A Phase 1 First-In-Human Study of BGB-16673, a Bruton Tyrosine Kinase Protein Degrader, in Patients With B-Cell Malignancies (Trial in Progress)

Abstract P686

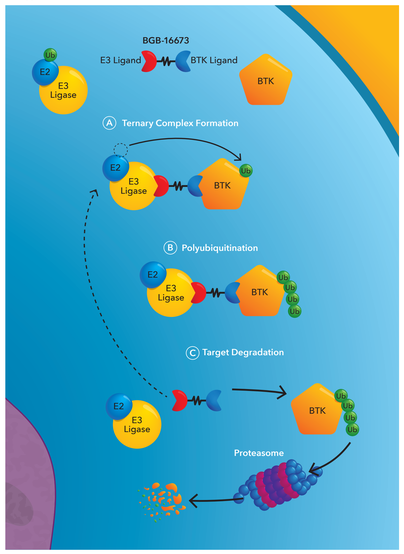
Constantine S. Tam,[1] Chan Cheah,[2,3,4] Don A. Stevens,[5] Kunthel By,[6] Xiangmei Chen,[6] Bilal Tariq,[6] Gregory S. Vosganian,[6] Jane Huang,[6] and Maan Alwan[7]

[1]Alfred Hospital and Monash University, Melbourne, Victoria, Australia; [2]Department of Haematology, Sir Charles Gairdner Hospital and Pathwest Laboratory Medicine, Nedlands, Western Australia, Australia; [3]Medical School, University of Western Australia, Crawley, Western Australia, Australia; [4]Linear Clinical Research, Nedlands, Western Australia, Australia; [5]Norton Cancer Institute, Louisville, KY, USA; [6]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; and [7]Perth Blood Institute, West Perth, Western Australia, Australia

INTRODUCTION

- Bruton tyrosine kinase (BTK) functions downstream of the B-cell antigen receptor (BCR) and plays a critical role within the BCR signaling pathway and the pathogenesis of several B-cell malignancies[1,2]
- BTK inhibitors are critical components in the clinical armamentarium in the management of B-cell malignancies[3-5]
- However, *BTK* mutations can abrogate BTK inhibitor binding capacity, resulting in resistance that may limit therapeutic options in subsequent lines of therapy[6-8]
- Therapeutics that can overcome on-target resistance mutations emerging from BTK inhibitor treatment may represent a novel treatment option
- BGB-16673 is an investigational BTK-targeting chimeric degradation activation compound (CDAC) active against both wild-type and mutant BTK (**Figure 1**)

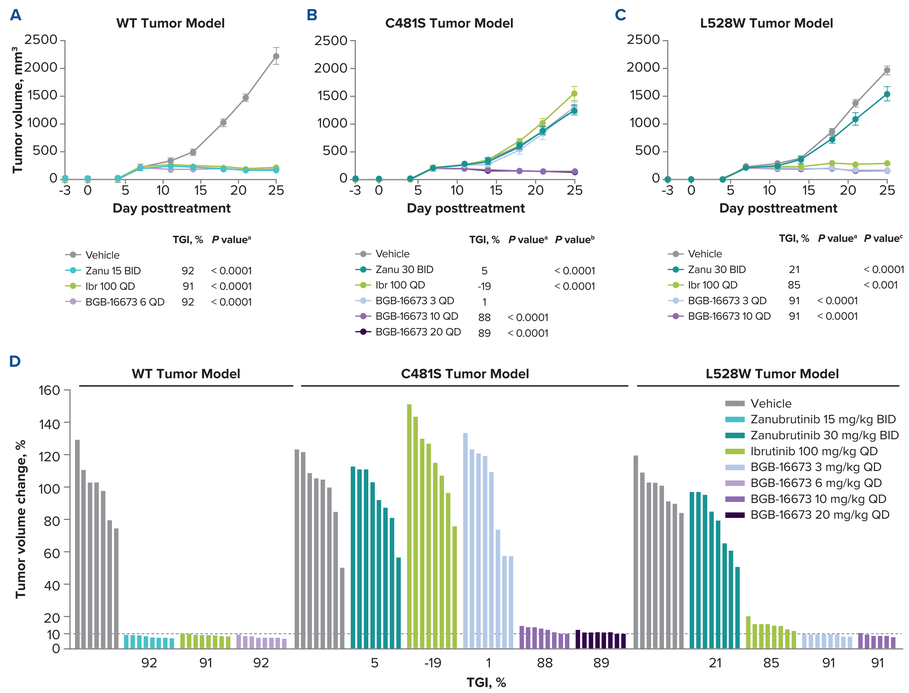
Figure 1. CDAC Mechanism of Action



BTK, Bruton tyrosine kinase; CDAC, chimeric degradation activation compound; E2, ubiquitin-conjugating enzymes; E3, ubiquitin ligases; Ub, ubiquitin.

- BGB-16673 has demonstrated antitumor activity in murine xenograft models with wild-type BTK and models with BTK inhibitor–resistant mutations commonly observed in patients who have progressed on prior BTK inhibitor treatment (**Figure 2**)

Figure 2. BGB-16673 Antitumor Activity in (A) Wild-Type, (B) C481S, and (C) L528W Tumor Models With (D) Waterfall Plot



3 QD, 3 mg/kg QD; 6 QD, 6 mg/kg QD; 6 mg/kg BID; 10 QD, 10 mg/kg QD; 15 BID, 15 mg/kg BID; 20 QD, 20 mg/kg QD; 30 BID, BID, twice a day; 100 QD, 100 mg/kg QD; BTKi, BTK inhibitor; Ibr, ibrutinib; QD, once a day; TGI, tumor growth inhibition; WT, wild type; Zanu, zanubrutinib.
[a]Versus vehicle group for each tumor model. [b]Versus BGB-16673 10 mg/kg. [c]Versus BGB-16673 3 mg/kg. Welch ANOVA with Tamhane multiple comparison test was used for all statistical analyses. Tumor cells were implanted subcutaneously in female NCG mice. Starting on day 3 after inoculation, mice were treated with vehicle, BGB-16673, zanubrutinib, or ibrutinib for 27 days. Tumor volume was measured twice a week starting at Day 6 posttreatment. Data are presented as mean tumor volume ± SEM of 7 or 8 animals in each group. Waterfall plot depicts tumor volume change on day 25 posttreatment.

OBJECTIVES

- BGB-16673-101 (NCT05006716) is a phase 1 open-label, dose-escalation, and dose-expansion study evaluating BGB-16673 in adult patients with relapsed/refractory (R/R) B-cell malignancies

Dose Escalation

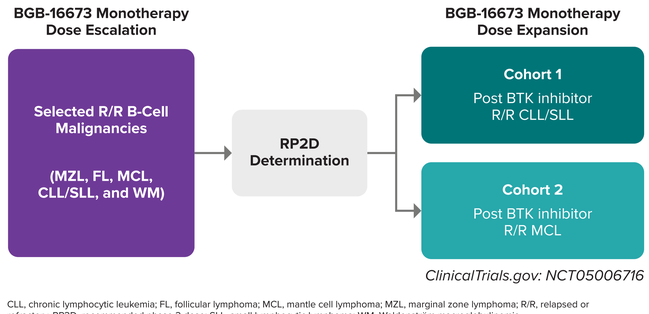
- To assess the safety and tolerability of BGB-16673 in select R/R B-cell malignancies
- To characterize the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of BGB-16673
- To define the recommended phase 2 dose (RP2D) of BGB-16673

Dose Expansion

- To evaluate the safety, tolerability, PK, PD, and antitumor activity of BGB-16673 monotherapy at the RP2D in patients with post-BTK inhibitor R/R CLL/SLL and MCL

METHODS

Figure 3. Study Design



ClinicalTrials.gov: NCT05006716

CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; R/R, relapsed or refractory, RP2D, recommended phase 2 dose; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia.

Key Inclusion Criteria

- Age ≥ 18 years
- Confirmed diagnosis of R/R B-cell malignancy (including marginal zone lymphoma, follicular lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, and Waldenström macroglobulinemia [WM])
- Eastern Cooperative Oncology Group performance status score of 0 to 2
- Measurable disease by radiographic assessment or serum IgM level (WM only)

Key Exclusion Criteria

- Current or history of central nervous system involvement
- Autologous stem cell transplant within 3 months of the first dose of BGB-16673
- Chimeric antigen receptor T-cell therapy or allogeneic stem cell transplantation within 6 months of the first dose of BGB-16673
- Requires treatment with strong inhibitors or inducers of CYP3A
- Requires ongoing systemic treatment for any other malignancy
- Requires ongoing systemic (defined as ≥10 mg/day of prednisone or equivalent) corticosteroid treatment

- All patients will be followed for safety and tolerability, including treatment-emergent adverse events that occur during treatment and up to 30 days after treatment discontinuation, or until the initiation of another anticancer therapy, whichever occurs first
- The totality of the available safety, efficacy, PK, and PD data from the dose-escalation part will be used by the safety monitoring committee to determine the RP2D
- Responses will be evaluated per the 2014 Lugano Classification,[9] the 2018 International Workshop on CLL guidelines response assessment with modification for treatment-related lymphocytosis,[10] or the 6th International Workshop on WM consensus criteria[11]
- Additional efficacy analyses will include progression-free survival and overall survival
- All patients will give informed consent

RESULTS

- This is a trial in progress; safety and tolerability results of BGB-16673 are expected

CONCLUSIONS

- BGB-16673-101 is the first-in-human study of the BTK degrader BGB-16673

REFERENCES

1. Good L, et al. *Cancer Immunol Immunother.* 2021;70(9):2439-2451.
2. Singh SP, et al. *Mol Cancer.* 2018;17(1):57.
3. NCCN Guidelines® for B-cell lymphomas version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf Accessed April 25, 2022.
4. NCCN Guidelines® for Chronic lymphocytic leukemia/small lymphocytic lymphoma version 2.2022 https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf Accessed January 18, 2022
5. NCCN Guidelines® for Waldenström macroglobulinemia/lymphoplasmacytic lymphoma version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf Accessed May 2, 2022
6. Preetesh J, et al. *Br J Haematol.* 2018;183(4):578-87.
7. Xu L, et al. *Blood.* 2017;129(18):2519-2525.
8. Woyach J, et al. *Blood.* 2019;134(1):504.
9. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.
10. Hallek M, et al. *Blood.* 2018;131(25):2745-2760.
11. Owen RG, et al. *Br J Haematol.* 2013;160:171-176.

DISCLOSURES

CST: honoraria with Janssen, AbbVie, BeiGene, Loxo, Novartis; research funding from Janssen, AbbVie, BeiGene

CC: honoraria and consulting role with Roche, Janssen, MSD, Gilead, Ascentage Pharma, AstraZeneca, Lilly, TG Therapeutics, BeiGene, Novartis, BMS; research funding from BMS, Roche, AbbVie; travel expenses from Roche

KB: employment with BeiGene

BT: employment, stock ownership, and research funding from BeiGene

GSV: employment with BeiGene; stock ownership with BeiGene, Abbvie, Roche

JH: employment with BeiGene; leadership role with BeiGene, Protara; stock ownership with BeiGene, Roche; research funding and patents from BeiGene

MA: employment with Western Diagnostic Pathology

DAS, XC: nothing to disclose

CORRESPONDENCE

Constantine S. Tam, MBBS (Hons), MD, FRACP, FRCPA
Alfred Hospital and Monash University
55 Commercial Road
Melbourne, Victoria 3004
Australia
constantine.tam@alfred.org.au

ACKNOWLEDGMENTS

We would like to thank Xi Wu and Xiangmei Chen from BeiGene for support regarding preclinical and translational data, the investigators, site support staff, and especially the patients for participating in this study.

This study was sponsored by BeiGene. Editorial support was provided by Bio Connections LLC and funded by BeiGene.

Copies of this poster obtained through the Quick Response (QR) Code are for personal use only and may not be reproduced without permission from EHA® and the author of this poster.