324 ALLOGENEIC CAR T CELLS TARGETING LIV-1 FOR BREAST CANCER

Lauren Zakas, Minh Pham, Laura Bartle, Zejun Li, Kelly Maeng, Luke Hanley, Avanti Ganpule, Jason Sagert, Jonathan Terrett, Demetrios Kalaitzidis*. *CRISPR Therapeutics, South Boston, MA, USA*

Background While HER2 is an important target of several approved breast cancer treatments, limitations include the lower prevalence of HER2 overexpression (in ~20% of all breast cancer cases) and these therapies' well-characterized respiratory and cardiac toxicities. Furthermore, triple negative breast cancer, which is the clinical subtype with the poorest prognosis and accounts for ~15% of all breast cancer cases, does not express HER2. Liv1 is a zinc transporter protein expressed on all clinical subtypes of breast cancer, including high expression in triple negative breast cancer. Expression of Liv1 has been associated with cancer progression and metastasis, including increased risk of nodal involvement by breast cancer. Importantly, normal tissues have limited Liv1 expression, reducing the risk of off-target toxicity. Further, Liv1 expression has been shown to persist following hormonal treatment, a common first line therapy for ER+ and PR+ breast cancer cases. Liv1 is being explored clinically as a target via an antibody drug conjugate (ADC: Ladiratuzumab vedotin) which has shown encouraging safety and anti tumor data. We have produced and assessed in pre-clinical models anti-Liv1 allogeneic CAR T cells for breast cancer.

Methods We produced allogeneic human CAR T cells containing anti-Liv1 CAR constructs with CRISPR/Cas9 and AAV6 and screened for constructs that confer T cell activity against a panel of human breast cancer cell lines. We also assessed in vivo anti-tumor activity against subcutaneous or mammary fat pad implanted breast cancers in xenogeneic models in NSG mice and compared them to HER2-specific CAR-T cells.

Results We identified anti-Liv1 CAR constructs that confer potent anti-breast cancer CAR T activity against a panel of cell lines in vitro including ones derived from different subtypes ZR-75–1, MCF-7 and MDA-MB-231. Lead constructs are Liv1 specific as they are not active against Liv1 deficient cells. Liv1 CAR T cells showed in vivo anti-tumor activity in subcutaneous and mammary fat pad injected ZR-75–1 NSG mice. This activity was equivalent to that observed from HER2 CAR T cell treated mice

Conclusions Liv1 is a promising CAR T target in breast cancer that is expressed across a wide range of breast cancer subtypes, including triple-negative and hormone receptor-positive subtypes. Its specific expression in breast cancer, as opposed to other tissues, reduces the risk of off-target toxicity. We have demonstrated that anti-Liv1 CAR T cells can be produced with potent in vitro and in vivo CAR T cell activity against multiple breast cancer cell lines.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0324