EVOLVE-106, A T CELL ENGAGER WITH INTEGRATED CD2 COSTIMULATION TARGETING B7-H4, IS A PRECISION THERAPY FOR ESTROGEN AND HER2 RECEPTOR LOW BREAST CANCERS


Background There have been significant advances in breast cancer treatments, including endocrine, Her2-targeted, chemotherapy, and immune checkpoint inhibitors. However, treatment-resistant, metastatic, and recurrent disease often lead to poor patient outcomes, highlighting the need for more effective and durable therapies. B7-H4 is an attractive target for breast cancer due to its frequent and robust expression in breast cancers and relatively low expression in normal tissues. Our gene expression analysis of breast cancer patient tumors indicated significantly higher VTCN1 (gene encoding B7-H4) levels in tumors that lack estrogen and Her2 receptor expression, including triple-negative breast cancers (TNBC). Interestingly, VTCN1-positive breast cancer patients, especially patients lacking estrogen receptor expression, display higher levels of T cell infiltration, suggesting the potential for T cell engager therapies in these patients. Immunohistochemical analysis of breast cancer tumor microarrays validated highest B7-H4 protein levels in TNBC, but high levels in Her2 low tumors that may be estrogen positive.

Methods Based on these observations, we have progressed EVOLVE-106, a B7-H4 T cell engager biologic that integrates affinity-tuned anti-CD3 binding and CD2 costimulation in a single biotherapeutic molecule as an optimized T cell redirecting agent, to initiate anti-tumor responses in Her2 receptor low breast cancers. Our EVOLVE-106 candidate was selected from a lead series based on optimal biophysical properties, robust in vitro tumor killing, and the lack of peripheral immune activation and superagonism.

Results Our candidate displays B7-H4-dependent tumor killing and tumor-localized cytokine release, while the reduced CD3 affinity and costimulation simultaneously allow T cells to delay exhaustion and retain durable effector activity. The EC50 for activated T cell co-culture in vitro tumor killing ranges from 20–100 pM at low tumor antigen density to 1–10 pM at high tumor antigen density. Our unique EVOLVE-106 T cell engager has been benchmarked to other B7-H4 bispecific agents in phase I/II clinical trials. Given the observed inverse relationship between estrogen receptor and B7-H4 expression, we investigated whether pharmacologically-induced loss of estrogen receptor by anti-endocrine therapies may increase tumor B7-H4 levels. We found that HR+ breast cancer cell lines treated with the selective estrogen-degrader fulvestrant, displayed increased B7-H4 levels and combination treatment of EVOLVE-106 with fulvestrant increases EC50 of tumor killing by 5–8 fold.

Conclusions These data support the potential positioning of EVOLVE-106 as a first-in-category immunotherapeutic approach for patients with Her2 receptor low breast cancers, and both estrogen receptor positive and negative tumors, including TNBC.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1386