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

Chan Y. Cheah,[1-3] John F. Seymour,[4] Masa Lasica,[5] Herbert Eradat,[6] Anna Maria Frustaci,[7] John N. Allan,[8] Victor T.G. Lin,[9] Judith Trotman,[10] Ranjana Advani,[11] Xiangmei Chen,[12] Kunthel By,[13] Shannon Fabre,[13] Amit Agarwal,[13] Constantine S. Tam[14]

[1]Sir Charles Gairdner Hospital and PathWest Laboratory Medicine, Nedlands, WA, Australia; [2]Medical School, University of Western Australia, Crawley, WA, Australia; [3]Linear Clinical Research, Nedlands, WA, Australia; [4]Peter MacCallum Cancer Centre, Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia; [5]St. Vincent's Hospital Melbourne, Fitzroy, VIC, Australia; [6]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [7]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [8]Weill Cornell Medicine, New York, NY, USA; [9]Mary Bird Perkins Cancer Center, Baton Rouge, LA, USA; [10]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [11]Stanford Cancer Institute, Stanford, CA, USA; [12]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [13]BeiGene USA, Inc, San Mateo, CA, USA; [14]Alfred Hospital and Monash University, Melbourne, VIC, Australia

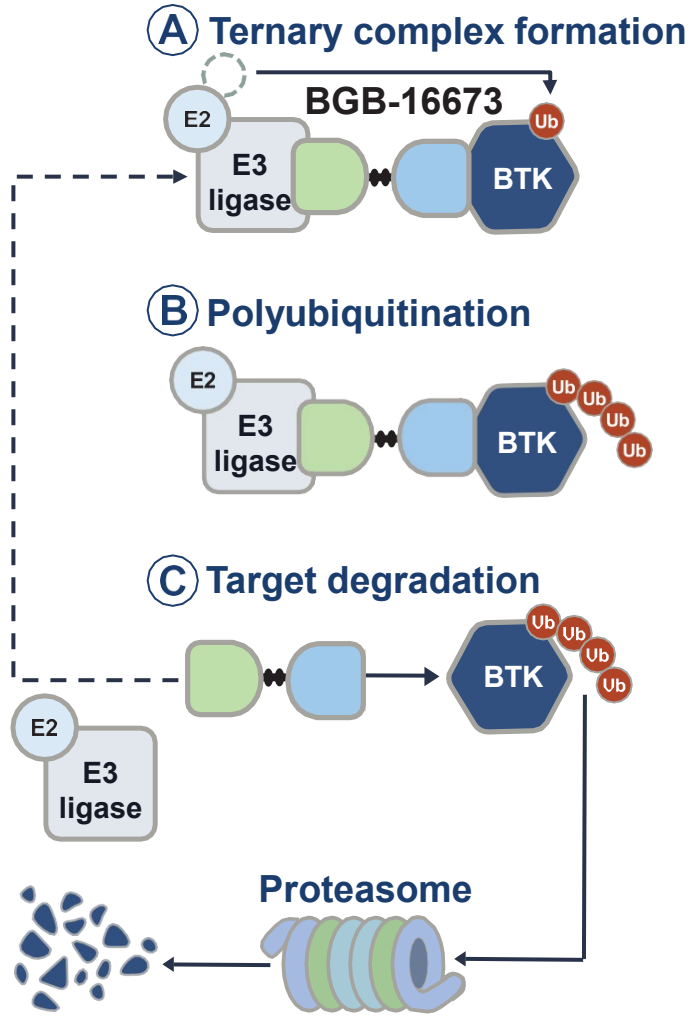
Presenter: Erna Yang

Disclosures for Erna Yang

- Employment and may own stock: BeiGene, Inc.

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

- Many patients with B-cell malignancies experience disease progression after BTK inhibitors[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 regardless of whether the mutation is associated with covalent (C481S, C481F, C481Y, L528W, and T474I) or noncovalent (V416L, M437R, T474I, and L528W) inhibitors, leading to tumor suppression[4,5]
- BGB-16673 led to substantial reductions in BTK protein levels in peripheral blood and tumor tissue in the first-in-human study[6]
- Here, updated safety and efficacy results are presented from patients with FL, MZL, and WM in the ongoing CaDAnCe-101 study



CDAC, chimeric degradation activating compound; ub, ubiquitin.

1. Woyach JA, et al. *N Engl J Med*. 2014;370:2286-2294; 2. Wang E, et al. *N Engl J Med.* 2022;386:735-743; 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 Study Design

Key eligibility criteria

- Received ≥2 prior therapies (≥1 prior therapy for RT)
- Received a cBTKi if approved for their disease
- ECOG PS 0-2
- Adequate end-organ function
- No current or history of central nervous system involvement by B-cell malignancy

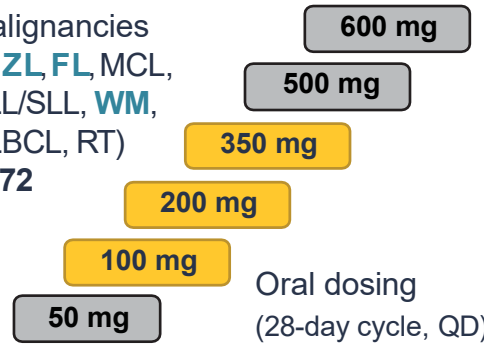
Key study objectives for part 1

- Primary: safety[b] and tolerability, define MTD and RP2D
- Secondary: characterize PK, pharmacodynamics, and preliminary antitumor activity[c]

Part 1: Monotherapy dose finding

Part 1a: Dose escalation[a]

Selected R/R B-cell malignancies (**MZL**, **FL**, MCL, CLL/SLL, **WM**, DLBCL, RT)
n≤72



Oral dosing
(28-day cycle, QD)

Part 1b: Safety expansion

Selected R/R B-cell malignancies
(**MZL**, MCL, CLL/SLL, **WM**)
n≤120

Up to 20 patients enrolled at doses that are cleared in part 1a: dose escalation and recommended for additional evaluation by the safety monitoring committee

Part 1c: Additional safety expansion

Selected R/R B-cell malignancies
(MZL, WM, RT, DLBCL, FL)
n≤40

After part 2 is opened, up to 40 patients enrolled in up to 3 dose levels as recommended by the safety monitoring committee

Determination of BGB-16673 RP2D

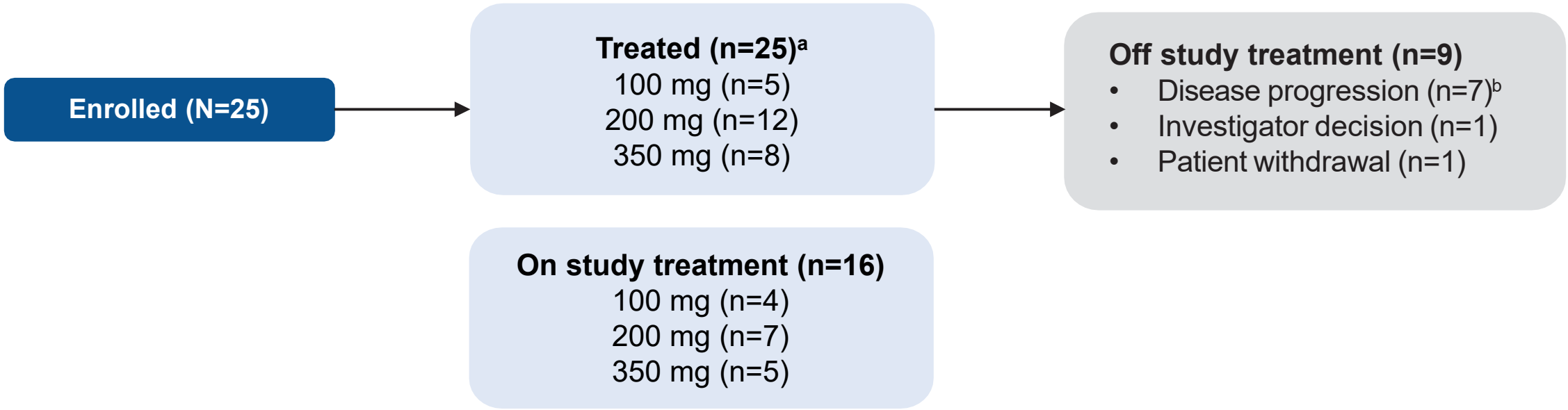
Phase 2

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

[a] Bayesian optimal interval design with 6 dose levels (50-600 mg orally QD). [b] Safety was assessed according to CTCAE v5.0 in all patients; DLTs were assessed during the first 4 weeks.
[c] Response was assessed per Lugano 2014 criteria after 12 weeks in patients with FL and MZL and per IWWM-6 criteria after 4 weeks in patients with WM.
cBTKi, covalent Bruton tyrosine kinase inhibitor; GCB, germinal center B-cell; RT, Richter transformation.

Patient Disposition

- As of February 14, 2024, a total of 25 patients with FL (n=7), MZL (n=5), and WM (n=13) had received BGB-16673, and 16 (64%) remained on treatment; median follow-up time was 5.85 months



[a] Dose per day until disease progression or unacceptable toxicity. [b] Includes 1 patient who discontinued treatment due to an AE in the context of disease progression.

Demographic and Baseline Characteristics

Parameter	All with FL/MZL/WM (N=25)
Age, median (range), years	72.0 (56-88)
Sex, n (%)	
Male	15 (60)
Female	10 (40)
ECOG performance status, n (%)	
0	10 (40)
1	14 (56)
2	1 (4)
Disease type, n (%)	
WM	13 (52)
FL	7 (28)
MZL	5 (20)
No. of prior lines of therapy, median (range)[a]	4 (2-11)
Prior covalent BTK inhibitor, n (%)	16 (64)
Prior noncovalent BTK inhibitor, n (%)	4 (16)
Discontinued BTK inhibitor due to PD, n/N (%)[b]	14/17 (82)
Prior BCL2 inhibitor, n (%)	6 (24)
BTK mutation present, n/N (%)	2/14 (14)
Ann Arbor stage III/IV at study entry (FL/MZL), n/N (%)	9/12 (75)
IWWM stage (WM), n/N (%)[c]	
Low risk	3/13 (23)
Intermediate risk	5/13 (38)
High risk	4/13 (31)

[a] Must include prior anti-CD20 in patients with FL, WM, and MZL in the US and EU, and cBTKi in patients with WM in the US and EU, and in patients with MZL in the US.
[b] One patient had prior treatment with noncovalent BTK inhibitor without prior covalent BTK inhibitor. [c] One patient had unknown risk.

Overall Safety Summary

Patients, n (%)	All with FL/MZL/WM (N=25)
Any TEAE	24 (96)
Any treatment-related	18 (72)
Grade ≥3	13 (52)
Treatment-related grade ≥3	6 (24)
Serious	8 (32)
Treatment-related serious	0
Leading to death	1 (4)[a]
Treatment-related leading to death	0
Leading to treatment discontinuation	1 (4)[b]
Treatment-related leading to treatment discontinuation	0
Leading to treatment modification	5 (20)
Dose interruption	5 (20)
Dose reduction	0

No patients experienced a DLT during the DLT window

[a] Septic shock (WM, 200 mg) in the context of possible disease progression. [b] Pleural effusion (MZL, 200 mg) in the context of disease progression.

Most Common TEAEs (All Grade ≥10%)

- No atrial fibrillation
- 1 case of grade ≥3 hypertension (88-year-old patient with a history of hypertension not on antihypertensives)
- Five patients experienced grade ≥3 infections (1 in the context of PD and 1 possibly in the context of PD)

	All With FL/MZL/WM (N=25)	
Patients, n (%)	All Grade	Grade ≥3
Contusion	8 (32)	0
Neutropenia/neutrophil count decreased[a]	6 (24)	5 (20)
Upper respiratory tract infection	6 (24)	1 (4)
Amylase increased[b]	6 (24)	0
Fatigue	6 (24)	0
Lipase increased[b]	5 (20)	1 (4)
Anemia	4 (16)	2 (8)
Diarrhea	4 (16)	0
Dizziness	3 (12)	0
Dyspnea	3 (12)	1 (4)
Headache	3 (12)	0
Petechiae	3 (12)	0

[a] There were no cases of febrile neutropenia. [b] All events were lab findings and were transient, mostly occurring during the first 1-3 cycles of treatment, with no clinical pancreatitis. A total of 6 patients reported TEAEs of increased amylase or lipase.

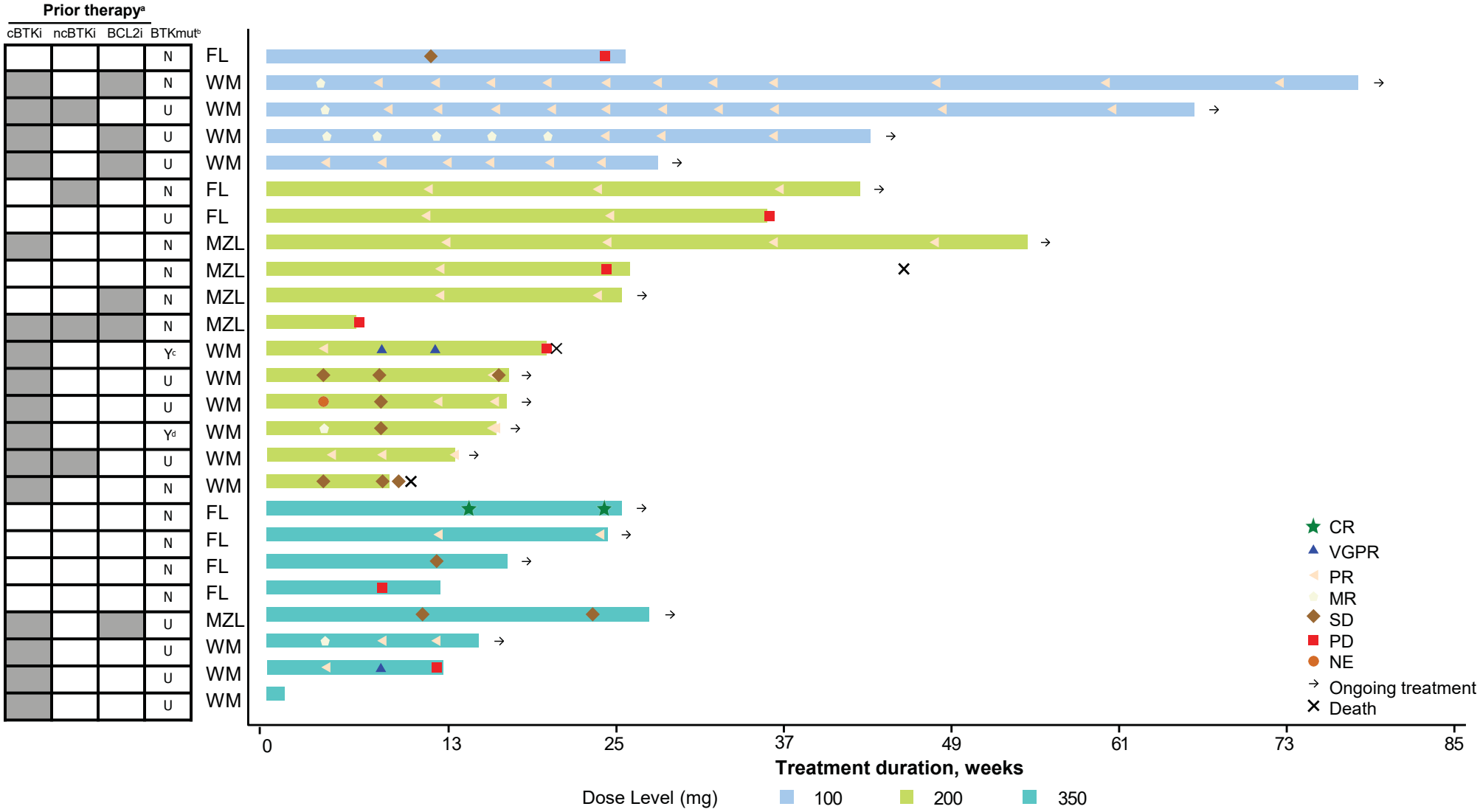
Responses by Histology in Evaluable Patients

	WM (n=12)	FL (n=7)	MZL (n=5)
Best overall response, n (%)			
CR	0	1 (14)	0
VGPR	2 (17)	0	0
PR	9 (75)	3 (43)	3 (60)
SD	1 (8)	2 (29)	1 (20)
PD	0	1 (14)	1 (20)
Disease control rate, n (%)[a]	12 (100)	6 (86)	4 (80)
ORR[b]	11 (92)	4 (57)	3 (60)
Time to first response, median (range), months[c]	0.95 (0.9-3.7)	2.71 (2.6-3.3)	2.83 (2.8-2.9)

- Responses were seen in patients who previously received covalent BTK inhibitor (n=12; 11 WM, 1 MZL) and noncovalent BTK inhibitor (n=3; 1 FL, 2 WM)
- Both patients with detected BTK mutations responded (WM; 200 mg; 1 PR, 1 VGPR)

[a] Proportion of patients with a best overall response of SD or higher. [b] Proportion of patients who achieved a best overall response better than SD. [c] Time to first qualifying response in patients with a best overall response better than SD.
VGPR, very good PR.

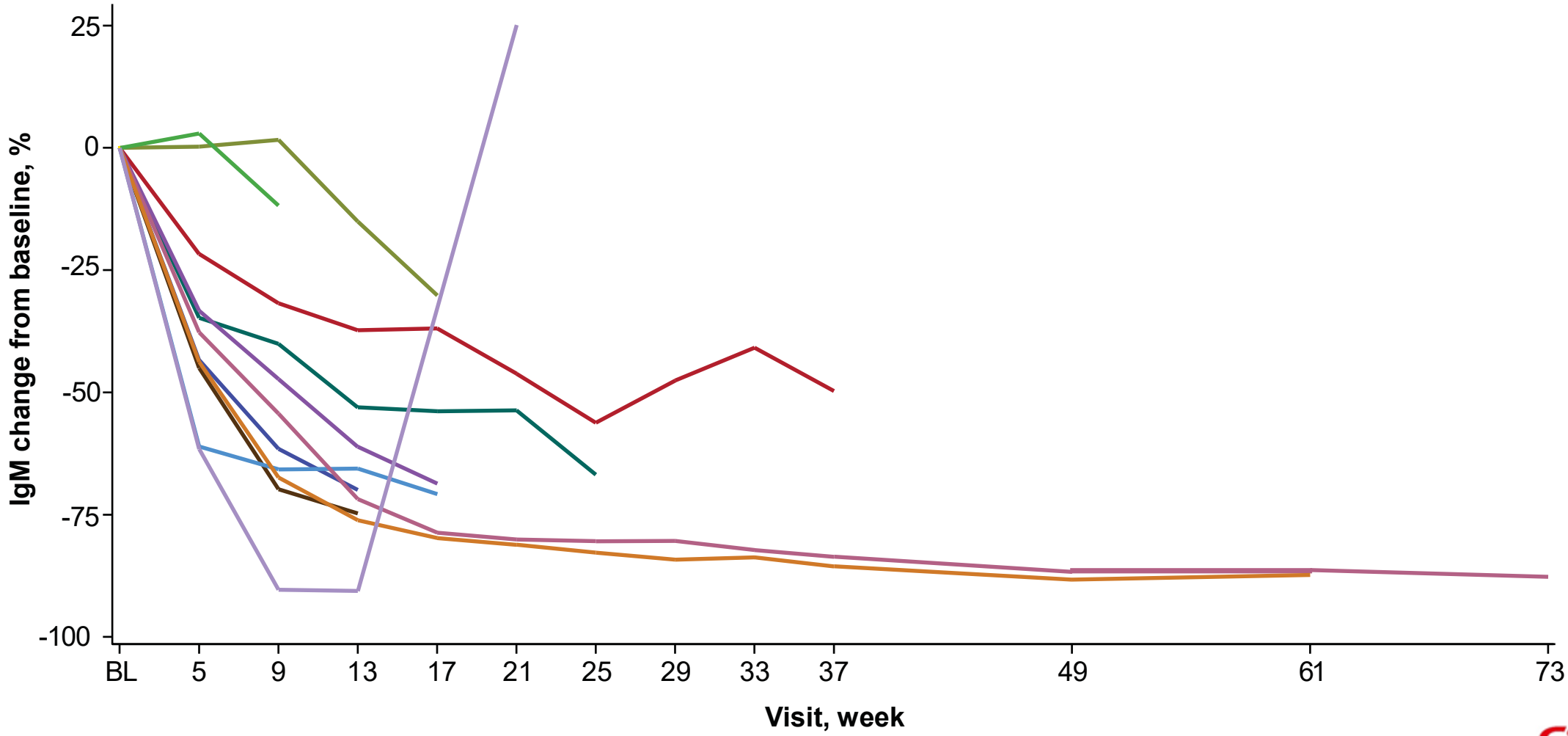
Treatment Duration and Response Assessment



[a] Gray shading = patient had the indicated prior therapy; [b] BTK mutation status was classified as present (Y), absent (N), or unknown (U).
[c] Mutated L528F, L528W, C481S. [d] Mutated C481Y and C481S.
BCL2i, B-cell lymphoma 2 inhibitor; cBTKi, covalent BTK inhibitor; MR, minor response; mut, mutation; ncBTKi, noncovalent BTK inhibitor, VGPR, very good PR.

Percent Change From Baseline in IgM for Patients With WM

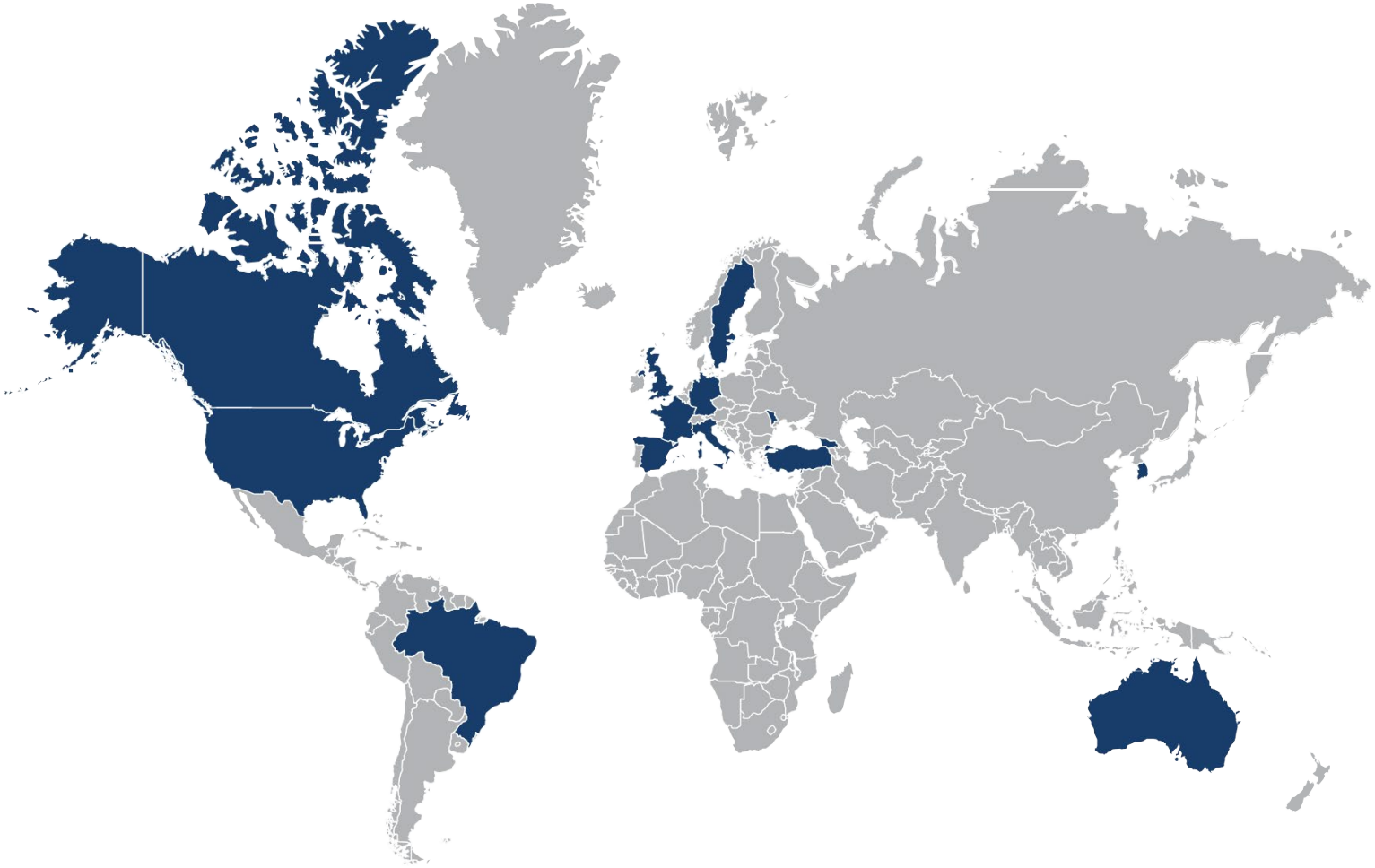
- All patients with WM had a numerical reduction from baseline in IgM



BL, baseline; IgM, Immunoglobulin M.

CaDAnCe-101 Study Status

- Enrollment for CaDAnCe-101 part 1c and phase 2 is ongoing at 90 of 110 planned study sites across the US, Canada, Brazil, the UK, France, Germany, Italy, Spain, Sweden, Moldova, Turkey, Georgia, South Korea and Australia



Conclusions

- Updated data from this ongoing, first-in-human study show that the novel BTK degrader BGB-16673 appears to have a safe and tolerable profile, with no DLTs in patients with MZL, WM, or FL
  - Discontinuations due to TEAEs were low (1 of 25 patients)
  - No atrial fibrillation has been reported so far
- BGB-16673 had durable antitumor activity with a short time to response in heavily pretreated patients with NHL, including those with BTK inhibitor–resistant disease
  - In the high-risk heavily pretreated (median of 4 prior lines of therapy) population of patients with NHL, the ORR was 75%
  - The ORR was 57% in patients with FL, 60% in patients with MZL, and 92% in patients with WM
- These data support further investigation of the clinical activity of BGB-16673 in patients with NHL; dose finding and additional safety expansion (part 1c) are ongoing and enrollment continues in the CaDAnCe-101 study

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Corresponding author:
Erna Yang, erna.yang@beigene.com