD.

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

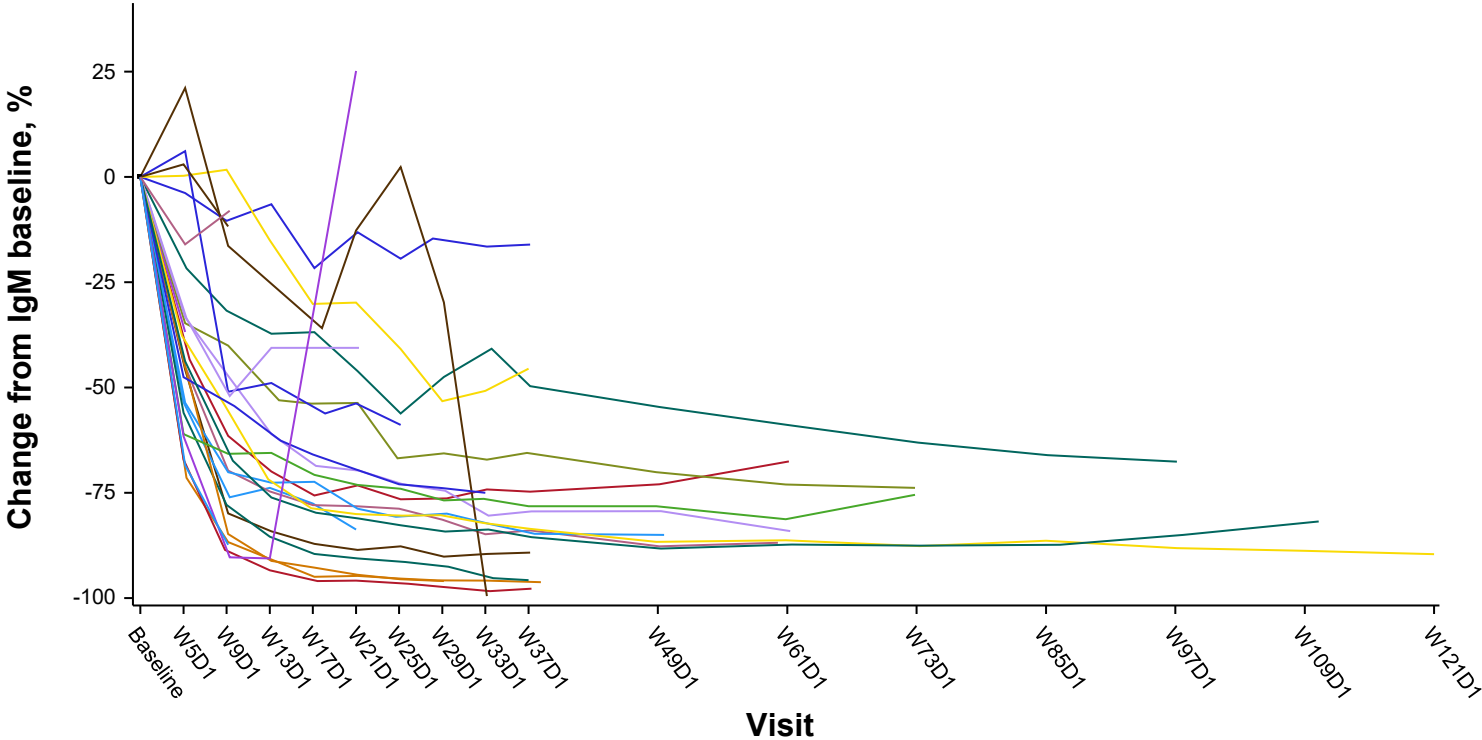
	Baseline	W9D1
Neutrophil count, median, 10 <sup>9</sup> /L	0.9	1.1
Hemoglobin level, median, g/L	98.0	114.0
Platelet count, median, 10 <sup>9</sup> /L	39.5	126.0

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



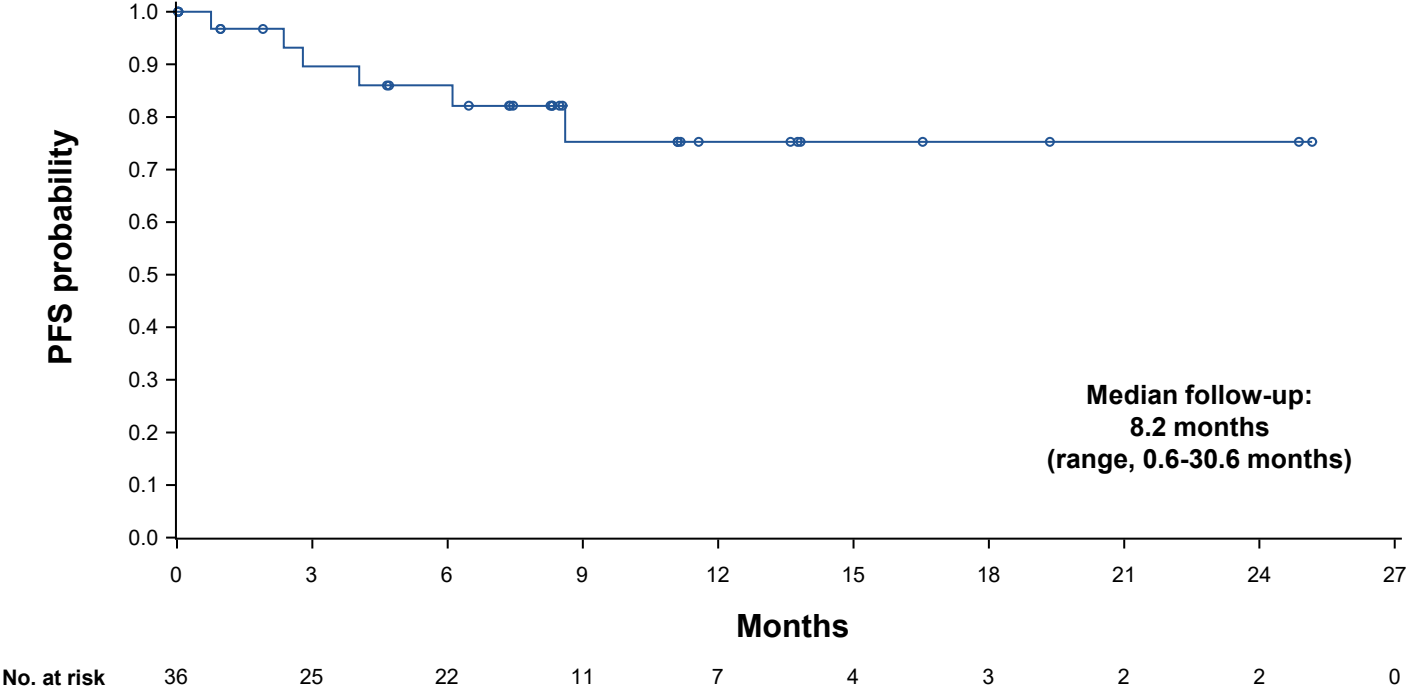
# IgM Decreased in All Patients

## Rapid and sustained decrease in IgM in most patients

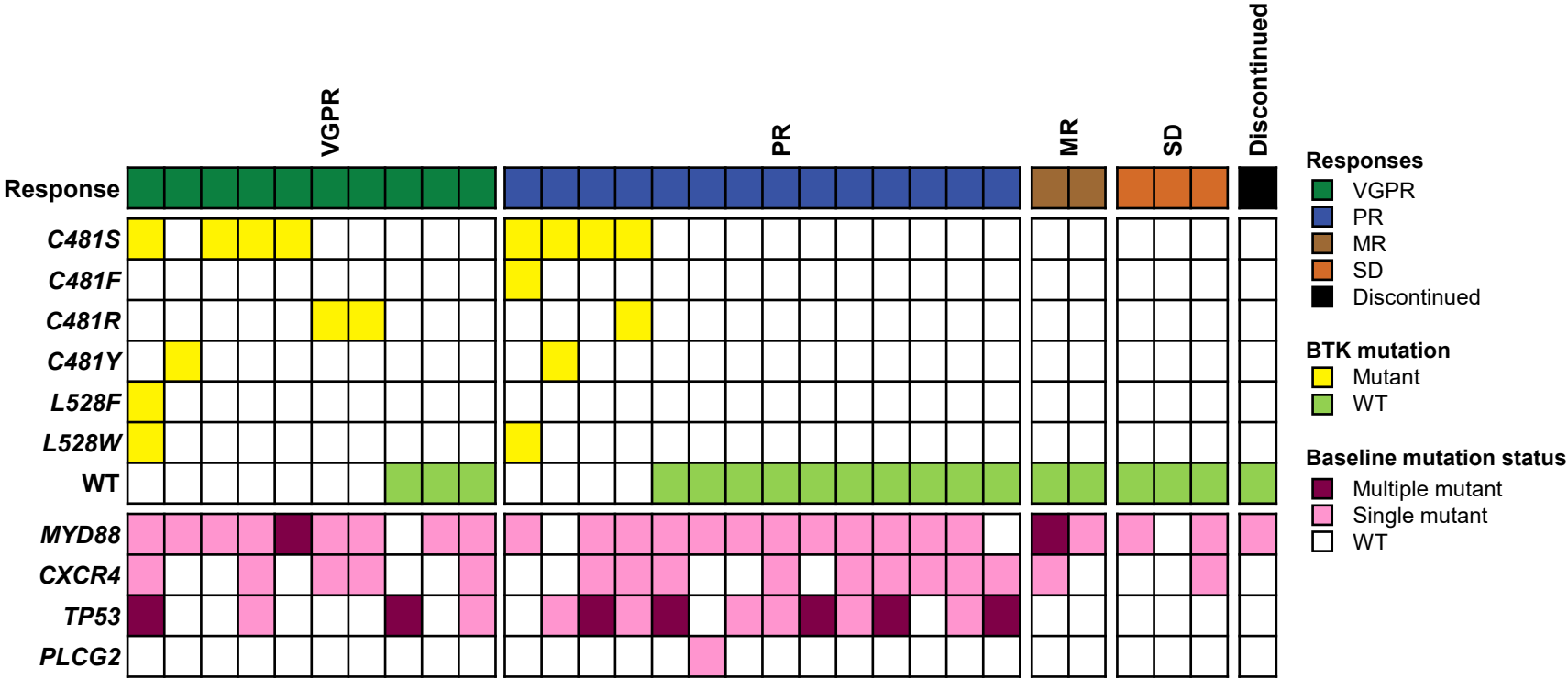


Patient with rapid IgM increase had *BTK*, *MYD88*, *CXCR4*, and *TP53* mutations at baseline, paused treatment for 2-3 weeks due to COVID-19 infection, and developed rapid progression shortly after restarting treatment. D, day; IgM, immunoglobulin M; W, week.

# Median PFS Was Not Reached



# Responses Occurred Regardless of Baseline Mutations (Best Overall Response vs Baseline Mutation)<sup>a</sup>



<sup>a</sup>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

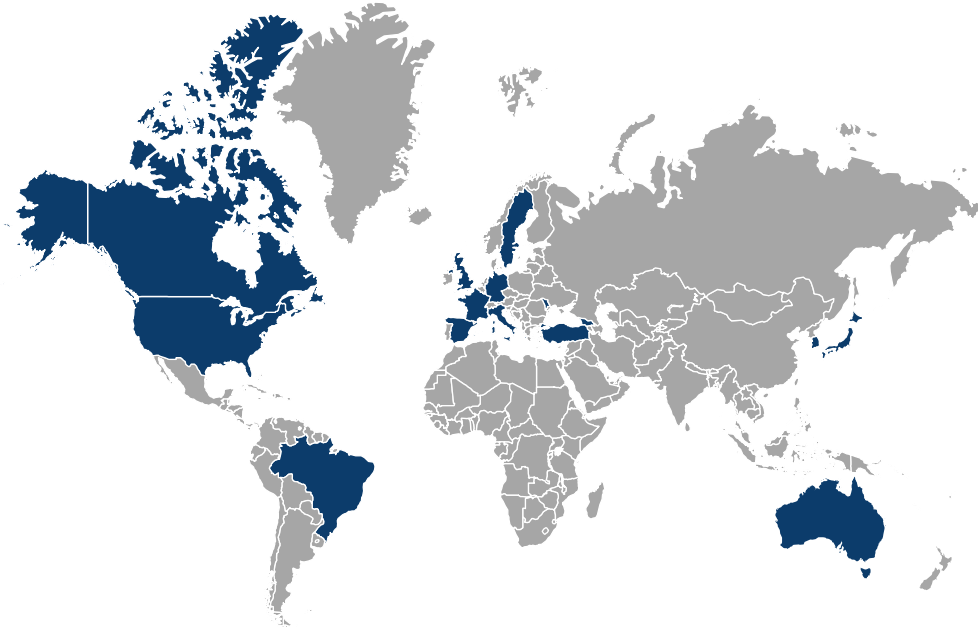
---

- 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

**Corresponding author:** Anna Maria Frustaci, [annamaria.frustaci@ospedaleniguarda.it](mailto:annamaria.frustaci@ospedaleniguarda.it)