Background Squamous non-small cell lung cancer (SQ-NSCLC) is the 2nd most common type of lung cancer. Given the paucity of actionable oncogene drivers, and lack of efficacy from multiple therapies in the Lung-MAP trial, there is a high unmet need in SQ-NSCLC to develop effective 2nd-line immunotherapies for patients with disease progression after immune checkpoint inhibitors (ICI).

The melanoma antigen gene A4 (MAGE-A4) is exclusively expressed in cancer and absent in somatic tissues. MAGE-A4-derived peptides presented on HLA molecules at the cell surface recently emerged as a novel therapeutic opportunity. Thus, the two key objectives of this study were to: 1). Evaluate MAGE-A4 expression in human SQ-NSCLC; 2). Demonstrate the anti-cancer activity of CDR404, an antibody-based bispecific and bivalent T-cell engager targeted against MAGE-A4 230-239 peptide in vitro and in vivo xenograft models of SQ-NSCLC.

Methods MAGE-A4 mRNA prevalence and expression in SQ-NSCLC was analyzed using the TCGA database (https://www.cancer.gov/tcga). Protein expression of MAGE-A4 was confirmed using immunohistochemistry (IHC) in fifty FFPE human SQ-NSCLC samples (clone E7O1U).

CDR404 target cell killing in the presence of human PBMCs was assessed using the human SQ-NSCLC cell line NCI-H1703. HLA-A*02:01+MAGE-A4neg cancer cells were used as controls. To exclude reactivity of CDR404 in healthy tissues, HLA-A*02:01+ primary cells presenting peptides with high MAGE-A4 similarity were co-cultured with human PBMCs. In vitro activity of CDR404 in SQ-NSCLC was evaluated with an NCI-H1703 xenograft model in NSG mice.

Results SQ-NSCLC had the highest MAGE-A4 mRNA expression levels among solid cancers in the TCGA database. IHC showed positive MAGE-A4 staining in 28/50 (56%) of SQ-NSCLC samples.

In vitro, CDR404 showed efficient target cell lysis across all effector-to-target ratios tested. Similarly, simultaneous target engagement and resulting synapse formation induced T cell activation and secretion of cytolytic molecules in an effector-to-target ratio-dependent fashion. No reactivity was observed using co-cultured HLA-A*02:01+MAGE-A4neg cancer cells. Lack of T cell activation/cytolytic molecule release in the presence of HLA-A*02:01+ primary cells confirmed the specificity profile of CDR404. In vivo, treatment with four different doses of CDR404 induced complete tumor regression in the SQ-NSCLC NCI-H1703 xenograft model.

Conclusions The high MAGE-A4 expression levels and the highly specific anti-cancer cell activity of CDR404 make it a highly attractive immunotherapy for development post-progression on ICI for patients with HLA-A*02:01+ SQ-NSCLC. A multi-tumor phase 1 trial of CDR404, including SQ-NSCLC, is expected to begin in 2024 with prospective patient selection for both HLA-A*02:01 and tumor MAGE-A4.