Background: Recurrent and treatment-refractory solid tumors are especially lethal, leading to the spread of tumors to distant sites forming metastases in vital tissues, and are the primary cause of death in solid tumor patients. Distinct tumor lineages are implicated as the source of these solid tumors owing to the ability of these lineages to persist regardless of treatment and to the potential of these lineages to actively suppress anti-tumor immunity. However, tractable targets preferentially expressed in these lineages have not been determined. The identification of such tumor-associated antigens as targets for T cell-redirecting therapies may offer the potential to simultaneously enhance adaptive anti-tumor responses and eradicate sources of immunosuppression which contributes to poor patient treatment outcomes.

Methods: Here we describe EVOLVE-104, a T cell engager biotherapeutic that integrates optimized CD3 agonism with CD2 costimulation and selectively targets ULBP2, a novel tumor-associated antigen. Our gene expression analysis of diverse solid tumor patients reveals higher levels of ULBP2 expression in tumors that display basal and squamous molecular signatures. These tumors also exhibit a greater degree of T cell infiltration and higher expression of PD-(L)1 and HLA-E immune checkpoints. Immunohistochemical analysis of bladder tumor tissue microarrays demonstrated higher levels of ULBP2 expression in high-grade and bladder tumors with squamous histology.

Results: Regarding therapeutic performance, EVOLVE-104 showed superior cytotoxicity in vitro in diverse cancer models compared to a CD3-affinity matched CD3-bispecific which does not induce costimulation. The superiority of EVOLVE-104 extended to >1000 and >100-fold improvements in tumor-killing IC50s compared to cisplatin and gemcitabine respectively, for 7 of 7 ULBP2 bladder cancer cell models across a range of ULBP2 surface expression levels with tumor-antigen dependent T cell activation and cytokine induction. No evidence of off-target peripheral human immune cell activation or superagonism was observed. In in vitro tumor rechallenge assays, where additional tumor cells were added during co-culture, EVOLVE-104 displayed impressive combination activity with pembrolizumab, providing a strong rationale for anti-PD-1 combination approaches. In vivo, EVOLVE-104 exhibited greater than 90% tumor growth inhibition in CORL-105 lung xenograft tumor-bearing humanized mice as monotherapy.

Conclusions: EVOLVE-104 is highly developable as evidenced by its optimal biophysical properties, favorable pharmacokinetics, and absence of cytokine release syndrome or toxicity in cynomolgus monkeys at efficacious dose levels. EVOLVE-104 represents a first-in-category precision immunotherapeutic strategy to address aggressive solid tumors of basal and squamous lineages.

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