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Conclusions HPN601 is a conditionally active EpCAM-targeting T cell engager with a ten-fold improved therapeutic window compared to a constitutively active EpCAM-targeting T cell engager. An EpCAM-specific T cell engager with an improved safety profile could address unmet needs in many solid tumors and demonstrate the feasibility of using conditionally active T cell engagers to target more solid tumor antigens.

Ethics Approval The study was reviewed and approved by Harpoon’s Institutional Animal Care and Use Committee.

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633 DUAL-TARGETING OF 4-1BB AND OX40 WITH AN ADAPTIRM™ BISPECIFIC ANTIBODY ENHANCES ANTITUMOR RESPONSES TO SOLID TUMOR

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Background 4-1BB (CD137) and OX40 (CD134) are critical activation-induced co-stimulatory receptors that regulate immune responses of activated T and NK cells by enhancing proliferation, cytokine production, survival, and cytolytic activity. A superagonist 4-1BB antibody has shown clinical activity but severe toxicities. APVO603, is a 4-1BB x OX40 targeting bispecific antibody with conditional agonism, activating these receptors only when both are co-engaged. The Fc portion was mutated to eliminate FcγR-mediated interactions. Co-stimulation through 4-1BB and OX40 has the potential to amplify the cytotoxic function and the number of activated T and NK cells in multiple solid tumor indications.1-3

Methods scFv binding domains to 4-1BB and OX40 were optimized to increase affinity, function and stability, and then incorporated into the ADAPTIRM™ bispecific antibody platform to produce the APVO603 lead candidate. NF-kB/luciferase reporter cell lines expressing OX40 or 4-1BB were initially used to assess the agonistic function of APVO603’s binding domains. Primary PBMC were sub-optimally stimulated with an anti-CD3 antibody and T and NK cell proliferation was assessed using Cell TraceTM-labelled PBMC. Cytokine secretion was measured at 48 hrs using Luminesin-based assays. For in vitro tumor lysis studies, PBMC were co-cultured with tumor cells expressing a tumor-associated antigen (TAA) and activated with TAA x CD3 bispecific protein. 7-AAD expression was assessed on tumor cells at 72 hrs. The in vivo therapeutic efficacy of APVO603 was evaluated using a murine MB49 bladder cancer model in human 4-1BB and OX40 double knock-in mice.

Results APVO603 stimulates 4-1BB and OX40 NF-kB/luciferase reporter activity in a dose-dependent manner, and is strictly dependent on engagement of the reciprocal receptor to elicit 4-1BB or OX40 activity. In primary PBMC assays, APVO603 induces synergistic proliferation of CD4+ T cells and induction of CD8+ T and NK cells when compared to OX40 or 4-1BB monospecific molecules with a wt Fc, either individually or in combination. Additionally, APVO603 enhances proinflammatory cytokine production and granzyme B expression, and augments in vitro tumor cell lysis induced by a TAAx CD3 engager. In vivo, APVO603 reduces growth of established MB49 tumors in human 4-1BB and OX40 double knock-in mice.

Conclusions APVO603 is a dual-agonistic bispecific antibody that augments the effector function of activated CD4+ and CD8+ T cells, and has shown clinical activity and safety in a Phase I/II clinical trial in solid tumors.