SYN101, A FIRST IN CLASS, IMMUNE CELL TARGETED TGF-BETA INHIBITOR THERAPY, SELECTIVELY BLOCKS IMMUNE SUPPRESSION AND DRIVES TUMOR CLEARANCE IN VITRO AND IN VIVO

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Background TGF-b is both a validated pro-tumorigenic pathway and a fundamental immunosuppressive cytokine that is overexpressed in virtually all solid tumors. In cancer patients, elevated TGF-b levels limit T cell activation and drive resistance to immune checkpoint inhibitors. Preclinically, mice with a genetic blockade of TGF-b signaling only in T cells reject multiple tumors, including melanoma, lymphoma and colorectal cancers. However, because TGF-b is also essential in maintaining host tissue homeostasis, systemic TGF-b therapies, such as the TGF-b receptor I/ALK5 inhibitors, cause significant host toxicity and have fallen far short in clinical efficacy. Novel, targeted TGF-b therapies are required to improve safety and increase patient response rates.

Methods To improve immune function, efficacy and safety relative to systemic TGF-b therapies, Synthetis has developed a first in class, immune cell targeted TGF-b therapy, SYN101, for cancer patients. Utilizing proprietary antibody drug conjugate (ADC) components, SYN101 is comprised of an immune cell specific antibody linked to a potent ALK5 inhibitor payload to selectively block TGF-b signaling in immune cells.

Results As a monotherapy, SYN101 reversed TGF-b mediated immune suppression in primary human T cells and increased expression by 3-4 fold of critical T cell functions required for tumor clearance, such as Granzyme B in cytotoxic killer CD8+ T cells and IFNg levels and fully restored T cell proliferation. In combination studies, SYN101 plus antiPD1 increased IFNg expression by 4-fold, compared to only 2-fold with monotherapy treatment. In the EMT6 breast tumor model, SYN101 + antiPD1 combination led to >93% tumor regression in vivo, with 3/5 complete and 1/5 partial responders (p=0.0003, versus antiPD1 alone). Mice with complete responses to SYN101 combination therapy were resistant to subsequent tumor rechallenge, demonstrating immunological memory. In circulating immune cells, combination therapy significantly increased pharmacodynamic markers, CD69 and Ki67+ (CD4+ and CD8+ T cell activation and expansion, respectively), relative to antiPD1 alone (p<0.05), correlating with tumor clearance. Similar in vivo efficacy and PD markers were observed with colorectal tumor models, CT26 and MC38.

Conclusions Synthetis is the only company developing a non-cytotoxic ADC therapeutic that inhibits TGF-b induced immune suppression and drives tumor clearance in vivo. Current studies will expand in vivo efficacy studies and demonstrating improved safety. Safer, more effective TGF-b therapies, like SYN101, will provide novel monotherapy options for cancer patients. Additionally, because TGF-b sets the overall threshold for T cell activation, SYN101 could improve the efficacy of a variety of therapies, including checkpoint inhibition, radiation and NK/CAR-T therapies.

REFERENCES