Safety and Activity of BTK Inhibitor Zanubrutinib (BGB-3111) in Combination with the PD1 Inhibitor Tislelizumab (BGB-A317) in Patients with B-Cell Lymphoid Malignancies

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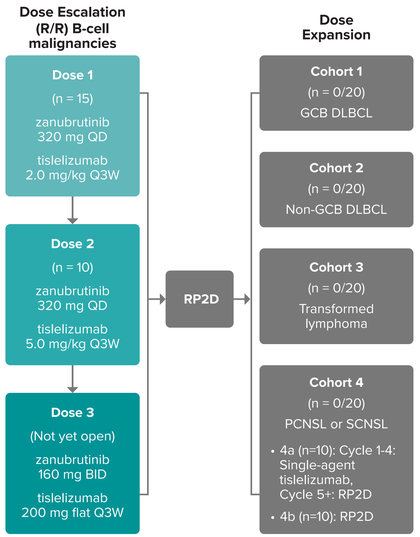
INTRODUCTION

- Bruton's Tyrosine Kinase (BTK) plays a critical role in B cell receptor (BCR) signaling, which mediates B cell proliferation, migration, and adhesion[1-3]
- Based on preclinical data, zanubrutinib (BGB-3111) was shown to be a potent, highly specific, and irreversible BTK inhibitor with greater selectivity for BTK vs other TEC- and EGFR-family kinases and favorable pharmacokinetic and pharmacodynamic properties[4]
- Immune checkpoint inhibitor tislelizumab (BGB-A317) is a humanized IgG4 variant monoclonal antibody, which targets the programmed cell death 1 (PD1) receptor and which is engineered to have no Fc gamma receptor binding
  - Under development for the treatment of solid tumors and hematologic malignancies
- Preclinical data has shown BTK inhibitors to be synergistic with checkpoint inhibitors,[5] with their combination expected to result in greater benefit for patients with B-cell malignancies
- Here, we present early safety data from a Phase 1b trial exploring the combination of zanubrutinib and tislelizumab

METHODS

- First-in-human, open-label, multicenter, Phase 1b trial to evaluate safety, tolerability, and efficacy of zanubrutinib in combination with tislelizumab in patients with B-cell lymphoid malignancies (**Figure 1**)
  - Patients are to be treated until progression or unacceptable toxicity
  - Primary endpoints
    - Dose escalation: maximum tolerated dose and recommended Phase 2 dose, based on the incidence of protocol-defined dose-limiting toxicities (DLTs), safety, tolerability, and pharmacokinetic (PK) profile
    - Dose expansion: safety and tolerability of the combination determined by occurrence and severity of adverse events (AEs) per CTCAE v 4.03
  - Select secondary endpoints
    - Efficacy, including overall response rate, progression-free survival, and duration of response
    - PK profiles
    - Incidence and development of anti-drug antibody to tislelizumab

Figure 1. Trial Design

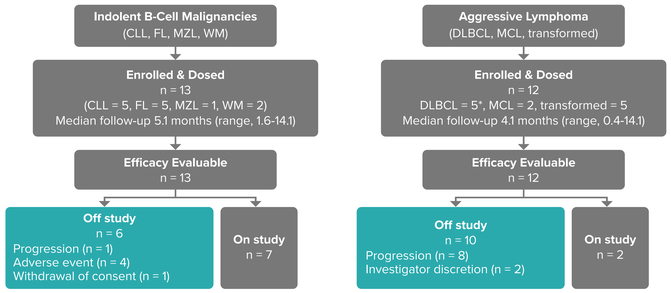


BID, twice daily; GCB DLBCL, germinal center B-cell diffuse B-cell lymphoma; PCNSL, primary central nervous system lymphoma; Q3W, every 3 weeks; QD, once daily; RP2D, recommended Phase 2 dose; SCNSL, secondary central nervous system lymphoma.

RESULTS

- Patient disposition at the current cutoff is shown in **Figure 2**
  - Median follow-up 5.1 months (range, 0.4-14.1) and 4.1 (0.4-14.1) for indolent B-cell maligiancies and aggressive lymphoma, respectively

Figure 2. Patient Disposition as of 15-SEP-2017



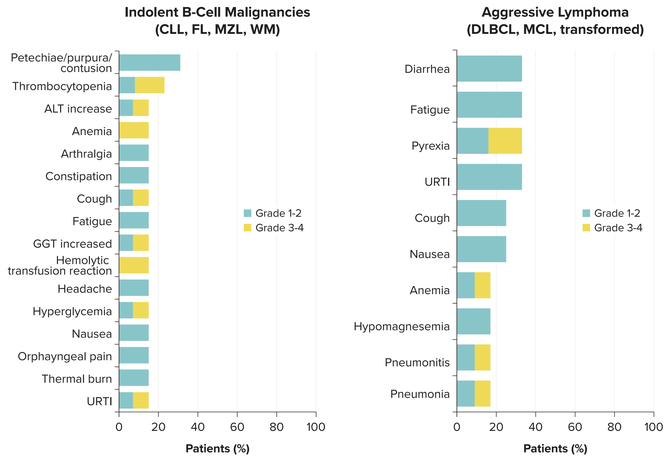
CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; FU, follow-up; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenstrøm's macroglobulinemia.
*3 non-GBC; 2 GBC.

Table 1. Patient and Disease Characteristics

Characteristic	Indolent (n = 13)	Aggressive (n = 12)	Total (N = 25)
Age, years, median (range)	62 (47-76)	62.5 (27-71)	62 (27-76)
ECOG performances status, n (%)			
0	7 (54)	3 (25)	10 (40)
1	3 (23)	7 (58)	10 (40)
2	3 (23)	1 (8)	4 (16)
3	0	1 (8)	1 (4)
Number of prior therapies, median (range)	4 (1-6)	4 (1-6)	4 (1-6)
Bulky disease,* n (%)	1 (8)	1 (8)	2 (8)
Dose 1 (zanubrutinib 320 mg QD, tislelizumab 2.0 mg/kg Q3W)	7 (54)	8 (67)	15 (60)
Dose 2 (zanubrutinib 320 mg QD, tislelizumab 5.0 mg/kg Q3W)	6 (46)	4 (33)	10 (40)

ECOG, Eastern Cooperative Oncology Group; GBC, germinal center B-cell; LDH, lactate dehydroganase; Q3W, every 3 weeks; QD, once daily.
* Any lymph node >10 cm in maximum diameter.

Figure 3. Most Common Adverse Events (> 10%) Regardless of Causality



CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; URTI, upper respiratory tract infection; WM, Waldenstrøm's macroblobulinemia.

- Immune-related AEs were reported in 20% of patients (**Table 2**)
- Serious adverse events were reported in approximately 70% of patients
- Serious AEs and AEs leading to treatment discontinuation were more commonly reported with Dose 2 (**Table 3**)

Table 2. Events of Special Interest

Events, n (%)	Indolent (n = 13)	Aggressive (n = 12)
Immune-related events		
Pneumonitis	0	2 (17)
Colitis	0	0
Hepatitis	0	0
Nephritis	0	0
Hemolytic transfusion reaction	2 (15)	0
Autoimmune encephalitis	1 (8)	0
Additional adverse events of special interest		
Atrial fibrillation/flutter	1 (8)	0
Petechiae/purpura/contusion	4 (31)	0
Hypertension	0	1 (8)
Diarrhea	1 (8)	4 (33)
Severe hemorrhage	0	0

- Serious adverse events of hemolytic transfusion reaction were reported in 2 patients with WM
  - Both patients were previously treated with multiple regimens of chemoimmunotherapy and required ongoing red cell transfusions for anemia
  - Shortly after initiating therapy with tislelizumab in combination with zanubrutinib, and during red cell transfusion, the patients reported abdominal pain and fever and had hematuria
  - Laboratory analysis showed worsening anemia, elevated LDH and negative Coomb's test
  - Both patients were treated with immunosuppressive therapy, including high-dose glucocorticoids, and the events resolved slowly over time
- A serious adverse event of autoimmune encephalitis was reported in a patient with CLL and a biopsy suggestive of large cell transformation
  - Approximately 2 months after initiating therapy tislelizumab in combination with zanubrutinib, the patient presented with functional decline, acute confusion, hypertonia and twitching in face and neck, and delirium
  - During a four-month hospitalization for this event, the patients mental status waxed and waned, at one point he was comatose
  - He was treated with aggressive immunosuppressive therapy and gradually improved over time
  - A thorough diagnostic work up ruled out other causes of encephalitis

Table 3. Safety Summary, Dose Comparison

Event, n (%)	Dose 1 (n = 15)	Dose 2 (n = 10)
Any AE	15 (100)	9 (90)
Grade ≥ 3 AE	11 (73)	8 (80)
Serious AE	10 (67)	8 (80)
Fatal AE	0	1* (10)
AE leading to discontinuation of either or both drugs	3 (20)	5 (50)
Death	4** (27)	2** (20)

AE, adverse event.
*Multiple organ dysfunction syndrome related to progression; **Deaths determined to be due to progressive disease.

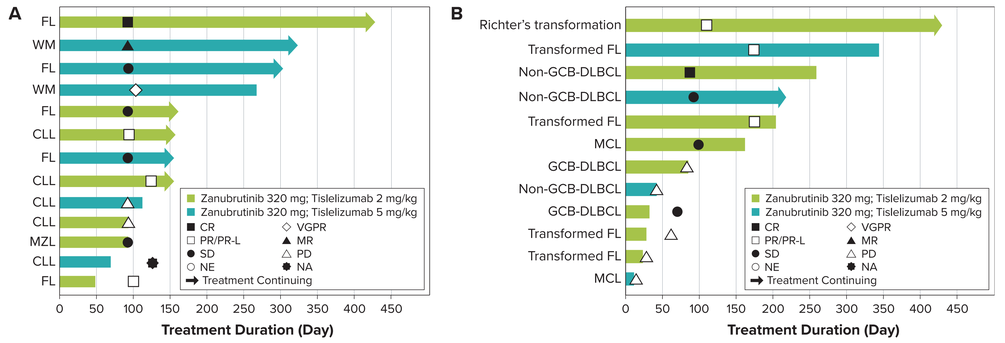
- 40% of patients experienced an objective response (**Table 4**, **Figure 4**)
  - Responses were seen in patients with indolent B-cell malignancies and aggressive lymphomas
- 36% of patients remain on treatment, the majority of which (7 of 9) have indolent B-cell malignancies (**Figure 4**)

Table 4. Best Response

Response	Indolent CLL (n = 5)	Indolent FL (n = 5)	Indolent MZL (n = 1)	Indolent WM (n = 2)	Aggressive DLBCL (n = 5)	Aggressive MCL (n = 2)	Aggressive Transformed (n = 5)	Total (N=25)
Median follow-up, mo (range)	3.7 (2.3-5.2)	5.3 (1.6-14.1)	3.1	9.1 (7.6-10.6)	2.8 (1.1-8.5)	2.8 (0.4-5.3)	6.7 (0.8-14.1)	5.1 (0.4-14.1)
Best Response, n (%)								
ORR	**2 (40)**	**2 (40)**	**0**	**2 (100)**	**1 (20)**	**0**	**3 (60)**	**10 (40)**
CR	0	1 (20)	0	0	1 (20)	0	0	2 (8)
VGPR	–	–	–	1 (50)	–	–	–	1 (4)
PR/PR-L	2 (40)	1 (20)	0	0	–	0	3 (60)	6 (24)
MR	–	–	–	1 (50)	–	–	–	1 (4)
SD	0	3 (60)	1 (100)	0	2 (40)	1 (50)	0	7 (28)
PD	2 (40)	0	0	0	2 (40)	1 (50)	2 (40)	7 (28)
Discontinuation or NE or ND*	1 (20)	0	0	0	0	0	0	1 (4)

CR, complete response; D/C, discontinuation; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease.
* Patient discontinued for reason other than PD before 1st response assessment or response assessment was either not evaluable or not done.

Figure 4. Duration of Treatment in Patients With (A) Indolent B-cell malignancies or (B) Aggressive Lymphoma



Note: symbols on figures indicate best response.
CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, folliular lymphoma; GCB, germinal center B-cell-like; MCL, mantle cell lymphoma; MR, minor response; MZL, marginal zone lymphoma; NA, not assessed; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

CONCLUSIONS

- Preliminary results from the Phase 1b trial suggest that the combination of BTK inhibitor zanubrutinib (BGB-3111) and the checkpoint inhibitor tislelizumab (BGB-A317) had a manageable toxicity profile in a wide variety of B-cell malignancies
  - Adverse events were attributed to the known single-agent toxicity profiles
- Autoimmune adverse events, consistent with anti-PD1 therapy, were observed and managed with supportive care
  - Pneumonitis (n=1) and encephalitis (n=1) led to discontinuation of tislelizumab
  - The severe hemolytic transfusion reactions following PRBC transfusions in 2 patients with WM suggests a unique limitation of this combination for WM given the high response rate seen in WM with single-agent zanubrutinib; 1 patient continued on zanubrutinib monotherapy
- Responses have been seen in both indolent B-cell malignancies and aggressive lymphomas, and further investigation into the activity of the combination in aggressive diseases such as in Richter's Transformation is warranted
- Enrollment into Dose 3 is ongoing

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.* 2015;126:832.
5. Sagiv-Barfi I, et al. *PNAS.* 2015;112:E966-72.

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