BI 905711 selectively induces apoptosis and anti-tumor response in TRAILR2/CDH17- expressing pancreatic cancer models

INTRODUCTION

• Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal adult cancers with an average 5-year survival rate of less than 10% due to the limited number of effective therapies. Activation of TRAILR2 (Tumor necrosis factor (TNF)-Related Apoptosis-Inducing Ligand Receptor 2) has emerged as an important therapeutic concept in cancer treatment. Traditional TRAILR2 agonists have had limited clinical success due to lack of efficacy or, importantly, severe hepatotoxicity. Here we present anti-tumor activity in preclinical PDAC models for BI 905711, a first-in-class tetravalent bispecific antibody specifically designed to overcome the limitations of previous strategies targeting TRAILR2.

BI 905711 only targets tumors that co-express TRAILR2 and another cell surface protein CDH17. This bispecific feature promotes this as a uniquely specific and liver-sparing therapeutic, as CDH17 has ~40% prevalence in PDAC and is not expressed in normal liver. Working from a large cohort of molecularly characterized PDAC PDX models, we provide the first preclinical evidence of BI 905711 exhibiting robust anti-tumor activity in PDAC PDX models.

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Patient Stratification Assay Developed Using RNAscope

Preclinical efficacy of TRAILR2-CDH17 Ab in PDAC PDXs and Responder Identification

Figure 1. A large cohort of molecularly characterized PDAC PDX models were tested with BI 905711 (1.67 mg/kg, Q7D) or Vehicle. Robust anti-tumor activity was observed in a subset of PDAC PDX models. Representative images of singlets and multiplex analysis of representative differential responses of responders (green) and non-responders (red). B. Correlation between percentage of tumor growth inhibition (TGI%) with TRAILR2 and CDH17 expression profiles (TPM values of RNA-seq) helped define the expression threshold for each target that is associated with response.

CC3 and CCB Validated as Reliable Response Biomarkers

Figure 3. TRAIL-mediated cleavage of caspase-3 (CC3) and caspase-8 (CCB) is a key indicator of triggering apoptosis, therefore, induction of CC3 and CCB was evaluated to inform on potential response biomarkers for BI 905711. Acute pharmacodynamic (PD) tumors were collected 24 hr post-single dose of BI 905711 or Vehicle. A. Immunofluorescence staining revealed induction of CC3 and CCB in PDX05 acute PD Tumors. B. Acute PD quantification across a panel of 7 PDAC PDXs show consistent induction of CC3 and CCB in responders, not in non-responders (**p<0.005, *p<0.05).

SUMMARY

Leveraging a large cohort of molecularly characterized PDAC PDX models, we provide the first preclinical evidence of BI 905711 exhibiting robust anti-tumor activity in PDAC models.

• Differential response in PDAC PDX models is informing on responder ID hypothesis.

• RNAscope for TRAILR2 and CDH17 has been established to guide patient selection.

• Apoptotic markers CC3/8 have been identified as promising acute PD biomarkers.

• Robust preclinical anti-tumor activity of BI 905711 in TRAILR2 and CDH17-expressing PDAC PDX models, along with this antibody’s potential for a favorable safety profile, has informed on design of the ongoing BI 905711 FIH Phase I clinical trial (NCT04117289).

REFERENCES