# An Update on Safety and Preliminary Efficacy of Highly Specific Bruton Tyrosine Kinase (BTK) Inhibitor Zanubrutinib in Combination With PD-1 Inhibitor Tislelizumab in Patients With Previously Treated B-Cell Lymphoid Malignancies

Abstract 1594


Constantine S. Tam, MBBS, MD[1-4]; Gavin Cull, MBBS, DM, FRACP, FRCPA[5,6]; Stephen Opat, MBBS (Hons), FRACP, FRCPA[7,8]; Gareth P. Gregory, MBBS (Hons), PhD, FRACP, FRCPA[7,8]; Aichun Liu, MD[9]; Anna M. Johnston, FRACP, FRCPA, MBBS[10]; Weili Zhao, MD, PhD[11,12]; Fernando Roncolato, BMed, FRACP, FRCPA[13]; Sasanka M. Handunnetti, MBBS (Hons), FRACP, FRCPA[1,4]; H. Miles Prince, MBBS (Hons), MD, FRACP, FRCPA, AFRCMA, MACD[1,2,14]; Costas K. Yannakou, MBBS (Hons), FRACP, FRCPA[14]; Wenyu Li, MD, PhD[15]; Ted Shih, PharmD[16]; Xiaoping Zhang, MD, MS[16]; Ken Wu, PhD[16]; Yuan Liu[16]; Jane Huang, MD[16]; and Judith Trotman, MBChB, FRACP, FRCPA[17,18]

[1]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia; [2]University of Melbourne, Parkville, Victoria, Australia; [3]St Vincent's Hospital, Fitzroy, Victoria, Australia; [4]Royal Melbourne Hospital, Parkville, Victoria, Australia; [5]Sir Charles Gairdner Hospital, Perth, Western Australia, Australia; [6]University of Western Australia, Perth, Western Australia, Australia; [7]Monash Health, Clayton, Victoria, Australia; [8]Monash University, Clayton, Victoria, Australia; [9]Harbin Medical University Cancer Hospital, Harbin, Heilongjiang Province, China; [10]Royal Hobart Hospital, Hobart, Tasmania, Australia; [11]Department of Hematology, Shanghai Institute of Hematology, Shanghai, China; [12]Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [13]St George Hospital, Kogarah, New South Wales, Australia; [14]Epworth HealthCare, East Melbourne, Victoria, Australia; [15]Guangdong General Hospital, Guangzhou, Guangdong Province, China; [16]BeiGene (Beijing) Co., Ltd., Beijing, China, and BeiGene USA, Inc., San Mateo, CA, USA; [17]Concord Repatriation General Hospital, Concord, New South Wales, Australia; and [18]University of Sydney, Concord, New South Wales, Australia

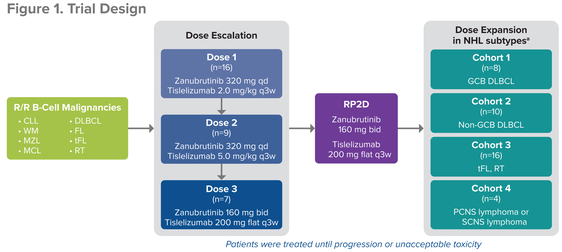

## INTRODUCTION

- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1-3]
- Zanubrutinib (BGB-3111) is an investigational, next-generation, irreversible BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases[4]
  - Has been shown in nonclinical studies to be a highly potent, selective, bioavailable, and irreversible BTK inhibitor with potentially advantageous pharmacokinetic (PK)/pharmacodynamic properties
  - Complete and sustained BTK occupancy observed in both peripheral blood mononuclear cells and in lymph nodes
- Tislelizumab is an investigational IgG4 variant monoclonal antibody with high affinity and specificity for the programmed cell death-1 (PD-1) receptor[5,6]
  - Engineered to minimize binding to Fc-γ receptor on macrophages to mitigate macrophage-driven killing of effector T cells, which may compromise the antitumor activity of PD-1 inhibitors
  - Currently under development for the treatment of solid tumors and hematologic malignancies
- Zanubrutinib and tislelizumab have shown encouraging efficacy as monotherapies in phase 2 studies for hematologic malignancies[6,7]
- PD-1/programmed death ligand 1 and B-cell receptor pathway inhibitors are being evaluated in combination for various B-cell malignancies, with the expectation of an additive or synergistic effect[8]

## OBJECTIVE

- To evaluate safety, tolerability, and efficacy of zanubrutinib in combination with tislelizumab in patients with relapsed/refractory aggressive non-Hodgkin lymphomas (NHLs)

### Figure 1. Trial Design




*Patients were treated until progression or unacceptable toxicity*

Data cutoff date: August 31, 2019.
bid, twice daily; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B cell; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PCNS, primary central nervous system; q3w, every 3 weeks; qd, once daily; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; RT, Richter transformation; SCNS, secondary central nervous system; tFL, transformed FL; WM, Waldenström macroglobulinemia.
[a]Cohorts 1, 2, and 4 had slots available for up to 10 patients; cohort 3 had slots available for up to 20 patients.

- Open-label, multicenter, phase 1b trial (NCT02795182) of zanubrutinib in combination with tislelizumab in patients with relapsed/refractory B-cell malignancies (**Figure 1**)

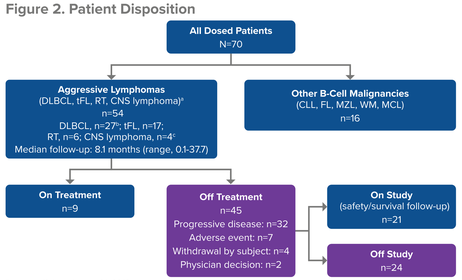
## METHODS

### End Points

- Primary
  - Dose escalation: maximum tolerated dose and recommended phase 2 dose (RP2D), based on the incidence of dose-limiting toxicities, safety, tolerability, and PK profile
  - Dose expansion: safety and tolerability of the combination determined by occurrence and severity of adverse events (AEs) per Common Terminology Criteria for AEs, version 4.03
- Secondary
  - Overall response rate, progression-free survival, and duration of response
  - Incidence and development of antidrug antibody to tislelizumab when administered in combination with zanubrutinib
- Exploratory analyses
  - PK profiles of the combination treatment
  - Predictive biomarkers (eg, mutation analysis), changes in tumor microenvironment, and mechanisms of resistance
  - Cerebral spinal fluid concentrations of study drugs for patients with central nervous system lymphoma

## RESULTS

### Figure 2. Patient Disposition




Data cutoff date: August 31, 2019
CLL, chronic lymphocytic leukemia; CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B cell; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; RT, Richter transformation; tFL, transformed follicular lymphoma.
[a]MCL is considered aggressive, but was not selectively enrolled in dose expansion and thus was not included here.
[b]15 Non-GCB; 12 GCB.
[c]3 Primary CNS lymphoma; 1 secondary CNS lymphoma.

- In total, 70 patients with B-cell malignancies (safety population) were enrolled and treated in dose escalation and expansion, of which 54 patients had aggressive NHL subtypes (efficacy population; **Figure 2** and **Table 1**)
- The maximum tolerated dose was not reached in dose escalation; 1 dose-limiting toxicity (grade 3 hypersensitivity reaction) occurred at the RP2D in a patient with Richter transformation

### Table 1. Patient and Disease Characteristics (Aggressive NHLs)

| Characteristic | Aggressive NHLs (n=54) |
|---|---|
| **Age, median (range), y** | 68 (27-86) |
| **ECOG PS, n (%)** | |
| 0 | 21 (39) |
| 1 | 25 (46) |
| 2 | 8 (15) |
| **No. of prior systemic therapies, median (range)** | 3 (1-10) |
| **Refractory to most recent systemic therapy, n (%)** | 20 (37) |
| **Time from end of most recent systemic therapy to study entry, median (range), mo** | 2.3 (0-62.5) |

ECOG PS, Eastern Cooperative Oncology Group performance status; NHL, non-Hodgkin lymphoma.

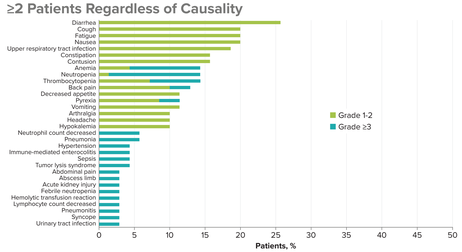
- Grade ≥3 treatment-emergent AEs were reported in approximately 71% of patients (**Table 2**)
- Related serious AEs occurred in approximately 33% of patients
  - Events reported in ≥2 patients were
    - Immune-related (IR) enterocolitis (n=3)
    - Abscess limb, anemia, back pain, hematuria, pneumonia, pneumonitis, and urosepsis (n=2)
    - Hemolytic transfusion reaction (n=2)
      - Occurred in 2 patients with Waldenström macroglobulinemia and led to discontinuation of further enrollment of patients with this subtype[9]
- AEs leading to study drug discontinuation (≥1 drug) in 14% of patients were mostly serious and IR, including pneumonitis, IR hepatitis, IR enterocolitis, and IR encephalitis
- Fatal AEs (grade 5) in the 5 patients were
  - Multi-organ dysfunction (in the setting of progressive disease [PD])
  - Septic shock and pneumonia (in the setting of PD)
  - Respiratory failure (in the setting of PD)
  - Aspiration pneumonia (in the setting of PD)
  - Toxic epidermal necrolysis (related to tislelizumab)
    - Toxic epidermal necrolysis, an IR AE, was observed in a patient after 2 doses; patient died despite study treatment discontinuation and use of antibiotics, intravenous immunoglobulin, and corticosteroids

### Table 2. Safety Summary

| AEs, n (%) | N=70[a] |
|---|---|
| **Total** | 68 (97.1) |
| Grade ≥3 | 50 (71.4) |
| Related SAEs[b] | 23 (32.9) |
| Leading to discontinuation of either or both drugs | 10 (14.3) |
| Fatal | 5 (7.1) |

AE, adverse event; SAE serious AE.
[a]Safety data are pooled across all patient cohorts in dose escalation and expansion phases. In addition to aggressive non-Hodgkin lymphoma subtypes, also includes patients with chronic lymphocytic leukemia (n=5), Waldenström macroglobulinemia (n=2), marginal zone lymphoma (n=1), follicular lymphoma (n=6), and mantle cell lymphoma (n=2) enrolled during dose escalation. [b]Patients with serious treatment-related AE related to either study drug.

### Figure 3. TEAEs in ≥10% of Patients or Grade ≥3 TEAEs in ≥2 Patients Regardless of Causality




TEAE, treatment-emergent adverse event.

- The most common treatment-emergent AEs were diarrhea (26%); fatigue, cough, and nausea (each 20%); and upper respiratory tract infection (19%; **Figure 3**)

### Table 3. Grade ≥3 IR AEs

| Events, n (%) | N=70 |
|---|---|
| **Patients with ≥1 specific grade ≥3 IR AE** | 11 (15.7) |
| **Immune-mediated enterocolitis** | 3 (4.3) |
| **Pneumonitis** | 2 (2.9) |
| **ALT increased, GGT increased, diarrhea, eczema, autoimmune encephalitis, immune-mediated hepatitis, maculopapular rash, toxic epidermal necrolysis, immune synovitis** | each 1 (1.4) |

AE, adverse event; ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; IR, immune-related.

- Grade ≥3 IR AEs were reported in 15.7% of patients (**Table 3**).

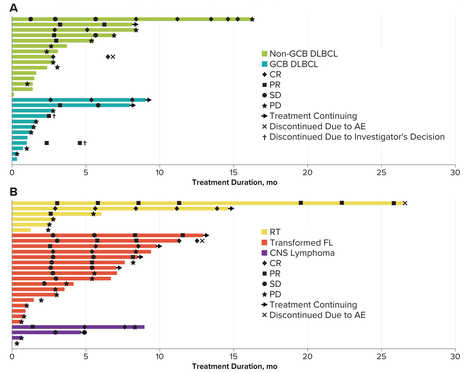
### Table 4. Best Response

| Response | DLBCL GCB (n=12) | DLBCL Non-GCB (n=15) | DLBCL All DLBCL (n=27) | CNS lymphoma (n=4) | RT (n=6) | tFL (n=17) | Aggressive Total (n=54)[a] |
|---|---|---|---|---|---|---|---|
| **Follow-up, median (range), mo** | 5.4 (0.6-29.8) | 8.9 (0.1-30.8) | 7.7 (0.1-30.8) | 3.2 (1.0-10.8) | 14.5 (3.5-37.7) | 8.4 (0.9-34.4) | 8.1 (0.1-37.7) |
| **ORR, n (%)** | **4 (33.3)** | **6 (40.0)** | **10 (37.0)** | **1 (25.0)** | **3 (50.0)** | **6 (35.3)** | **20 (37.0)** |
| **Best overall response, n (%)** | | | | | | | |
| CR | 1 (8.3) | 3 (20.0) | 4 (14.8) | 1 (25.0) | 1 (16.7) | 3 (17.6) | 9 (16.7) |
| PR | 3 (25.0) | 3 (20.0) | 6 (22.2) | 0 (0.0) | 2 (33.3) | 3 (17.6) | 11 (20.4) |
| SD | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (25.0) | 0 (0.0) | 4 (23.5) | 5 (9.3) |
| PD | 7 (58.3) | 8 (53.3) | 15 (55.6) | 2 (50.0) | 3 (50.0) | 7 (41.2) | 27 (50.0)[b] |
| Discontinued before first assessment | 1 (8.3) | 1 (6.7) | 2 (7.4) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2 (3.7) |

CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B cell; ORR, overall response rate; PD, progressive disease; PR, partial response; RT, Richter transformation; SD, stable disease; tFL, transformed follicular lymphoma.
[a]Includes patients with any postbaseline disease assessments or who had discontinued from the study as of the data cutoff date. One patient with secondary CNS lymphoma and 2 patients with tFL were excluded from the evaluable population because they were still on study and had no disease assessments as of the data cutoff date.
[b]Includes patients who have progressed clinically or died from disease under study based on investigator judgment and without confirmed imaging by positron emission tomography-computed tomography or computed tomography.

- 37% of patients with aggressive NHLs experienced an overall response, with median follow-up of 8.1 months (**Table 4**)
  - Responses were comparable across subtypes of NHLs; of note, 50% of patients with Richter transformation achieved an objective response
  - Complete responses were observed across all aggressive NHL subtypes

### Figure 4. Duration of Treatment in Patients With (A) DLBCL and (B) Other Aggressive Lymphomas (CNS Lymphoma, Transformed FL, RT)




AE, adverse event; CNS, CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GBC, germinal center B cell; PD, progressive disease; PR, partial response; RT, Richter transformation; SD, stable disease.

- 17% of patients remain on treatment, most of whom (6 of 9) have other aggressive lymphomas (**Figure 4**)

### Table 5. Progression-Free Survival

| | DLBCL (n=27) | CNS lymphoma (n=4) | RT (n=6) | tFL (n=17) |
|---|---|---|---|---|
| **PFS, median (95% CI), mo** | 2.7 (1.4-5.3) | 4.5 (0.3-8.3) | 4.1 (2.4-NE) | 5.4 (1.7-8.3) |
| **Follow-up time, median, mo** | 6.5 | NE | 23.9 | 8.5 |

CNS, central nervous system; DLBCL, diffuse large B-cell lymphoma; NE, not estimable; PFS, progression-free survival; RT, Richter transformation; tFL, transformed follicular lymphoma.

- Median progression-free survival ranged from nearly 3 to 5 months in treated patients (**Table 5**)

## CONCLUSIONS

- The RP2Ds from dose escalation are the established full single-agent doses of zanubrutinib 160 mg twice daily and tislelizumab 200 mg administered every 3 weeks
- The combination of zanubrutinib and tislelizumab demonstrated a safety profile that is consistent with known class toxicities of BTK and PD-1 inhibitors in B-cell malignancies
  - Overall, 14% of patients discontinued study treatment (≥1 drug)
  - Most frequent grade ≥3 AEs were neutropenia (n=9), anemia (n=7), and thrombocytopenia (n=5)
  - Grade ≥3 IR AEs were reported in 15.7% of patients, with IR enterocolitis (n=3) and pneumonitis (n=2) occurring in >1 patient
  - Related serious AEs in ≥2 patients included IR enterocolitis, anemia, hemolytic transfusion reaction, and pneumonitis
  - Grade 5 (fatal) events occurred in 5 (7.1%) patients, 4 of which were in the context of progressive disease
- IR AEs consistent with anti–PD-1 therapy were observed and managed with supportive therapy including corticosteroids; however, treatment termination was necessary in a subset of patients
- Clinical activity based on an overall response rate of 37% was observed in aggressive subtypes of NHL that included specific subtype responses as follows: diffuse large B-cell lymphoma (37%), transformed follicular lymphoma (35%), Richter transformation (50%), and central nervous system lymphoma (25%)

## REFERENCES


1. Rickert RC. *Nat Rev Immunol.* 2013;13:578-591.
2. Choe H, Ruan J. *Oncology (Williston Park).* 2016;15:pii:218737.
3. Aalipour A, Advani RH. *Br J Haematol.* 2013;163:436-443.
4. Tam CS, et al. *Blood.* 2019;34:851-859.
5. Qin S, et al. *Future Oncol.* 2019;15:1811-1822.
6. Song Y, et al. *HemoSphere.* 2019;3:185-186.
7. Song Y, et al. *Hematological Oncol.* 2019;37(suppl 2):45-46.
8. Cull G, et al. *Blood.* 2017;130(suppl 1, abstr):4057.
9. Othman J, et al. *Haematologica.* 2018;103(5):e223-e225.


## DISCLOSURES

**CST:** research funding from Janssen and AbbVie and honoraria from Janssen, AbbVie, BeiGene, Novartis, and Roche. **GC:** travel and accommodations expenses from Amgen, GlycoMimetics, and AbbVie. **SO:** consultancy with and honoraria from AbbVie, Janssen, Gilead, Roche, Mundipharma, Merck, Bristol-Myers Squibb, and Celgene and research funding from AbbVie, BeiGene, Janssen, Gilead, Roche, Celgene, and Epizyme. **GPG:** research funding from Monash University. **AMJ:** consultancy with Roche and member of board of directors/advisory committees for Roche and Janssen. **FR:** employed by St George Hospital. **SMH:** employed by Peter MacCallum Cancer Centre; honoraria from Gilead; and expenses from AbbVie. **HMP:** consulting with Takeda, Janssen, Amgen, and Allergan; research funding from Allergan; and honoraria from Takeda, Janssen, Amgen, Celgene, and Allergan. **WL:** employed by Guangdong Province Hospital. **TS, XZ, KW, YL, and JH:** employed by and equity ownership in BeiGene. **JT:** research funding from BeiGene, Janssen, Celgene, Pharmacyclics, and Roche. **AL, WZ, and CKY:** no relevant financial conflicts to disclose.

## CORRESPONDENCE


Constantine.Tam@petermac.org


## ACKNOWLEDGMENTS


We would like to thank 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.





*Presented at the 61st American Society of Hematology Annual Meeting, December 7-10, 2019; Orlando, FL*