EMERGING INSIGHTS ON THE ASSOCIATION OF TUMOR MOLECULAR PHENOTYPE WITH CLINICAL BENEFIT IN METASTATIC COLORECTAL CANCER (mCRC) SUBJECTS TREATED WITH AB928 + MODIFIED FOLFOX-6 (mFOLFOX-6)

Akshata Udyavar*, Michael Cecchini, Daniel DiRenzo, Sean Cho, Lisa Seitz, Kristen Zhang, Stephen Young, Amy Anderson, Kimberline Gerrick, Matthew Walters, Houston Gilbert, Olivia Gardner, Cheng Quah, Juan Jaen, William Grossman, Arcus Biosciences Inc, Hayward, CA, USA; Yale University, New Haven, CT, USA

Background

The release of ATP from dying cancer cells in response to platinum-based chemotherapy increases extracellular adenosine, which binds to and activates A2aR and A2bR receptors to generate an immunosuppressive microenvironment. This is mediated by the activation of A2aR on intratumoral T and NK cells, A2aR and A2bR on tumor-infiltrating myeloid cells, and A2bR on cancer cells. Importantly, expression of A2bR and CD73, an adenosine-producing enzyme, on cancer cells is upregulated by oncogenic drivers such as KRAS. Consistent with this, tumors from CRC subjects express high levels of A2bR. Adenosine receptor blockade may therefore enhance the therapeutic efficacy of certain chemotherapeutic agents. AB928 is the first clinical-stage small-molecule dual adenosine receptor antagonist, targeting both A2aR and A2bR. The preliminary safety and clinical efficacy of AB928 + mFOLFOX-6 in metastatic colorectal cancer (ARC-3; NCT03720678) were recently described. This presentation describes the preliminary identification of molecular markers that correlate with the extent of clinical benefit in this trial.

Methods

A total of 35 subjects enrolled in this study: 12 (1L); 4 (2L); and 19 (3L+). Baseline and on-treatment biopsy samples were subjected to immunofluorescent staining as well as WES and RNAseq analysis.

Results

Analysis of the primary CRC dataset in TCGA highlights this tumor type as having high levels of CD73, coupled with a paucity of Tissue Nonspecific Alkaline Phosphatase (TNAP), another enzyme that can produce adenosine. In our mCRC study samples, TNAP was often present, being expressed on either stroma or tumor and in a non-overlapping manner with CD73. Analysis of the expression levels of these