442-C A BEST-IN-CLASS HSC-DERIVED CAR-MONOCYTE PRODUCT WITH A NOVEL CAR COSTIMULATORY DOMAIN SIGNIFICANTLY IMPROVES CAR-M ACTIVITY AGAINST SOLID TUMORS

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Background Myeloid cells, unlike other immune cells such as T cells or NK cells, are known residents in the solid tumor microenvironment (TME). In the absence of checkpoints and in proinflammatory conditions, M1 macrophages are known to be capable of direct phagocytosis of tumor cells and can present tumor-associated antigens to the host immune system. However, the immunosuppressive conditions within the TME restrict and limit the anti-tumor response of tumor associated macrophages (TAMs), including their ability to recruit and activate other immune cells against the tumor.

Engineered CAR-Monocytes can serve a unique function in cell therapy by bridging a key gap in the treatment of solid tumors. We are developing an autologous engineered CAR-M cell therapy product targeting Glypican-3 to treat hepatocellular carcinoma. The CAR serves as a homing ‘GPS’ signal for trafficking directly to the tumor site, and directs phagocytosis specifically at targeted tumor cells. Our proprietary M83.CAR molecule contains a macrophage-specific costimulatory domain that significantly increases the phagocytosis function of the CAR-M cells. Furthermore, we have demonstrated that the M83.CAR-M cells are not inhibited by the prevalent CD47 ‘do not eat me’ checkpoint, which is known to restrict myeloid function in the TME.

Methods Primary hematopoietic stem cells (HSCs) were harvested and engineered to express a CAR molecule by lentivirus transduction generating CAR-HSCs. The CAR-HSCs underwent our proprietary ex-vivo HSC differentiation process to yield CAR-Monocytes.

Results Effective phagocytosis of engineered CAR-M cells is central to subsequent mechanisms of actions that can elicit robust anti-tumor immunity against patient-specific neoantigens. However, the first barrier to overcome is effective infiltration of engineered CAR-M into the tumor from the periphery. We have demonstrated that our engineered CAR-Monocyte drug product can successfully home to the targeted tumor specifically, from the periphery. Subsequent in situ differentiation of CAR-monocytes into CAR-macrophages enables robust tumor cell phagocytosis, the central mechanism that results in the following: 1) proinflammatory shift in the TME, 2) recruitment of APCs and immune cells, 3) activation of T-cells against tumor neoantigens.

Conclusions The above summarizes a unique outcome of the CAR-M mechanism of action that is not capitulated by CAR-T or CAR-NK cells. Leveraging and further enhancing CAR-M function could lead to the rejection of the tumor and its metastases, particularly in combination with other immune-modulating therapies. Our proprietary HSC-derived CAR-M platform yields a unique product that demonstrates durability and superior function, which we expect to translate to the clinic.

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