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2413 CD38 x ICAM1 Bispecific Antibody Is a Novel Approach for Treating Multiple Myeloma and Lymphoma

Program: Oral and Poster Abstracts
Session: 622. Lymphomas: Translational—Non-Genetic: Poster II
Hematology Disease Topics & Pathways:
Translational Research

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Targeting cluster of differentiation 38 (CD38) with monoclonal antibodies has resulted in outstanding responses in patients with multiple myeloma (MM). However, a significant portion of patients failed to respond and nearly all patients eventually relapsed. Furthermore, daratumumab, an anti-CD38 antibody, only showed limited monotherapy activity in relapsed/refractory Non-Hodgkin lymphoma (NHL) patients in a phase 2 study. One of the mechanisms of resistance has been partially attributed to lower CD38 expression. Intercellular adhesion molecule 1 (ICAM1), an immunoglobulin (Ig)-like cell adhesion molecule, is highly expressed in multiple myeloma and lymphoma. Antibody against ICAM1, bersanlimab (BI505, BioInvent), was well-tolerated, but only showed limited clinical efficacy in MM patients. Here, we generated bispecific CD38 x ICAM1 antibody to target ICAM1$^+$ tumor types with low to medium CD38 expression. RNA sequencing (RNAseq) results from the Cancer Cell Line Encyclopedia (CCLE) database showed that ICAM1 is highly expressed on myeloma and lymphoma cell lines. ICAM1 expression levels for selected myeloma and lymphoma cell lines were then validated using flow cytometry. The CD38 x ICAM1 bispecific antibody was constructed by paring a novel CD38 antibody and a novel ICAM1 antibody through an asymmetric three chain knob-into-hole format. The bispecific antibody showed potent *in vitro* antibody-dependent cellular cytotoxicity (ADCC) activities on ICAM1$^+$ tumor cells with medium to low CD38 levels, where daratumumab has low or minimal effect. The bispecific antibody also showed potent *in vitro* antibody-dependent cellular phagocytosis (ADCP) activities on cell lines with a range of CD38 expression. The CD38 x ICAM1 bispecific antibody further demonstrated potent tumor inhibition activities in *in vivo* myeloma and lymphoma cell line-derived xenograft (CDX) models, including cell lines with low to medium CD38 expression. We then evaluated CD38 and ICAM1 expressions in lymphoma patient-derived xenograft (PDX) samples by RNAseq. Among the 37 PDX samples, 27 of them showed ICAM1 expression above 2^5 fragments per kilobase of transcript per million map reads (FPKM). On the contrary, there is a wide range of CD38 expression levels with only 6 samples having CD38 expression above 2^5 FPKM. The ICAM1 and CD38 expressions in the selected PDX samples were further validated with IHC staining. Most importantly, the CD38 x ICAM1 bispecific antibody showed complete tumor inhibition in a rituximab-resistant lymphoma PDX model, whereas daratumumab only showed minimal efficacy. In conclusion, the CD38 x ICAM1 bispecific antibody demonstrated improved efficacy and specificity toward CD38$^+$ and ICAM1$^+$ tumor cells and represents a novel approach for treating multiple myeloma and lymphoma.

Disclosures: No relevant conflicts of interest to declare.

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