ELSEVIER

Blood 142 (2023) 1887–1888

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

641.CHRONIC LYMPHOCYTIC LEUKEMIAS: BASIC AND TRANSLATIONAL

Abbv-101, a Highly Potent and Selective Clinical Stage Bruton Tyrosine Kinase Degrader for the Treatment of B-Cell Malignancies

Chin Pan, PhD[1], Tarikere L Gururaja, PhD[1], Haiyan Li, MDPhDMPH[1], Henry Nguyen, PhD[1], Yongjiao Zhai[1], Xiaoping Xie, PhD[1], Rong-Xian Ding[1], Rebecca Mathew, PhD[1], Hana Y Hoh, MSc[1], Zhaozhong J Jia, PhD[1], Bo Liu, PhD[1], Cassandra Shu, PhD[1], Wissam Assaily, PhD[1], Lloyd T Lam, PhD[2], Jacob J Riehm, MS[2], Claudina Stevenson, PhD[2], Christine Will, MS[2], Federico Innocenti, MDPhD[1], Alexey Rivkin, PhD[3]

[1] AbbVie Bay Area, South San Francisco, CA
[2] AbbVie Inc., North Chicago, IL
[3] AbbVie Bay Area, SAN FRANCISCO, CA

Bruton tyrosine kinase (BTK), a clinically validated target for various B-cell malignancies, plays a critical role in regulating cell growth, adhesion and homing to key lymphoid tissues that provide a microenvironment favorable to cancer cells. Despite the success of approved covalent BTK inhibitors in diseases such as CLL, most patients do not achieve complete response with monotherapy and eventually relapse, often via the emergence of the BTK-C481S mutation. Additionally, covalent BTK inhibitors have not shown sufficient differentiation from standard-of-care (SoC) in B-cell malignancies such as diffuse large B cell lymphoma (DLBCL) to warrant approval to date. To address these unmet needs, a next-generation orally bioavailable BTK degrader ABBV-101 has been developed. Unlike BTK inhibitors that solely bind to and impede the catalytic domain of BTK, ABBV-101 eliminates the protein in a highly selective fashion. This degradation mechanism targets both the catalytic and scaffolding functions of BTK, and thus may enable deeper and more durable responses in patients with B-cell malignancies. In preclinical studies, the BTK degrader ABBV-101 has shown potent in vitro and in vivo efficacy in BCR pathway-dependent leukemia/lymphoma models, including covalent BTK inhibitor resistant BTK-C481S systemic mouse CLL and human DLBCL models. ABBV-101 degrades BTK-WT and BTK-C481S with similar sub-nanomolar potency in the human DLBCL cell line TMD8 which translates to potent cellular growth inhibition. In addition to the BTK-C481S mutation, ABBV-101 demonstrates similar potent activity against novel BTK mutations associated with resistance to reversible BTK inhibitors in the clinic, an emerging unmet need. ABBV-101 induces complete tumor regression in the BTK-C481S TMD8 DLBCL xenograft model. A spontaneous mouse CLL model carrying BTK-C481S mutation was developed through crossing BTK-C481S knock-in mice with the Emu-TCL1 transgenic mice in the C57BL/6 background. ABBV-101 completely inhibits BTK-C481S Emu-TCL1 CLL burden increase in the blood compartment and reduces CLL burden in the spleen and lymph nodes, whereas covalent BTK inhibitors show no activity. Further, ABBV-101 induces complete tumor regressions in multiple non-GCB DLBCL PDX models, demonstrating deeper and more durable response than covalent and reversible inhibitors. Combination with a BCL-2 inhibitor enhances the efficacy of ABBV-101 in CLL and DLBCL models. Kinome and global proteomics profiling showed ABBV-101 to be highly selective, a designed feature that may enable favorable tolerability in patients. ABBV-101 is currently in phase 1 clinical trial for a variety of B-cell malignancies. ClinicalTrials.gov identifier: NCT05753501

Disclosures Pan: *AbbVie:* Current Employment. **Gururaja:** *AbbVie:* Current Employment. **Li:** *AbbVie:* Current Employment. **Nguyen:** *AbbVie:* Current Employment. **Zhai:** *AbbVie:* Current Employment. **Xie:** *AbbVie:* Current Employment. **Ding:** *AbbVie:* Current Employment. **Mathew:** *AbbVie:* Current Employment. **Hoh:** *AbbVie:* Current Employment. **Jia:** *AbbVIe:* Current Employment. **Liu:** *AbbVie:* Current Employment. **Shu:** *AbbVie:* Current Employment. **Assaily:** *AbbVie:* Current Employment. **Lam:** *AbbVie:* Current Employment. **Riehm:** *AbbVie:* Current Employment. **Stevenson:** *AbbVie:* Current Employment. **Will:** *AbbVie Inc.:* Current Employment, Other: may own stock. **Innocenti:** *AbbVie:* Current Employment. **Rivkin:** *AbbVie:* Current Employment.

OffLabel Disclosure: Abbv-101, a Highly Potent and Selective Clinical Stage Bruton Tyrosine Kinase Degrader for the Treatment of B-Cell Malignancies

https://doi.org/10.1182/blood-2023-184835