

Company

BeiGene

Drug or Device Name

Brukinsa®

Category

Biotechnology

Compound/Technical Name

BGB-3111

Trade Name

Brukinsa®

Date of Approval

11/14/2019

Therapeutic Categories

B-cell malignancies

Indications

Date of FDA Approval: November 14, 2019 (relapsed/refractory mantle cell lymphoma); September 1, 2021 (Waldenström macroglobulinemia); September 16, 2021 (relapsed/refractory marginal zone lymphoma).

Background

The addition of ibrutinib, a first-generation Bruton tyrosine kinase inhibitor (BTKi), to the armamentarium of B-cell malignancies revolutionized treatment. However, ibrutinib has well-described, off-target effects, notably an increased risk for atrial fibrillation, hypertension, and hemorrhage, that limit its use.¹

Development

The design of zanubrutinib, a next-generation BTKi, was guided by a structure-activity strategy to ensure greater BTK specificity than ibrutinib to avoid off-target binding and associated toxicities.² During discovery, multiple BTKi structural permutations were assessed. After testing more than 3,000 compounds, the structure with the most favorable profile of oral bioavailability, potency (to ensure efficacy), and kinase selectivity (to ensure a safer BTKi) was selected and developed as zanubrutinib.

Innovation

Zanubrutinib provides improved BTK occupancy across disease-relevant tissues and greater selectivity than ibrutinib. Treatment with zanubrutinib results in 100% BTK inhibition in peripheral blood mononuclear cells (PBMC) and in nodal tissue.³ In contrast, ibrutinib BTK occupancy in PBMC in some

patients was sub-optimal for efficacy (<80%).⁴ Of the 370 kinases tested, zanubrutinib and ibrutinib demonstrated >50% inhibition in seven and 17 kinases, respectively.⁵ This increased selectivity has translated to an improved safety/tolerability profile; a pooled safety analysis of 779 patients who received zanubrutinib across six clinical trials (median duration, 26 months) demonstrated consistently low (<3.5%) rates of cardiovascular events known to be associated with ibrutinib.⁶ Zanubrutinib has been compared head-to-head with ibrutinib in two phase 3 studies in WM and CLL/SLL. In these studies (NCT03053440; NCT03734016), zanubrutinib demonstrated similar-to-improved efficacy and a more favorable safety/tolerability profile than ibrutinib.^{7,8} Across both studies, response observed with zanubrutinib was generally irrespective of patient subgroups (eg, age, sex, prior treatment status). Zanubrutinib provides a range of important clinical advantages with an improved safety/tolerability profile, regardless of individual characteristics of patients with B-cell malignancies. Given the prospect of synergy with other targeted therapies, zanubrutinib is poised to become a BTKi backbone for combination therapies across B-cell malignancies. Parlaying the learnings and developmental approach beyond oncology, zanubrutinib may also have clinical effects in other therapeutic areas. Currently, zanubrutinib is in phase 2 clinical trials for lupus nephritis (NCT04643470), and there are plans to explore zanubrutinib in other indications.

Pubmed

1. Estupiñán HY, Berglöf A, Zain R, Smith CIE. Comparative analysis of BTK inhibitors and mechanisms underlying adverse effects. *Front Cell Dev Biol.* 2021;9. 2. Guo Y, Liu Y, Hu N, et al. Discovery of zanubrutinib (BGB-3111), a novel, potent, and selective covalent inhibitor of Bruton's tyrosine kinase. *J Med Chem.* 2019;62(17):7923-7940. 3. Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. *Blood.* 2019;134(11):851-859. 4. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. *N Engl J Med.* 2013;369(1):32-42. 5. Shadman M, Flinn IW, Levy MY, et al. Phase 2 study of zanubrutinib in BTK inhibitor-intolerant patients with relapsed/refractory B-cell malignancies. *Blood.* 2021;138(Supplement 1):1410-1410. 6. Tam CS, Dimopoulos M, Garcia-Sanz R, et al. Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. *Blood Adv.* 2022;6(4):1296-1308. 7. Tam CS, Giannopoulos K, Jurczak W, et al. SEQUOIA: Results of a phase 3 randomized study of zanubrutinib versus bendamustine + rituximab in patients with treatment-naïve chronic lymphocytic leukemia/small lymphocytic lymphoma. *Blood.* 2021;138:396. 8. Hillmen P, Eichhorst B, Brown JR, et al. First interim analysis of ALPINE study: Results of a phase 3 randomized study of zanubrutinib vs ibrutinib in patients with relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma. Oral presentation at The EHA Virtual Congress; June 9-17, 2021.

Attachments

- 1651669964BTK_Occupancy_and_Selectivity_-_Prix_Galien.pdf
- 1651756834Zanu_fast_facts.pdf

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