PHASE 1 CLINICAL TRIAL DESIGN OF ZM008, A FIRST-IN-CLASS ANTI LLT1 ANTIBODY IS A PROMISING THERAPY FOR MULTIPLE SOLID CANCERS

Maloy Ghosh*, Arunag Tiwari, Ashvini Kumar Dubey, Sanghamitra Bhattacharjee, Yogendra Manjunath, Shalini Kashipathi, Subhith Khithna, Thirtha Mandal, Sorna Gnanasegaran, Ignacio Garcia-Ribas. Zumotor Biologics Pvt Ltd, Bangalore, India

Background Lectin-like transcript 1 (LLT1) interaction with CD161 on NK cells facilitates tumor immune escape.1-3 The novel anti LLT1 antibody, ZM008 disrupts LLT1-CD161 interaction to activate NK cells, improve immune cell infiltration and enhance tumor cell cytotoxicity.4-6 Present work describes biomarker strategy and unique clinical protocol to conduct phase 1 studies with ZM008.

Methods The Cancer Genome Atlas (TCGA) data was used to understand expression of LLT1 in 33 cancers. Correlation analysis was performed to compare LLT1 expression with immune gene signatures. Multiple pharmacodynamics (PD) parameters were used to determine minimum anticipated biologic effect level (MABEL), biological effective dose (BED) including, in vitro assays for cytokine release, PBMC receptor occupancy, proliferation assays, in vivo and ex vivo efficacy studies, safety and toxicity studies.

Results TCGA data analysis revealed high expression of LLT1 in multiple cancers like, NSCLC, TNBC, head and neck, prostate and urothelial cancers. In addition, high LLT1 expression is negatively correlated with proinflammatory signals (IL-2, IL-6, EOMES, and LAMP1), and positively correlated with high Treg, CD33+ MDSC, high PD1, LAG3, TIM3, TIGIT, ICOS, high TMB and MSI scores. ZM008 phase I clinical trial will primarily determine single agent safety and tolerability followed by unique BED based dosing strategy to initiate combinatorial arm with Pembrolizumab. Solid tumor patients with advanced metastatic disease with no available therapeutic options will be recruited. Accelerated single patient cohorts and 3+3 study design will evaluate patient safety, tolerability and benefits with ZM008 mediated immune activation following RECIST v1.1. Pembrolizumab combination arm will initiate only after thorough safety evaluation of ZM008 at BED dosing to ensure manageable adverse events with combination treatment (figure 1). Multicohort dose-expansion trial is designed with ZM008 single agent and in combination with Pembrolizumab; RP2D will be determined.

Conclusions The biomarker analysis revealed clear association of high LLT1 expression with immune nonresponsive gene signatures. Retrospective analysis of patient samples from phase 1 study will be explored to identify relevant PD markers for future patient recruitment. ZM008 activates immune cells, hence the clinical protocol was designed with ‘safety first’ approach with MABEL dosing and extensive patient monitoring. In addition, to avoid adverse reactions with Pembrolizumab combination arm we have designed a staggered parallel approach with detailed safety data discussion with the agency at the BED dosing. This unique design allows maximum patient safety while evaluation of novel standalone I/O therapy or combination therapies.

REFERENCES