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Abstract 7535: First-in-human phase 1 clinical trial of ZM008, a monoclonal IgG1 targeting LLT1, monotherapy and in combination with pembrolizumab in advanced solid tumors

Maloy Ghosh; Anurag Tiwari; Ashvini Kumar Dubey; Sanghamitra Bhattacharjee; Yogendra Manjunath; Shalini Kashipathi; Subith Krishna; Tirtha Mandal; M. S. Madhusudhan; Golding Rodrigues

+ Author & Article Information

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Abstract

Lectin-like transcript 1 (LLT1) interaction with CD161 receptor on NK cells facilitates tumor immune escape. Hence, blocking LLT1-CD161 interaction could potentially activate NK cells and resulted tumor cell cytotoxicity. ZM008 is a first-in-class anti LLT1 monoclonal antibody with promising pre-clinical safety, efficacy data and received IND approval from USFDA. Clinical study will start soon at multiple US sites. TCGA data analysis revealed high LLT1 gene expression in multiple solid cancers BRCA, CHOL, ESCA, GBM, HNSC, KIRC, KIRP, LIHC, LUAD, STAD, SARC. Several immune checkpoint genes PDL1, LAG3, TIM3, TIGIT, ICOS, B7-H3, are positively correlated ($p<0.05$) with high LLT1 expression. CIBERSORT analysis of immune cells revealed significant presence of Treg and CD33+ immune cells along with IL4, IL10, Arg1 and IDO1 in the TME with high LLT1 expression. Cox regression analysis suggests high LLT1 is a risk factor for survival ($p<0.05$) in patients with COAD, KICH and KIRC. High TMB and MSI scores were significantly correlated ($p<0.05$) with LLT1 expression in Colon and Kidney cancers, suggesting plausible biomarker application. Overall, transcriptome data analysis strongly suggests immune repressive gene signatures are prevalent with high LLT1 TMEs in multiple solid cancers. In vitro studies with human PBMC revealed ZM008 activates immune cells by inducing expression of CD69, NKG2D, CD107a, proinflammatory cytokines (IFN-γ, IL2, etc.,) secretion, and tumor cytotoxicity. In MLR assay,

pembrolizumab combination. An open-label, dose-escalation phase 1 trial for ZM008 is planned [illegible] tumors with no therapeutic standard alter[illegible] d efficacy of ZM008, as monotherapy and in comb[illegible] 0.15mg/Kg was determined based on MAE[illegible] g high LLT1 expression in patients non-responsive to[illegible] ndicate the potential benefit to the patients from[illegible] atment. ZM008 treatment will release the immune br[illegible] nd provide anti tumor effects in solid cancers eit[illegible] ion therapy. Retrospective analysis of[illegible] nent will identify relevant biomarkers for patient recr[illegible]

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