A multi tumor survey of Nectin-4 expression to guide BT8009 indication selection


ABSTRACT

• BT8009 is a Bicycle®-Toxin Conjugate (BTC), a novel class of chemically synthesized molecules, comprising a bicyclic peptide targeting the tumor antigen Nectin-4, linked to the cytotoxin monomethyl auristatin E (MMAE) via a molecular spacer and cleavable linker
• Nectin-4 is a clinically validated tumor target and has been reported to be highly expressed in a wide range of solid tumors [1]
• Precalical activity of BT8009 has been described previously, demonstrating increased efficacy is associated with high Nectin-4 tumor cell expression levels in xenograft models [2]
• An immunohistochemistry (IHC) assay using a proprietary Nectin-4 monoclonal antibody was developed to CAP/CLIA standards to quantify Nectin-4 tumor expression. This assay detects the extracellular domain (ECD) of Nectin-4 (BT8009 binding site)
• A Phase 1/2 dose escalation and expansion study with BT8009 (NCT04561362) began dosing in Sep 2020 in patients with advanced solid tumors associated with Nectin-4 expression

INTRODUCTION

• Cell adhesion molecule, widely expressed during development with restricted adult normal tissue expression (e.g. skin, esophagus)
• Expressed in many difficult to treat solid tumors such as bladder, breast (including triple negative breast cancer (TNBC)), lung, ovarian, esophageal, head & neck (HNSCC), pancreatic, and gastric cancers
• Approved Nectin-4 targeted ADC enfortumab vedotin is highly efficacious in heavily pretreated advanced bladder cancer and like BT8009 also contains MMAE linked via a vali-cit linker
• Multiple independent IHC assays using a variety of reagents have been used to study Nectin-4 expression across indications
• The proprietary Bicycle IHC assay was used to survey Nectin-4 ECD expression across a variety of tumor types to prioritize indications for clinical development and is employed for the assessment of Nectin-4 expression in patient tumor tissue in the BT8009-100 trial

METHODS

• Nectin-4 IHC assay was developed to CAP/CLIA standards on the Leica platform using a proprietary rabbit monoclonal anti-Nectin-4 primary antibody YMW-1-58 (Abcam, Burlington MA) and the BOND Polymer Refine detection kit
• TMAs (US Biomax) from indications reported to have high Nectin-4 expression
• H-score (the product of stain intensity on a scale of 0-3 and % positive tumor cells) were generated by a pathologist independently for tumor cell membrane and tumor cytoplasm. If tumor membrane or cytoplasm is not specified, H-score refers to the greater of the two metrics

RESULTS

Figure 1: Cell line controls with known Nectin-4 expression levels (% of cases above score cutoff C. Examples of images from bladder and breast cancer representing 4 bins of Nectin-4 expression

Table 1: Summary of Nectin-4 ECD expression by IHC in 8 indications.

CONCLUSIONS/SUMMARY

• An IHC assay has been established to CAP/CLIA standards to determine expression of Nectin-4 ECD in FFPE human tissue collected in the BT8009-100 trial
• Benchmarking YMW-1-58 antibody performance against published literature shows similar degree of Nectin-4 expression across most indications tested, excluding pancreatic cancer
• The prevalence and patterns of Nectin-4 expression, in both tumor cytoplasm and membrane, vary across indications, with the highest frequency observed in bladder and breast cancer.
• Consistent with the literature, Nectin-4 expression is significantly enriched in TNBC and in HER- and HER2+ breast cancer [3,4]


www.bicycletherapeutics.com

Bicycle Therapeutics
4 Harvard Place, Lexington, MA 02421
www.bicycletherapeutics.com