1060 EVOLVE™: A NOVEL COSTIMULATORY T CELL ENGAGER PLATFORM ENGINEERED FOR THE TREATMENT OF IMMUNE SUPPRESSIVE TUMORS

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Background CD3-bispecifics are antibody-based therapies that can simultaneously bind to a tumor cell surface antigen and T cells to establish a synapse between the tumor and T cell and activate T cell to induce specific killing of the tumor cell. CD3-bispecifics have demonstrated clinical success in B cell acute lymphoblastic leukemia and follicular lymphoma with approvals of that blinatumomab (Blincyto®) and mosunetuzumab (Lunsumio®) that target B cell lineage antigens CD19 and CD20, respectively. However, clinical progress in deploying CD3-bispecifics for positive patient outcomes in solid tumors has been slow, due to tumor microenvironmental factors such as induction of T cell exhaustion, as well as the potential of CD3-bispecifics to mediate T cell anergy and dysfunction in the absence of adequate costimulation.

Methods Here we describe the development and preclinical validation of the EVOLVE platform, a tumor-targeted biologic that induces the formation of a synthetic synapse that simultaneously activates the T cell receptor complex and the CD2 receptor to optimize CD8 T cell effector phenotype and improve tumor cell killing *ex vivo* and *in vivo*, compared to matched CD3-bispecifics.

Results We demonstrate that CD2 costimulation is superior to other forms of T cell costimulation in its ability to promote cytolytic costimulation, T cell cytokine production and T cell expansion. Furthermore, CD2 receptor expression is markedly elevated in tumor infiltrating lymphocytes across a broad set of tumor types, relative to the CD28 and 4-1BB costimulatory receptors. EVOLVE-mediated T cell activation is conditionally dependent on tumor antigen binding and can be tuned to promote optimal costimulation without increasing cytokine release relative to matched CD3-bispecifics. We also demonstrate the modular nature of the EVOLVE platform across diverse tumor antigens including B7H4 (VTCN1), the B cell lymphoma antigen CD20 and a novel squamous tumor antigen ULBP2.

Conclusions Our data highlight the broad applications of the EVOLVE platform to improve CD8 T cell-mediated anti-tumor immunity and suggest its potential as an emerging, first-in-category immunotherapeutic strategy to address unmet medical needs in oncology.

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