1397 CDR404, AN ANTIBODY-BASED BISPECIFIC & BIVALENT T-CELL ENGAGER TARGETED AGAINST MAGE-A4, FOR SQUAMOUS NON-SMALL CELL LUNG CANCER (SQ-NSCLC)

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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-A4^{neg} 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 vivo* 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-A4^{neg} 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.

Ethics Approval Animal studies were performed in compliance with the recommendations of the *Guide for Care and Use of Laboratory Animals* with respect to restraint, husbandry, surgical procedures, feed and fluid regulation, and veterinary care. The animal care and use program is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC), which assures compliance with accepted standards for the care and use of laboratory animals.

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