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In vitro Evaluation of a Novel Dual IRAK1/4 Degrader JH-XIII-05-1 in the Treatment of B Cell Lymphomas

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Background

Activating mutations in MYD88 are prevalent in various B-cell malignancies, including Waldenström Macroglobulinemia (WM) (95-97%), primary CNS lymphoma (70-80%), ABC DLBCL (40%), marginal zone lymphoma (5-10%), and CLL (5-15%). These mutations constitutively activate the SRC family member HCK, which in turn activates multiple pro-survival cascades in mutated MYD88 lymphoma cells, including the BTK/NF-κB, SYK, and ERK pathways (Blood 127:3237-52; Blood Adv 4:141-153; Blood Adv 6:3332-38). Treatments for MYD88-mutated B-cell malignancies often involve BTK inhibitors, which are active but typically fail to produce complete responses and show varying durations of response depending on the disease and depth of response. Essential to the Myddosome-dependent signaling pathway is the recruitment of IRAK1 and IRAK4, which complex with MYD88 to activate lymphomagenesis. Therefore, targeting IRAK1 and IRAK4 is a rational therapeutic approach in MYD88-mutated lymphomas. Degraders of IRAK1 (JNJ-1013) and IRAK4 (KTX-582) have been reported. We developed a dual degrader, JH-XIII-05-1, which is potent in degrading both IRAK1 and IRAK4 (**Figure 1A**). This study aimed to evaluate the effect of JH-XIII-05-1 in MYD88-mutated and wild-type malignancies and to explore potential synergistic drug combinations with a BTK inhibitor.

Methods

MYD88-L265P wild-type and MYD88-L265P mutated cell lines, as well as primary peripheral blood mononuclear cells (PBMCs) from treatment-naïve WM patients, were exposed to the novel IRAK1/4 degrader (JH-XIII-05-1), ibrutinib, and a combination of both. Cell viability was assessed using the CellTiter-Glo assay following 72-hour treatments. IC_{50} values were computed for each treatment, and synergistic effects were evaluated. Western blot analysis was used to

determine protein degradation. Cell death and apoptosis induction were evaluated by flow cytometry using the Annexin V and Propidium Iodide assay.

Results

Compared with commercially available IRAK1 (JNJ-1013) and IRAK4 (KTX-582) degraders, our novel IRAK1/4 dual degrader JH-XIII-05-1 exhibited the most potent degradation of IRAK1 and IRAK4 in TMD8 cells (**Figure 1B**). The biological efficacy of JH-XIII-05-1 was assessed on cell proliferation in MYD88-mutated (BCWM.1, TMD8, MWCL-1, HBL-1) and MYD88 wild-type (OCI-Ly7, OCI-Ly19, RPMI-8226, Ramos) cell lines using the CellTiter-Glo Luminescent Cell Viability Assay. JH-XIII-05-1 demonstrated activity with low nanomolar IC_{50} values in most tested cell lines, including BCWM.1, TMD8, HBL-1, OCI-Ly7, OCI-Ly19, and Ramos (**Figure 2A**). Combination treatment with the BTK inhibitor ibrutinib indicated a synergistic effect (**Figure 2B**). Cell death and apoptosis induction assays showed consistent activity across lymphoma cell lines regardless of MYD88 mutation status when used alone or in combination with ibrutinib (**Figure 2C**).

In PBMCs from four healthy donors and four WM patients, JH-XIII-05-1 exhibited higher cell death and apoptosis induction in the $CD19^+$ B cell population of WM patient PBMCs while demonstrating lower cytotoxicity than ibrutinib in T cells and monocytes of WM patients and in all PBMC populations of healthy donors (**Figure 2D**).

Conclusion

Our *in vitro* evaluation indicates that the novel IRAK1/4 dual degrader JH-XIII-05-1 is a potent compound for the treatment of various lymphomas, with cytotoxicity comparable to or less than that of ibrutinib.

Figures:

Figure 1

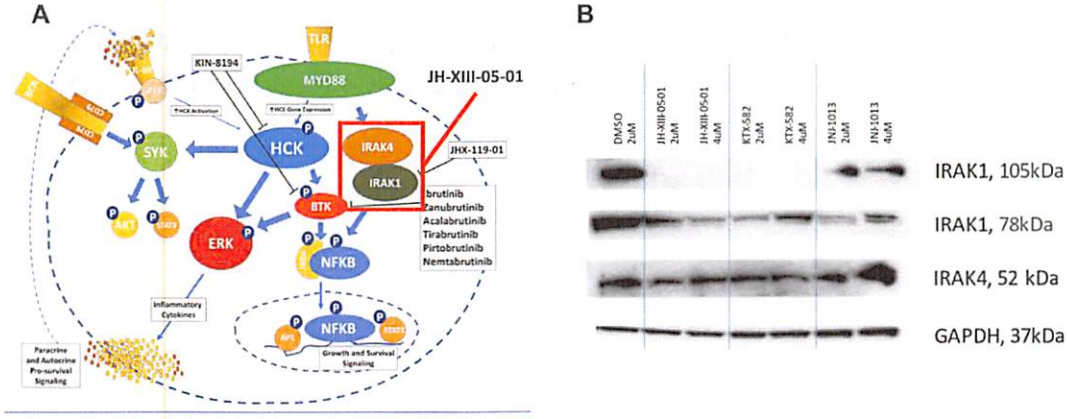

Figure 1. A. Schematic diagram of mutated MYD88 signaling and the targeting molecules of the novel degrader JH-XIII-05-1. **B.** Degradation of IRAK1 and IRAK4 by JH-XIII-05-1, compared to the commercially available degraders IRAK1 (JNJ-1013) and IRAK4 (KTX-582).

Figure 2

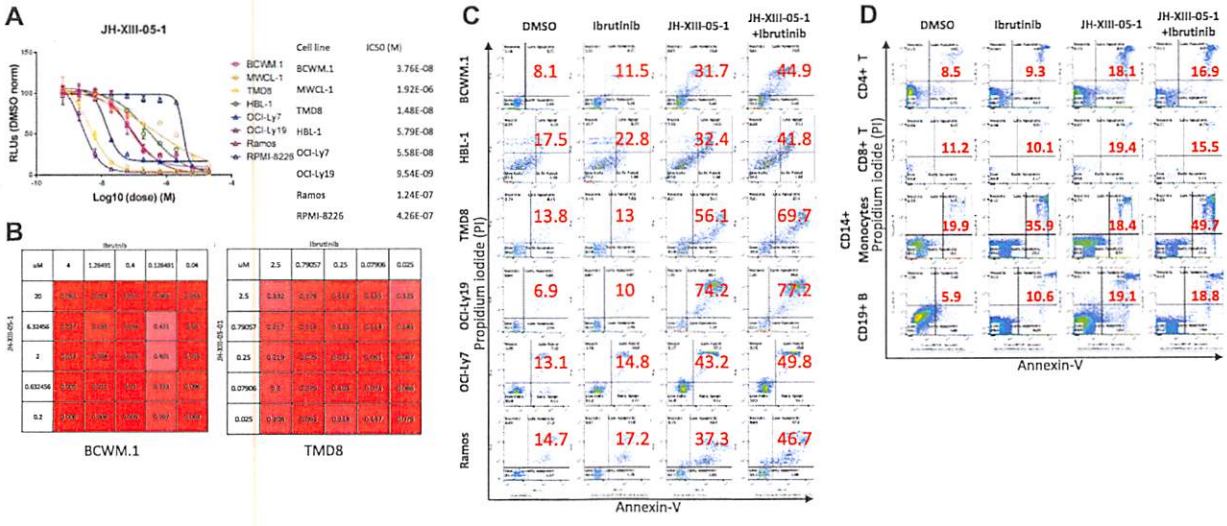

Figure 2. A. ATP-based CellTiter-Glo Luminescent Cell Viability Assay assessing the efficacy of JH-XIII-05-1 in MYD88-mutated (BCWM.1, TMD8, MWCL-1, HBL-1) and MYD88 wild-type (OCI-Ly7, OCI-Ly19, RPMI-8226, Ramos) cell lines. **B.** Synergy assay of JH-XIII-05-1 and ibrutinib in BCWM.1 and TMD8 cells. **C-D.** Evaluation of cell death and apoptosis induction by JH-XIII-05-1 and ibrutinib, both alone and in combination, in cell lines (**C**) and representative PBMCs from WM patients (**D**).