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Preclinical and clinical immune profiling of tacabrutideg (BGB-16673), a Bruton tyrosine kinase (BTK) degrader, shows preserved T-cell function and maintenance of key non-B-cell immune compartments in relapsed/refractory (R/R) chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)

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Introduction: Tacabrutideg (BGB-16673) is a potential first-in-class oral BTK degrader that induces BTK degradation through the proteasome pathway, leading to tumor regression. Tacabrutideg is currently being evaluated in the ongoing open-label, phase 1/2 CaDAnCe-101 study (BGB-16673-101; NCT05006716) in patients (pts) with B-cell malignancies. Infections remain an important consideration for pts with R/R CLL/SLL and for those receiving agents targeting B-cell receptor signaling, highlighting the need to understand treatment effects on broader non-B-cell compartments. Here we used preclinical selectivity, functional assays, and longitudinal clinical immune profiling to assess the impacts of tacabrutideg on selectivity and preservation of major non-B-cell immune compartments during treatment.

Methods: Ex vivo activity was evaluated using whole blood from healthy donors (n=6), incubated at 37°C for 16 hours with 160 nM of tacabrutideg, a clinically relevant concentration. After incubation, B cells, T cells, and neutrophils were isolated for proteomic analysis using liquid chromatography-tandem mass spectrometry. T-cell viability, proliferation, and activation were assessed in a staphylococcal enterotoxin B (SEB) stimulation assay using live/dead staining, carboxyfluorescein diacetate succinimidyl ester (CFSE) proliferation index, and IL-2 production, respectively. T-cell cytotoxic function was assessed in an EpCAM-CD3 T-cell engager–redirected killing assay against MKN45 cells. Clinical immune cell profiling was performed in pts with R/R CLL/SLL treated in the BGB-16673-101 trial using a validated TBNK flow cytometry panel. Absolute counts of $CD19^+$ B cells, $CD3^+$ T cells, $CD4^+$ and $CD8^+$ T-cell subsets, $CD3^-CD56^+/CD16^+$ natural killer (NK) cells, and $CD14^+$ monocytes were assessed at baseline and months 1, 6, 9, and 15. The analysis included 35 pts with evaluable baseline assessments and ≥1 post-baseline assessment. Data cutoff was March 25, 2026.

Results: In whole-blood proteomic profiling, tacabrutideg induced BTK degradation in BTK-expressing B cells and neutrophils. No off-target protein degradation was observed in T cells, which do not express BTK, demonstrating no off-target degradation with tacabrutideg. Tacabrutideg did not adversely affect T-cell viability, CFSE-defined T-cell proliferation, or IL-2 production in the SEB stimulation assay, and tacabrutideg did not impair T-cell mediated tumor-cell killing in the CD3 T-cell engager assay. Clinical immune cell profiles were available for 35 pts at baseline and for 30, 23, 21, and 5 pts at months 1, 6, 9, and 15, respectively. Tacabrutideg induced substantial and sustained depletion of $CD19^+$ B-cells with median counts decreasing from 20,664 cells/μL at baseline and 20,836 cells/μL at month 1, to 5741, 2405, and 252 cells/μL at months 6, 9, and 15, respectively. In contrast, non-B-cell immune compartments remained broadly preserved and showed no statistically significant ($p>0.05$) changes from baseline. Median $CD3^+$ T cell counts were 1925, 2839, 1494, 1755, and 1483 cells/μL at baseline and months 1, 6, 9, and 15, respectively. Corresponding median $CD4^+$ T cell counts were 1017, 1328, 798, 813, and 686 cells/μL and median $CD8^+$ T cell counts were 869,

1123, 676, 736, and 767 cells/μL. The median CD4:CD8 T cell ratio remained stable at 1.1, 1.2, 1.1, 1.0, and 0.9 across the same timepoints. Median NK cell counts were 214, 200, 168, 192, and 78 cells/μL, and median $CD14^+$ monocyte counts were 346, 399, 275, 331, and 375 cells/μL, at baseline and months 1, 6, 9, and 15, respectively. Overall, tacabrutideg selectively depleted $CD19^+$ B cells while quantitatively preserving T-cell subsets, NK cells, and monocytes.

Conclusions: These findings support a selective immune profile for tacabrutideg, characterized by expected B-cell depletion without evidence of broad host immune cell depletion of evaluated non–B-cell immune compartments. Preclinical assays showed preservation of T-cell viability and proliferation, IL-2 production, and T-cell–mediated killing, while clinical TBNK profiling showed maintenance of the T-cell, NK-cell, and monocyte compartments in pts with CLL treated with tacabrutideg. These data suggest that tacabrutideg has no major adverse impact on T cells, NK cells and monocytes.