EphA2/CD137 Bicycle® tumor-targeted cell agonists (TICAs™) induce tumor regressions, immunogenic memory, and reprogramming of the tumor immune microenvironment.

ABSTRACT

CD137/4-1BB is a member of the TNF receptor superfamily involved in the stimulation of several immune cell types, including T and NK cells.

Despite compelling preclinical data, anti-CD137 antibodies have been hampered by failure to elevate hematopoietic expression and achieve high avidity (1:1), likely due to suboptimal binding properties. Lack of co-stimulation and immune suppression may contribute to failure of co-stimulation and immune activation due to continuous exposure.

BCY12491 is a tumor-targeted immune cell agonist (TICA™) that exemplifies a new class of fully synthetic immunomodulatory conjugates comprised of bicyclic peptides (Bicycles®) targeting a tumor antigen and a co-stimulatory molecule. We developed this new class of synthetic molecules with antibody-like affinities and target selectivity to circumvent the before mentioned barriers to optimal target CD137 agonistic therapies.

BCY12491, an EphA2/CD137 TICA, is designed to deliver a highly potent CD137 agonist to EphA2 overexpressing tumors, including pancreatic, gastric, and colorectal, among others. BCY12491 is a potent EphA2-dependent CD137 agonist with rapid binding, pharmacokinetic, and biologic activity. BCY12491 promotes cytokine secretion in PC3 / cancer cell co-culture experiments. Phamacokinetic data from healthy donors were generated following BIW dosing in mice to demonstrate intermittent plasma exposure of BCY12491 produces robust anti-tumor immune responses.

The ability of BCY12491 to enter a novel class of therapies CD137 agonists for humans for the treatment of cancer.

INTRODUCTION

• Bicycles® differ from other TICAs, such as bispecific antibodies and bispecific T-cell engagers (BiTE®s) in that they are constructed from different scaffolds and present unique advantages in terms of attachment points, affinities, physicochemical properties. TICAs of varying valency (1:1, 1:2 and 1:3) achieve K(D) stimulatory molecule. We developed this new class of synthetic molecules with antibody-like affinities and target selectivity to circumvent the before mentioned barriers to optimal target CD137 agonistic therapies. BCY12491, an EphA2/CD137 TICA, is designed to deliver a highly potent CD137 agonist to EphA2 overexpressing tumors, including pancreatic, gastric, and colorectal, among others. BCY12491 is a potent EphA2-dependent CD137 agonist with rapid binding, pharmacokinetic, and biologic activity. BCY12491 promotes cytokine secretion in PC3 / cancer cell co-culture experiments. Phamacokinetic data from healthy donors were generated following BIW dosing in mice to demonstrate intermittent plasma exposure of BCY12491 produces robust anti-tumor immune responses.

• The ability of BCY12491 to enter a novel class of therapies CD137 agonists for humans for the treatment of cancer.

RESULTS

A. EphA2/CD137 Bicycle® tumor-targeted cell agonists (TICAs™) induce tumor regressions, immunogenic memory, and reprogramming of the tumor immune microenvironment.

B. Mouse CD8+ TICAs

C. Specific gene set (left) and gene (right) expression changes in tumor (NanoString)

Figure 1: A schematic of the process for generating CD137 TICA molecules using Bicycle® technology. The lead design strategy was then optimized to identify a Bicycle targeting a highly expressed tumor antigen, i.e. EphA2. Binding of these molecules would result in a multi-armed array of CD137 engaging Bicycles, enabling the clustering of the CD137 receptors in a tumor antigen-dependent manner.

Figure 2: The concept of a Bicycle tumor targeted immune cell agonist (TICA) for engaging EphA2 and CD137 receptors in a tumor antigen-dependent manner.

Figure 3: BCY12491 led to potent EphA2-dependent activity in CD137 reporter and primary immune cell co-culture assays. A) NF-κB-luc/CD137 Jurkat reporter cells were co-cultured with EphA2 expressing cancer cells and the dose response was determined. NF-κB activity was determined by luciferase reporter assay. B) BCY12491 promoted cytokine secretion in PC3 / cancer cell co-culture experiments. JEMC from healthy donors were generated following BIW dosing in mice to demonstrate intermittent plasma exposure of BCY12491 produces robust anti-tumor immune responses.

Figure 4: Intermittent dosing of BCY12491 led to significant anti-tumor activity and immunogenic memory in murine xenograft model. BCY13626 (ananti-CD137 antibody (Unitherapies, Creative BioTools), or vehicle. Tumors were harvested after 5 days and either used for in vitro cell culture experiments. PBMCs from healthy donors were cultured with EphA2 expressing cancer cells and the dose response was determined.

Figure 5: BCY12491 Treatment led to increased T-cell infiltration and reprogramming of the tumor immune microenvironment. Mice were treated with 15 mg/kg q3d IV of BCY12491, BCY13626 (ananti-CD137 antibody (Unitherapies, Creative BioTools), or vehicle. Tumors were harvested after 5 days and either used for in vitro cell culture experiments. PBMCs from healthy donors were cultured with EphA2 expressing cancer cells and the dose response was determined.

CONCLUSIONS

• BCY12491 is an EphA2/CD137 Bicycle TICA that exhibits highly potent, EphA2-dependent activity in vitro primary immune cell assays.

• BCY12491 causes tumor regression, complete responses, immunogenic memory, and significant modulation of the tumor immune microenvironment in preclinical syngeneic mouse models without continuous drug exposure in the periphery.

• Bicycle Therapeutics is advancing an EphA2/CD137 TICA clinical candidate to the clinic.

Questions? Contact meren@bicycletherapeutics.com

ABSTRACT# 700

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