CHARACTERIZATION OF THE PHARMACODYNAMIC ACTIVITY OF CLN-619, AN ANTI-MICA/B MONOCLONAL ANTIBODY, IN PATIENTS FROM AN ONGOING PHASE 1 TRIAL

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Background CLN-619 is a human IgG1 antibody that binds to and prevents proteolytic cleavage of NKG2D ligands MICA/B from the surface of tumor cells, thereby increasing tumor cell killing by innate and adaptive immune cells. CLN-619 is currently being investigated in a Phase I clinical trial in patients with advanced solid tumors as a monotherapy and in combination with pembrolizumab (NCT05117476). CLN-619 monotherapy demonstrated a favorable safety profile and objective RECIST responses in patients with multiple solid tumor types. Here we report pharmacodynamic activities associated with CLN-619 monotherapy.

Methods The monotherapy arm enrolled patients with advanced solid tumors to receive escalating doses of CLN-619 administered IV on a Q3W schedule. Serum samples, archival tumor samples, and pre-/on-treatment biopsies were collected. Soluble MICA (sMICA) concentration in serum was measured by ELISA. Membrane expression of MICA/B was analyzed by IHC. Multiplex immunofluorescence was used to assess tumor expression of MICA/B, CD8 T cell and NK cell infiltration and activation in response to CLN-619 in 8 paired biopsies collected at doses of 3 mg/kg (N=4), 6 mg/kg (N=3), and 10mg/kg (N=1) from patients with stable and/or progressive disease. Tumor mutational burden and gene expression were assessed by WES and RNASeq, respectively. MICA/B, FcγRIIIA and NKG2D genotyping were performed by targeted NGS or real-time PCR.

Results As a measure of target engagement, levels of sMICA were assessed in serum samples at baseline and following CLN-619 treatment. sMICA concentrations increased up to 10-fold in a CLN-619 dose-dependent manner and were accurately captured by the PK/PD model, suggesting that sMICA is stabilized in patients’ sera by binding to CLN-619. Consistent with the proposed mechanisms of action, intratumoral pharmacodynamic effects have been observed in patients dosed with CLN-619. Intratumoral MICA/B expression increased 2 to >100 fold on-treatment in 4/5 paired tumor biopsies. Notably, MICA/B localization to the tumor cell membrane increased in agreement with preclinical data showing stabilization of MICA/B on the cell surface in the presence of CLN-619. NK cell and TIL infiltration and activation were increased 2–4 fold in 3/8 and 3/7 paired tumor biopsies, respectively. Characterization of gene expression profiles and mutational analysis of tumor biopsies is ongoing.

Conclusions Pharmacodynamic data presented here are consistent with the proposed mechanisms of action of CLN-619, demonstrate stabilization of MICA/B expression in tumors, and support the potential of CLN-619 as a novel immunotherapy for the treatment of a range of solid tumors.

Ethics Approval CLN-619–001 clinical trial (NCT05117476) obtained ethics approval by institutional review boards from all participating clinical sites and all participants gave an informed consent to use their samples for analysis before enrollment into the clinical study.

Consent Written informed consent was obtained from all patients whose sample’s data is used for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

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