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 cytoplasmic (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. FMI).

WHY BICYCLIC?

- Nectin-4 is a cell adhesion molecule and has been reported to be pro-oncogenic.
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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 FoundationOne®CDx 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.
- Nectin-4 transcript expression across TCGA PanCancer Atlas studies. Copy number call indicated by color. *nominal significance determined by Bonferroni post-hoc followed by Bonferroni post-hoc: diploid vs. gain & diploid vs. amplification (p<0.001).
- 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 rho is annotated in top left. Labels as Bubble plots indicate TCGA cancer indication abbreviation (See references*).
- Figure 3: SDHC & Nectin-4 CN are highly correlated in 100 human TNBC samples.
- R²=0.93
- Figure 4: 100% Positive predictive value when using Nectin-4 CN 3 to determine Nectin-4 TM or TC H-score ≥ 100.
- Nectin-4 CN ratio plotted against SDHC CN ratio for 100 TNBC samples. Color indicates CN call (diploid=blue).

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

- Incorporate 2022-04-15 references, TCGA cancer indication abbreviations, and Nectin-4 CN, Nectin-4 transcript expression, and eligibility for BT8009-100 trial.

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