Abstracts

DEVELOPMENT OF A MUC16-SPECIFIC CAR-T CELL EXHIBITING POTENT ANTITUMOR ACTIVITY FOR THE TREATMENT OF PATIENTS WITH RECURRENT OVARIAN CANCER

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Background Despite significant improvements in surgical and medical treatments, ovarian cancer remains the most lethal gynecologic malignancy, with a 2- to 3-year recurrence rate, highlighting an unmet need for effective therapeutic options for patients.1 Mucin 16 (MUC16) is a type I integral membrane glycoprotein that is overexpressed in more than 80% of ovarian cancers.2 Proteolytic cleavage of full length MUC16 results in the shedding of CA125 into the bloodstream, leading to a truncated ectodomain at the cell surface.3 Here, we report the development of a chimeric antigen receptor (CAR) T cell product (BB4015) targeting the membrane-retained MUC16 ectodomain for the treatment of patients with recurrent ovarian cancer.

Methods in vitro assessment: Human ovarian tumor samples were evaluated for MUC16 expression via immunohistochemistry. BB4015’s phenotypic and functional assessments were evaluated using anti-MUC16 CAR T cells derived from LVV transduction of healthy donor PBMCs. BB4015 phenotype was defined via flow cytometry by CD4, CD8, CD62L, and CD45RA expression. BB4015 function was assessed for antigen-dependent cytokine release/cytotoxicity where BB4015 was co-incubated with antigen positive/negative tumor or primary cells. To determine the off-target binding potential of BB4015’s scFv, we employed a cellular microarray platform (Retrogenix/Charles River) encoding 5,868 full-length human plasma membrane and secreted proteins. in vivo assessment: BB4015 efficacy was evaluated for tumor growth suppression in female NSG mice inoculated with OVCAR3 tumor cells via intraperitoneal injection. Tumor burden and animal weight were measured 3 times a week from tumor-bearing mice infused with BB4015. Live blood draws were taken at various time points following infusion to determine BB4015 pharmacokinetics.

Results 96% of ovarian tumor biopsies evaluated stained positive for MUC16 expression with an antibody raised against the membrane-retained MUC16 ectodomain. BB4015 reactivity to recombinant MUC16 ectodomain elicited specific and dose-dependent cytokine release, with no detectable reactivity to soluble CA125 protein. BB4015’s scFv displayed no observable off-target binding. BB4015 exhibited phenotypic skewing toward a more central memory/naïve-like T cell subtype. This has been attributed to increased antitumor efficacy/greater antigen recall, compared to more effector memory subtypes.4 In mice bearing OVCAR3 ovarian tumors, BB4015 infusion inhibited tumor growth in a dose-dependent manner, with complete tumor regression upon the highest dose.

Conclusions BB4015 is a highly reactive anti-MUC16 CAR T cell that exhibits a clean on-target profile and potent antitumor activity in ovarian cancer tumor models. Thus, these findings support the clinical evaluation of BB4015 CAR T cells in the treatment of patients with ovarian cancer.

REFERENCES


Ethics Approval All mouse studies were conducted with the approval and oversight of the 2seveny bio-Institutional Animal Care and Use Committee.

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