Molecular-based enrichment strategy for Nectin-4 targeted Bicycle toxin conjugate BT8009

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ABSTRACT

• BT8009 consists of a bicyclic peptide targeting the tumor antigen Nectin-4, linked to the cytotoxin MMAE
• BT8009 is currently being investigated in a Phase 1/2 clinical trial (BT8009-100, NCT04561362) in relapsed and/or refractory solid tumor patients
• Provision of tumor tissue for Nectin-4 testing is required for enrollment
• Nectin-4 positivity will be determined by IHC (tumor membrane (TM) or tumor cytoplasmatic (TC) H-score ≥ 100)
• We have discovered an enrichment strategy that may help identify patients with Nectin-4 positive tumors
  • SDHC copy number (CN) can be used as a surrogate for Nectin-4 CN, Nectin-4 transcript expression, and Nectin-4 protein expression
  • Access to this enrichment strategy has been implemented at sites enrolling patients to BT8009-100

INTRODUCTION

• Nectin-4 is a cell adhesion molecule and has been reported to be pro-oncogenic
• Nectin-4 is overexpressed in various tumor types including bladder and TNBC and has limited expression in normal human tissue
• Nectin-4 is a validated target for cytotoxin delivery (enfortumab vedotin)
• The Nectin-4 targeted toxin conjugate, BT8009 has robust efficacy in both CDX and PDX preclinical models
• Nectin-4 is not included on most targeted NGS panels (e.g. FM1)

WHY BICYCLES?

• Nectin-4 transcript expression across TCGA PanCancer Atlas studies. Copy number call indicated by color: (*: gene expression determined by microsatellite analysis) followed by Bonferroni post-hoc: diploid vs. gain & diploid vs. amplification (p<0.002)

METHODS

• TCGA PanCancer Atlas datasets were tested for potential associations between Nectin-4 copy number and Nectin-4 transcript expression (Kruskall-Wallis & Bonferroni post-hoc)
• SDHC was identified as the gene physically closest to Nectin-4 that is included on the FoundationOneCDx panel (225 kb apart on 1q23)
• 100 TNBC human tumor samples were assayed for Nectin-4 and SDHC copy number (whole exome sequencing) as well as Nectin-4 protein expression status (IHC)

RESULTS

• Figure 1: Association between Nectin-4 CN and transcript expression in multiple cancer types
• Figure 2: SDHC and Nectin-4 CN are positively associated in TCGA PanCancer Atlas studies
• SDHC CN ratio plotted against Nectin-4 CN ratio and Spearman's r1 is annotated in top left. Labels on Barbel plots indicate TCGA cancer identification abbreviation (See references).

• Figure 3: SDHC & Nectin-4 CN are highly correlated in 100 human TNBC samples

• Figure 4: 100% Positive predictive value when using Nectin-4 CN ≥ 3 to determine Nectin-4 TM or TC H-score ≥ 100

CONCLUSIONS

• Identified a routinely measured molecular marker (SDHC amplification) that can be used to enrich for patients with Nectin-4 positive tumors
• Potential benefits include:
  • Provides a readily available molecular basis for screening subjects for BT8009-100
  • Increased yield of enrolled Nectin-4 positive patients

Implementation Strategy:

1) Determine if there is an association with Nectin-4 copy number and Nectin-4 transcript expression in patient’s cancer type
2) Investigate SDHC status on targeted NGS panel

REFERENCES


If patient tumor has an SDHC amplification this suggests a Nectin-4 amplification, higher likelihood of Nectin-4 protein expression, and eligibility for BT8009-100 trial

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