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POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Lbl-034, a Highly Differentiated T-Cell Engaging Bispecific Antibody Targeting GPRC5D for the Treatment of Relapsed or Refractory Multiple Myeloma

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G protein-coupled receptor, class C group 5 member D (GPRC5D) is a type-C 7-pass transmembrane receptor protein that selectively overexpresses on malignant plasma cells in multiple myeloma (MM). The expression of GPRC5D is rarely seen in normal tissues or cells, and is not detectable on other hematopoietic derived cells, therefore indicating that GPRC5D may be a novel target for anti-multiple myeloma therapy.

LBL-034, a novel T-cell engaging bispecific antibody targeting GPRC5D, is developed with a specifically designed molecular format and unique 2:1 structure. It showed a potent binding on cell lines with various levels of GPRC5D expression, while its binding to CD3 on Jurkat cells was much lower examined by flow cytometry. Furthermore, LBL-034 re-directed engagement of GPRC5D+ cells and T cells was validated by gating engaged cell population with flow cytometry and confirmed visually with laser scanning confocal microscopy.

LBL-034 induced potent T cell dependent cell killing (TDCC) of various types of GPRC5D expressing cells (high to low expression: MM.1R, NCI-H929, MOLP-8 and RPMI 8226 cells), and elevated activation marker (CD25, CD69) expression and cytokine release (IFN-γ, TNF-α, IL-6). LBL-034 demonstrated weak binding to CD3 and minimal effects on cytokine release in the absence of GPRC5D expressing cells and it indicates that LBL-034 activates T cells only in the presence of GPRC5D target cells. LBL-034 was further examined in the MC38-GPRC5D syngeneic model and NCI-H929 xenograft model. Robust antitumor efficacy was observed at the low dose of LBL-034 at 1 mg/kg and 0.3mg/kg respectively.

LBL-034 GLP toxicology study with repeated doses was conducted in cynomolgus monkeys. 5, 15 and 50 mg/kg of LBL-034 was given intravenously with Q1W for up to 5 doses. LBL-034 was well tolerated with a good safety profile as determined by pharmacology, pathology and biochemistry analysis. The NOAEL of LBL-034 in cynomolgus monkeys was confirmed at 50 mg/kg.

In summary, LBL-034 is a novel T cell engaging bispecific antibody targeting GPRC5D expressing R/R MM with well differentiated binding of GPRC5D and CD3 to enhance anti-tumor activity, while mitigate the risk of CD3-induced CRS, showing a great in *vitro* potency and *in vivo* anti-tumor efficacy. LBL-034 IND has been approved by both FDA and NMPA and a FIH study in patients with R/R MM will begin in the 2 nd half of 2023.

Disclosures No relevant conflicts of interest to declare.

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