CHARACTERIZATION OF SUPPRESSIVE MYELOID CELLS IN SOLID TUMORS TO REFINE DISEASE SELECTION IN A PHASE 1 STUDY OF THE MULTI-SIGLEC INHIBITOR AL009

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Background Inhibitory sialic acid-binding immunoglobulin-type lectins (Siglecs) are a subset of the Siglec family of cell surface receptors expressed predominantly on myeloid cells that potentiate immune suppression. Tumors increase the expression of sialic acid glycans and co-opt the immunosuppressive effects of Siglecs, driving tumor resident immune cells toward a cancer permissive phenotype. Disrupting Siglec-sialic acid signaling could confer a therapeutic benefit in cancer, particularly those cancers with high levels of myeloid derived suppressor cells (MDSCs). To accomplish this, we designed AL009, an engineered Siglec Fc fusion molecule that acts as a sialic acid trap and a multi-Siglec inhibitor, repolarizing suppressive myeloid cells and activating an anti-cancer response. The safety, tolerability, and efficacy of AL009 in patients with solid tumors will be evaluated in an upcoming Phase 1 study. Here we present data that help to refine disease selection for the Phase 1 study and efforts in testing potential predictive biomarkers for clinical use.

Methods Tissue microarrays from patients with various solid tumors were analyzed by immunohistochemistry (IHC). Markers detected included CD163, CD68, and a representative Siglec for multi-Siglec expression. IHC scoring methodology was prespecified focusing on proportion of cells expressing each of the above markers. Scoring was on a 4-point scale and based upon the number of cells stained with the marker of interest in reasonable proximity to the tumor (tissue without tumor was not scored).

Results Tumor profiling by IHC identified squamous cell lung cancer, colorectal cancer, ovarian cancer, kidney cancer as indications rich in MDSCs marked by high levels of CD163, CD68, and Siglec expression. These cancer indications may be particularly responsive to AL009. The use of PD-L1 expression data from The Cancer Genome Atlas for these various cancer indications provides further guidance on potential effective combination therapies coupled with AL009.

Conclusions We employed an IHC panel that marks CD163, CD68, and Siglecs to identify cancer indications rich in MDSCs. As AL009’s mechanism of action is to disrupt the Siglec-sialic acid signaling of MDSCs, we believe that patients with these particular cancers will be most likely to respond to AL009 treatment. This IHC panel will be utilized to retrospectively explore Siglecs, CD163, and CD68 as predictive biomarkers in an upcoming Phase 1 study.

Ethics Approval The human tissue microarrays were procured from a commercial vendor that collect human samples with the following ethical considerations: informed donor consent, IRB/EC approval, fully anonymized, and compliant with current US (HIPAA) International and EU regulations.