

News Release

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Carna Biosciences, Inc.

Publication of Preclinical and Early Clinical Data Demonstrating Best-in-Class, Pan-Mutant Activity of BTK Inhibitor Docirbrutinib

Carna Biosciences, Inc. today announces the publication of a research article in *Blood Cancer Journal*, a high-impact journal from the Nature Publishing Group focusing on hematologic malignancies. The article presents new preclinical and early clinical findings on docirbrutinib (AS-1763), a best-in-class noncovalent BTK inhibitor being developed by Carna Biosciences.

Bruton's tyrosine kinase (BTK) inhibitors are commonly used as standard therapy for chronic lymphocytic leukemia (CLL), yet resistance emerges through mutations affecting both covalent and noncovalent BTK inhibitors. To address this challenge, the newly published article evaluates the next-generation noncovalent BTK inhibitor docirbrutinib across 14 BTK mutants using biochemical assays, engineered cell models, primary CLL samples, and correlative data from an ongoing Phase 1b study. Docirbrutinib demonstrated broad pan-mutant activity across 14 BTK mutants, showing low-nanomolar potency and outperforming existing covalent and noncovalent BTK inhibitors against multiple resistant variants. It also enhanced sensitivity to venetoclax and AZD5991, exhibiting synergy in cell-line models and re-sensitizing BTK-mutant primary CLL samples to pro-apoptotic agents.

“Our preclinical and early clinical data suggest that docirbrutinib has the potential to benefit patients with resistant CLL, including those with C481, T474, and kinase-impaired mutations such as L528W. We look forward to continued clinical development to further evaluate its potential,” said Masaaki Sawa, Ph.D., Chief Scientific Officer at Carna Biosciences.

The results are based on collaborative research conducted by Carna Biosciences and Varsha Gandhi, Ph.D., co-collaborator of the trial and Professor of Translational Molecular Pathology & Leukemia at The University of Texas MD Anderson Cancer Center (UT MD Anderson). Nitin Jain, M.D., Professor of Leukemia at UT MD Anderson was a collaborator for the preclinical work in the paper.

“In addition to its pan-mutant activity, docirbrutinib enhanced sensitivity to venetoclax and AZD5991, with synergy in cell-line studies and re-sensitization in BTK-mutant primary CLL samples. These results provide a rationale to clinically evaluate docirbrutinib and venetoclax combination,” said Gandhi,

Docirbrutinib, an investigational small molecule drug designed to non-covalently inhibit BTK in a highly selective manner, is currently under development for the treatment of patients with CLL and other B-cell malignancies who have developed resistance or are intolerant to at least two prior lines of systemic therapy including existing covalent/noncovalent BTK inhibitors.

Publication

Journal: Blood Cancer Journal

Title: Docirbrutinib is a pan-mutant BTK inhibitor and inhibits B-cell receptor signaling in chronic lymphocytic leukemia cells in preclinical and early clinical investigations

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Abstract of the paper

BTK inhibitors (BTKi) have become standard of care for treatment of patients with chronic lymphocytic leukemia. Covalent BTKi (cBTKi) such as ibrutinib, acalabrutinib, and zanubrutinib are effective but alterations in the kinase domain at C481 or BTK gatekeeper residue T474 mutations result in development of resistance. Noncovalent BTK inhibitors (ncBTKi) such as pirtobrutinib are effective in patients with C481x mutations developed through use of cBTKi. However, resistance to ncBTKi can occur owing to second site aberrations in BTK generating novel mutations such as L528x and T316x. Sometimes, CLL cells with double BTK mutations are also observed. These BTK aberrations underscore a need for new inhibitors that target pan-BTK-mutants. We evaluated the efficacy of a new ncBTKi, docirbrutinib (AS-1763), against 14 BTK mutants, including C481S, T474x, and L528x, as well as gatekeeper and kinase domain double mutants using biochemical assays, cell-line models, and primary CLL lymphocytes. Docirbrutinib potently inhibited BTK autophosphorylation and mutant BTK-driven cell proliferation, with greater effects than ibrutinib and pirtobrutinib against certain mutants. In treatment-naïve and relapsed/refractory CLL samples, docirbrutinib disrupted B-cell receptor signaling and sensitized cells to apoptosis induced by venetoclax and AZD5991. In a dose-escalation trial (NCT05602363), docirbrutinib decreased CCL3/CCL4 biomarkers and inhibited the B-cell receptor pathway signaling in longitudinal samples from patients with relapsed/refractory CLL. These findings establish docirbrutinib as a pan-mutant ncBTKi with potential to improve outcomes for CLL patients, including those with disease resistant to cBTKi and other ncBTKi.

About docirbrutinib (AS-1763)

Docirbrutinib is a highly selective, orally bioavailable, non-covalent inhibitor of both the wild type and mutant BTKs for the treatment of CLL and other B cell malignancies. Covalent BTK inhibitors including ibrutinib are key therapeutic options for patients with B cell malignancies. However, patients are reported to develop resistance during the treatment due to substitution of cysteine residue at 481 position with serine (C481S - 2 -mutation) in BTK, which reduces the efficacy of the covalent BTK inhibitors. In addition, the emergence of other types of resistance mutations to non-covalent BTK inhibitor, recently approved pirtobrutinib, has been reported. Docirbrutinib potently inhibited both wild type and those mutant BTKs, strongly suggesting

that docirbrutinib will be a new therapeutic option for treating patients with B cell malignancies both having wild type and resistance mutations in BTK. Carna is advancing development of docirbrutinib as a next generation BTK inhibitor. The Phase 1b study of docirbrutinib is being conducted in the U.S. and dosing in the dose expansion part is ongoing (NCT05602363).

About Carna Biosciences, Inc.

Carna Biosciences is a clinical-stage biopharmaceutical company focused on the discovery and development of small molecule drugs to treat serious unmet medical needs in oncology and autoimmune diseases. Carna was founded in Kobe, Japan in 2003 as a spinoff of Japan Organon (Nippon Organon KK). Carna is advancing clinical development of three investigational drugs targeting cancer, autoimmune and inflammatory disease.

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