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

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- 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

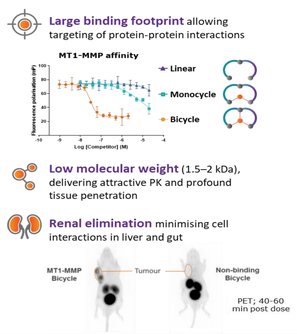
INTRODUCTION

- 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. FM1)

WHY BICYCLES?

New Class of Therapies

Novel modality delivers high affinity, favourable PK and rapid clearance.



METHODS

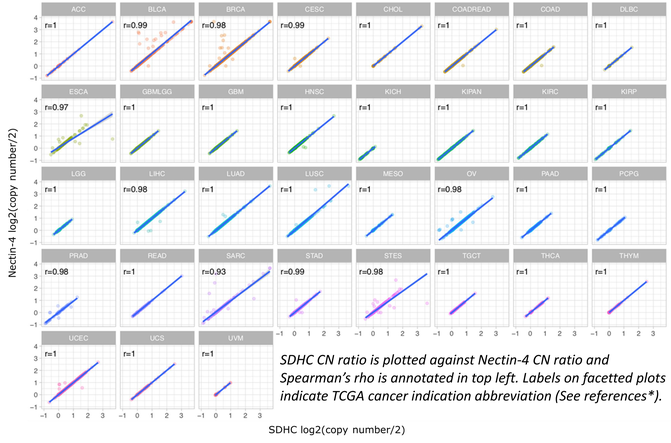
- TCGA PanCancer Atlas datasets were tested for potential associations between Nectin-4 copy number and Nectin-4 transcript expression (Kruskall-Wallis & Bonferonni post-hoc)
- SDHC was identified as the gene physically closest to Nectin-4 that is included on the FoundationOne®CDx panel (225 kb apart 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

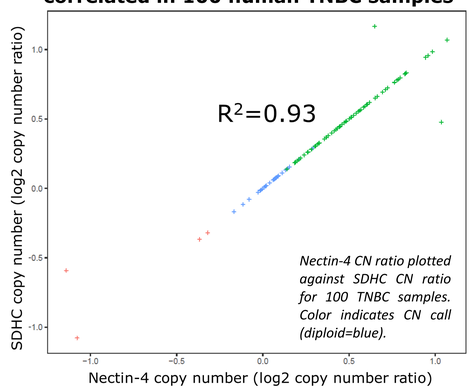
*Nectin-4 transcript expression across TCGA PanCancer Atlas studies. Copy number call indicated by color. *=statistical significance determined by Kruskal-Wallis p<0.01 followed by Bonferonni post-hoc: diploid vs. gain & diploid vs. amplification (p<0.025)*

Figure 2: SDHC and Nectin-4 CN are positively associated in TCGA PanCancer Atlas studies



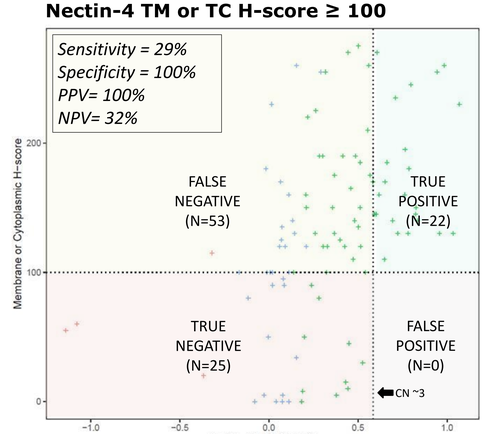
SDHC CN ratio is plotted against Nectin-4 CN ratio and Spearman's rho is annotated in top left. Labels on facetted plots indicate TCGA cancer indication abbreviation (See references).*

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



Nectin-4 CN ratio plotted against SDHC CN ratio for 100 TNBC samples. Color indicates CN call (diploid=blue).

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



Relative Nectin-4 CN plotted against Nectin-4 protein expression (higher value of TM or TC H-score) for 100 TNBC samples. PPV: positive predictive value. NPV: Negative predictive value.

CONCLUSIONS

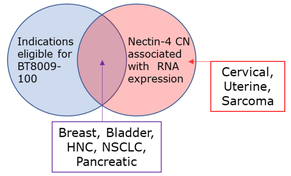
Identified a routinely measured molecular marker (SDHC amplification) that can be used to enrich for patients with Nectin-4 positive tumors

Potential benefits include:

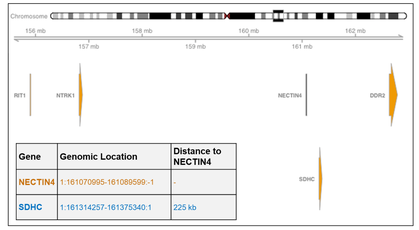
- Provides a readily available molecular basis for screening subjects for BT8009-100
- Increased yield of enrolled Nectin-4 positive patients

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



Gene	Genomic Location	Distance to NECTIN4
NECTIN4	1:161070995-161089599:-1	
SDHC	1:161314257-161375340:1	225 kb

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

REFERENCES

- Cerami et al. The cBio Cancer Genomics Portal: An Open Platform for Exploring Multidimensional Cancer Genomics Data. Cancer Discovery. May 2012 2; 401.
- Gao et al. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci. Signal. 6, pl1 (2013).
- *TCGA Study Abbreviations: https://gdc.cancer.gov/resources-tcga-users/tcga-code-tables/tcga-study-abbreviations