Targeting Antibody Checkpoint FcgRIIB Using Monoclonal Antibody BI-1206 to Overcome Therapeutic Resistance in Mantle Cell Lymphoma

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Mantle cell lymphoma (MCL) is a rare but aggressive B-cell non-Hodgkin's lymphoma that represents 6% of all lymphomas in the United States. Recent therapies including anti-CD20 antibody rituximab, BTK inhibitors, and BCL-2 inhibitors alone or in combination have shown great anti-MCL efficacy. However, primary and acquired resistance to one or multiple therapies commonly occurs, resulting in poor clinical outcome. Therefore, resistance to such therapies is currently an unmet clinical challenge in MCL patients. Therapeutic strategies to overcome this resistance holds promise to significantly improve survival of refractory/relapsed MCL patients. Recent studies showed Fc gamma receptors (FcγRs) play important roles in enhancing the efficacy of antibody-based immunotherapy. In particular, FcgRIIB (CD32B), an inhibitory member of the FcγR family, is implicated in the immune cell desensitization and tumor cell resistance through the internalization of therapeutic antibodies such as rituximab.

Based on our flow cytometry analysis, we demonstrated that FcgRIIB is highly expressed on the cell surface of MCL cell lines (n=10) and primary MCL patient samples (n=22). This indicates that FcgRIIB may play an important role in MCL malignancy and identifies FcgRIIB is a potential therapeutic target for the treatment of MCL. To address this, we tested the *in vivo* efficacy of BI-1206, a fully humanized monoclonal antibody targeting FcgRIIB, alone, or in combination with clinically approved or investigational drugs including rituximab, ibrutinib and venetoclax. In the first *in vivo* cohort, BI-1206, as a single agent, dramatically inhibited the tumor growth of ibrutinib-venetoclax dual-resistant PDX tumor models, suggesting that targeting FcgRIIB by BI-1206 alone has high anti-MCL activity *in vivo*. Next, we assessed whether BI-1206 can boost anti-MCL activity of antibody-based therapy such as rituximab in combination with ibrutinib or venetoclax using additional mice cohorts of cell line-derived xenograft and patient-derived xenograft models. BI-1206 significantly enhanced the *in vivo* efficacy of ibrutinib plus rituximab, and venetoclax plus rituximab, on tumor growth inhibition, including the JeKo-1 derived xenograft models, previously proven to be partially resistant to ibrutinib and venetoclax *in vivo*. This tumor-sensitizaton effect was further confirmed in the ibrutinib and venetoclax dual-resistant PDX models of MCL where BI-1206 was combined with venetoclax and rituximab. More detailed mechanistic studies are currently ongoing to reveal the mechanism of action of BI-1206-based combinations or as single therapy with the possibility that BI-1206 itself may have a cytotoxic anti-tumor direct activity in MCL.

In conclusion, BI-1206 as single agent showed potent efficacy in overcoming ibrutnib-venetoclax dual resistance. Moveover, BI-1206 enhanced the *in vivo* efficacy of ibrutinib plus rituximab and venetoclax plus rituximab and overcomes resistance to these treatments resulting in enhanced anti-tumor effects.