# 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

**John F. Seymour,**[1] Chan Y. Cheah,[2-4] Ricardo D. Parrondo,[5] John N. Allan,[6] Judith Trotman,[7] Ranjana Advani,[8] Herbert Eradat,[9] Eric Mou,[10] Pier Luigi Zinzani,[11] Masa Lasica,[12] Damien Roos-Weil,[13] Emmanuelle Tchernonog,[14] Jose Leis,[15] Xiangmei Chen,[16] Kunthel By,[17] Shannon Fabre,[17] Daniel Persky,[17] Amit Agarwal,[17] Constantine S. Tam*,[18] Anna Maria Frustaci*[19]

[1]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia; [2]Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [3]Medical School, University of Western Australia, Crawley, WA, Australia; [4]Linear Clinical Research, Nedlands, WA, Australia; [5]Mayo Clinic - Jacksonville, Jacksonville, FL, USA; [6]Weill Cornell Medicine, New York, NY, USA; [7]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [8]Stanford Cancer Institute, Stanford, CA, USA; [9]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [10]University of Iowa Hospitals and Clinics, Iowa City, IA, USA; [11]Institute of Hematology "Seràgnoli", University of Bologna, Bologna, Italy; [12]St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [13]Pitié-Salpêtrière Hospital, Paris, France; [14]CHRU Montpellier - Hôpital St Eloi, Montpellier, France; [15]Mayo Clinic Arizona, Phoenix, AZ, USA; [16]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [17]BeiGene USA, Inc, San Mateo, CA, USA; [18]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [19]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy.
*Joint senior co-authorship.

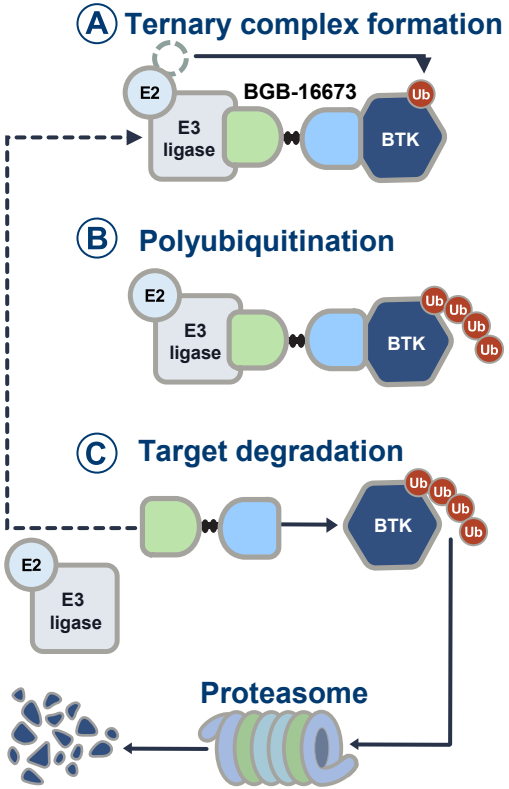
Presented at the 12th International Workshop on Waldenström's Macroglobulinemia (IWWM-12); October 17-19, 2024; Prague, Czech Republic

# Disclosures

- **John F. Seymour**: Advisory role: AbbVie, AstraZeneca, BeiGene, BMS, Genor Bio, Gilead, Janssen, Roche; Research funding: AbbVie, BMS, Janssen, Roche; Speakers bureau; AbbVie, BMS, Roche; Consultancy: TG Therapeutics.

# BGB-16673: A Chimeric Degradation Activating Compound (CDAC)

- BTK inhibition is a highly active treatment strategy in patients with WM; however, treatment with some BTK inhibitors is associated with toxicities and/or resistance development[1,2]
- BGB-16673, a CDAC, is a bivalent molecule comprising a BTK-binding moiety + linker + E3 ligase binder that induces BTK degradation via polyubiquitination[3]
- In preclinical models, BGB-16673 degraded both wild-type and mutant BTK resistant to covalent and noncovalent BTK inhibitors,[a] leading to tumor suppression[3,4]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue in the first-in-human study[5]
- Here, safety and efficacy results are presented from patients with R/R WM in the ongoing CaDAnCe-101 study




[a] Covalent BTK inhibitor–resistant mutations including C481S, C481F, C481Y, L528W, and T474I; non-covalent BTK inhibitor–resistant mutations including V416L, M437R, T474I, and L528W. R/R, relapsed/refractory; ub, ubiquitin; WM, Waldenström macroglobulinemia.

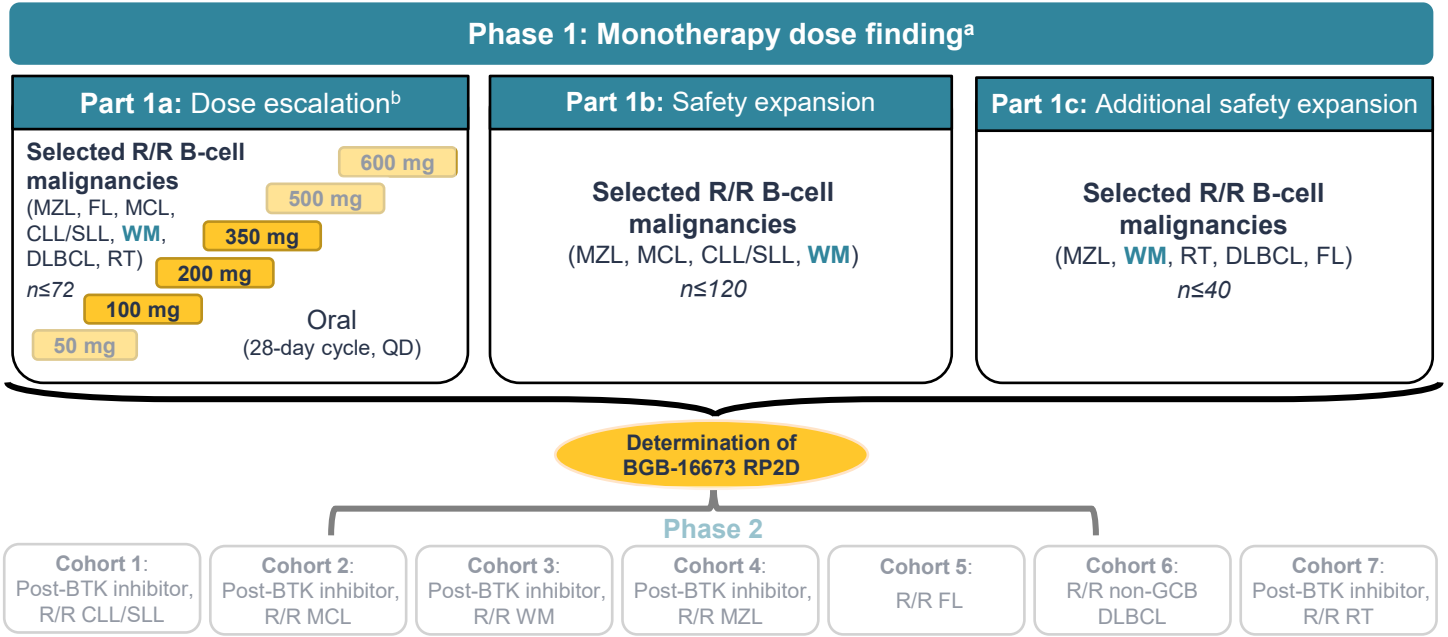
1. Castillo JJ, et al. *Lancet Haematol*. 2020;7(11):e827-e837; 2. Ntanasis-Stathopoulos I, et al. *Ther Adv Hematol*. 2021;12:2040620721989586; 3. Feng X, et al. EHA 2023. Abstract P1239; 4. Wang H, et al. EHA 2023. Abstract P1219; 5. Seymour JF, et al. ASH 2023. Abstract 4401.

# Study Design

- CaDAnCe-101 (BGB-16673-101, NCT05006716) is a phase 1/2, open-label, dose-escalation and dose-expansion study evaluating BGB-16673 in adults with R/R B-cell malignancies

**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

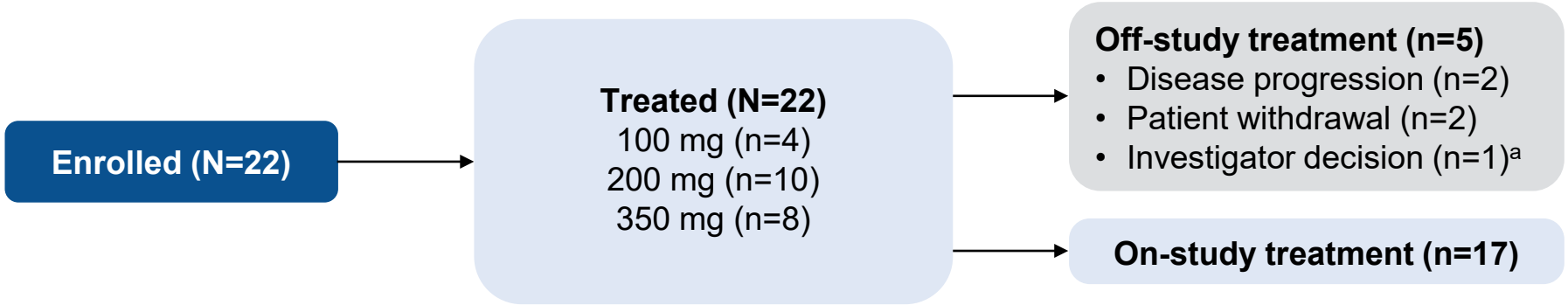
**Key study objectives for part 1**
- **Primary:** safety[c] and tolerability, MTD, and RP2D
- **Secondary:** PK, PD, and preliminary antitumor activity[d]




[a] Data from grey portions of figure are not included in this presentation. [b] Bayesian optimal interval design with 6 dose levels (50-600 mg orally QD). [c] Safety was assessed according to CTCAE v5.0; DLTs were assessed during the first 4 weeks. [d] Responses were assessed per IWWM-6, modified Owen 2013 criteria after 4 weeks.[1]
cBTK, covalent BTK; GCB, germinal center B-cell; R/R, relapsed/refractory; RT, Richter transformation; WM, Waldenström macroglobulinemia. 1. Owens RG, et al. *Br J Haematol.* 2013;160(2):171-176.

# Patient Disposition

- As of May 24, 2024, 22 patients with R/R WM enrolled in phase 1 and received BGB-16673
- Seventeen patients (77%) remained on treatment




**Median follow-up (range):**
4.3 months (0.3-21.3 months)

[a] Patient had no response in lymphoma mass and progressive lung changes consistent with fungal infection that had previously been thought to be lymphoma related.
R/R, relapsed/refractory; WM, Waldenström macroglobulinemia.

# Patient Characteristics

- Patients had a median of 3.5 (range, 2-11) prior lines of therapy
- The majority of patients (82%) discontinued prior BTK inhibitor therapy due to PD

| | Total (N=22) |
|---|---|
| **Age, median (range), years** | 73 (56-81) |
| **Male, n (%)** | 12 (55) |
| **ECOG PS, n (%)[a]** | |
| 0 | 11 (50) |
| 1 | 10 (46) |
| **Hemoglobin, median (range), g/dL[b]** | 10.1 (6.0-13.5) |
| **Neutrophils, median (range), $10^9$/L[b]** | 2.8 (0.2-7.4) |
| **Platelets, median (range), $10^9$/L[b]** | 155.0 (14.0-436.0) |
| **Mutation status, n/N with known status (%)** | |
| *MYD88* mutation present[c] | 20/22 (91) |
| *CXCR4* mutation present[c] | 8/21 (38) |
| *BTK* mutation present | 5/13 (38) |

| | Total (N=22) |
|---|---|
| **IgM, median (range), g/L[d]** | 36.2 (2.8-74.4) |
| **No. of prior lines of therapy, median (range)** | 3.5 (2-11) |
| **Prior therapy, n (%)** | |
| cBTK inhibitor | 22 (100) |
| Chemotherapy | 20 (91) |
| Proteasome inhibitor | 7 (32) |
| BCL2 inhibitor | 4 (18) |
| cBTK + BCL2 inhibitors | 4 (18) |
| ncBTK inhibitor | 3 (14) |
| cBTK + ncBTK + BCL2 inhibitors | 0 |
| **Discontinued prior BTK inhibitor due to PD, n (%)** | 18 (82) |

[a] 1 patient (5%) had ECOG PS of 2. [b] N=21. [c] Based on case report forms. [d] N=19.
cBTK, covalent BTK; ncBTK, noncovalent BTK.

# Safety Summary and Frequent Adverse Events

- No DLTs occurred[a]
- There were no cases of atrial fibrillation, hypertension, febrile neutropenia, or major hemorrhage

| Patients, n (%) | Total (N=22) |
|---|---|
| **Any TEAE** | 21 (96) |
| Any treatment related | 15 (68) |
| Grade ≥3 | 10 (46) |
| Treatment related grade ≥3 | 6 (27) |
| Serious | 5 (23) |
| Treatment related serious | 0 |
| Leading to death[b] | 1 (5) |
| Treatment related leading to death | 0 |
| Leading to treatment discontinuation | 0 |
| Leading to treatment modification | 4 (18) |
| Dose interruption | 4 (18) |
| Dose reduction | 0 |

| Patients, n (%) | Total (N=22)[c] | |
|---|---|---|
| | All Grade | Grade ≥3 |
| Neutropenia/neutrophil count decreased | 7 (32) | 5 (23) |
| Contusion | 5 (23) | 0 |
| Diarrhea | 5 (23) | 0 |
| Anemia | 4 (18) | 2 (9) |
| Pyrexia | 4 (18) | 1 (5) |
| Amylase increased | 4 (18) | 0 |
| Petechiae | 4 (18) | 0 |
| Dizziness | 4 (18) | 0 |
| Rash | 4 (18) | 0 |
| Thrombocytopenia/platelet count decreased | 3 (14) | 2 (9) |
| Lipase increased | 3 (14) | 1 (5) |
| Fall | 3 (14) | 0 |
| Upper respiratory tract infection | 3 (14) | 0 |

[a] DLTs were only assessed during the first 4 weeks of part 1a. [b] Septic shock (200-mg dose group). [c] All-grade TEAEs in ≥10% of patients.

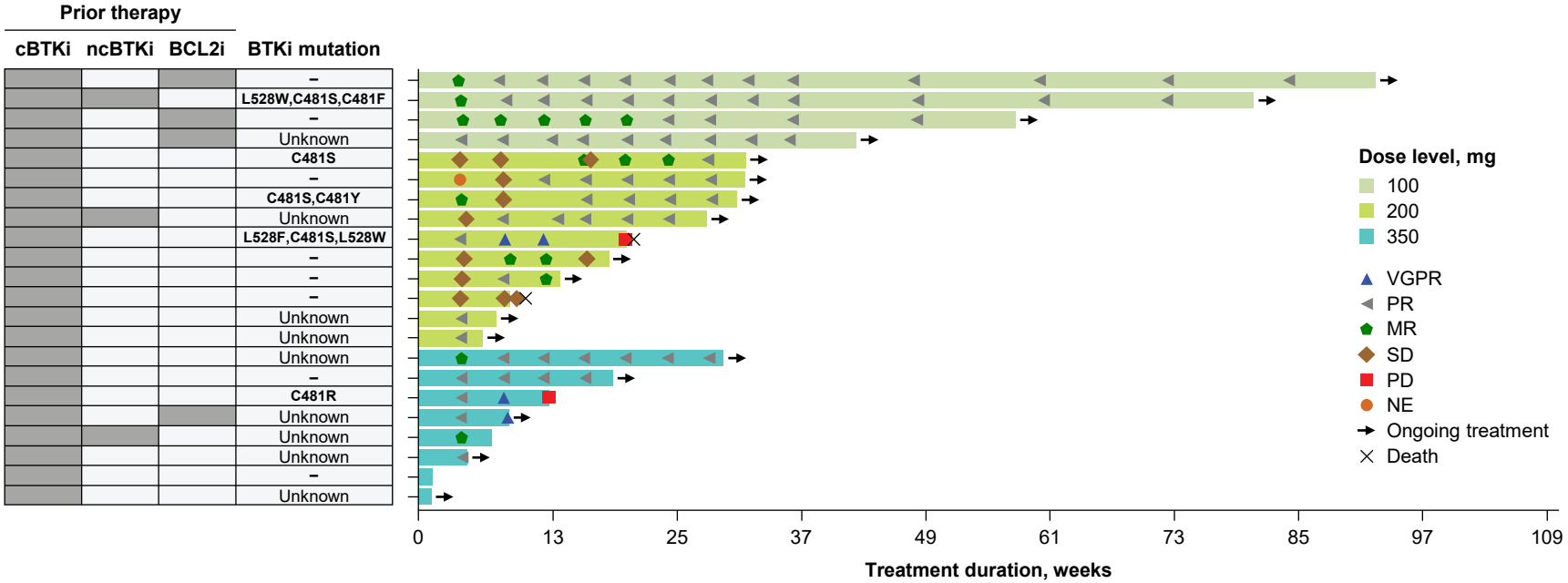
# Response by IWWM-6 Criteria[1]

- The ORR was 91% (19/21) in efficacy-evaluable patients with R/R WM
- One patient had an IgM flare and/or rebound 1 week after starting treatment and went on to develop a PR
- Responses were observed at the lowest dose (100 mg; 4/4 patients) and in patients with prior cBTK inhibitor (19/21) or ncBTK inhibitor (3/3)
- Responses also occurred in patients with or without mutations in:
  - *BTK* (with, 5/5 [100%]; without, 6/8 [75%]; unknown, 8/8 [100%])
  - *MYD88* (with, 18/20 [90%]; without, 1/1 [100%])
  - *CXCR4* (with, 8/8 [100%]; without, 11/13 [85%])

| | Total (N=21)[a] |
|---|---|
| **Best overall response, n (%)** | |
| VGPR | 3 (14) |
| PR | 14 (67) |
| MR | 2 (10) |
| SD | 1 (5) |
| Discontinued prior to first assessment | 1 (5) |
| **ORR, n (%)[b]** | 19 (91) |
| **Major response rate, n (%)[c]** | 17 (81) |
| **Disease control rate, n (%)[d]** | 20 (95) |
| **Follow-up time, median (range), months[e]** | 4.3 (0.3-21.3) |
| **Time to first response, median (range), months[f]** | 1.0 (0.9-3.7) |

[a] Efficacy-evaluable patients. [b] Proportion of patients who achieved a best overall response of MR or better. [c] Proportion of patients who achieved a best overall response of PR or better. [d] Proportion of patients who achieved a best overall response of SD or better. [e] Study follow-up in patients treated with ≥1 dose, N=22. [f] Time to first qualifying response in patients with a best overall response better than SD.
cBTK, covalent BTK; IgM, immunoglobulin M; MR, minor response; ncBTK, noncovalent BTK; R/R, relapsed/refractory; VGPR, very good PR; WM, Waldenström macroglobulinemia.
1. Owens RG, et al. *Br J Haematol*. 2013;160(2):171-176.

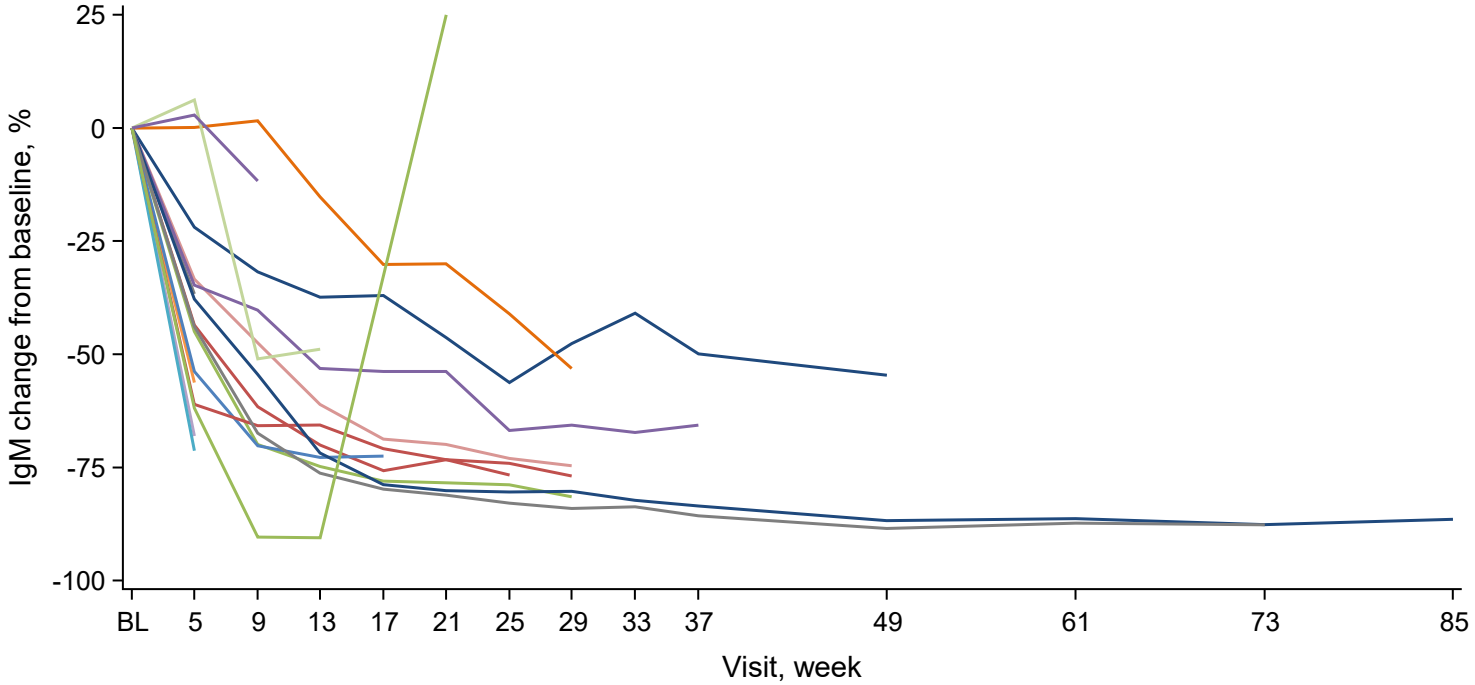
# Treatment Duration and Response




*BTK* mutation status absent is shown by (-).
BCL2i, B-cell lymphoma 2 inhibitor; BTKi, BTK inhibitor; cBTKi, covalent BTK inhibitor; MR, minor response; mut, mutation; ncBTKi, noncovalent BTK inhibitor; VGPR, very good PR.

# Percent Change From Baseline in IgM

- All patients experienced a numerical reduction from baseline in IgM




IgM, immunoglobulin M.

# Conclusions

- In this first-in-human study, the BTK degrader BGB-16673 was generally well tolerated in heavily pretreated R/R WM
  - No DLTs
  - MTD not reached
  - No atrial fibrillation or hypertension reported so far
- Promising antitumor activity, including in patients with:
  - BTK inhibitor–resistant mutations
  - previous exposure to cBTK inhibitors, ncBTK inhibitors, and BCL2 inhibitors
- ORR 91% (19/21 patients)
  - Median time to first response was 1.0 month
  - Responses continue to evolve (median 4.3-month follow-up)
  - Updated data will be presented at future congresses
- With promising clinical activity of BGB-16673 in the treatment of R/R WM, enrollment for the CaDAnCe-101 study is ongoing

# 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 BeiGene, Ltd. Medical writing support was provided by Kendall Foote, PhD, of Nucleus Global, an Inizio company, and supported by BeiGene