The LGR5 monoclonal antibody BNC101 has anti-tumor and anti-cancer stem cell activity in pancreatic cancer

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Abstract

Introduction

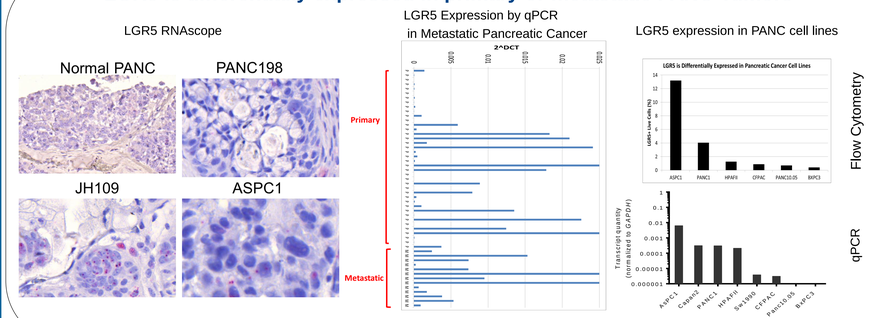
- LGR5 was originally identified as a cancer stem cell (CSC) specific receptor associated with the Wnt signaling pathway in colorectal cancer (CRC).
- BNC101 is a humanized monoclonal antibody (mAb) targeting LGR5 that has successfully completed IND-enabling studies for upcoming human clinical trials.
- BNC101 has significant anti-tumor and anti-CSC activity in multiple CRC patient-derived xenografts (PDX), consistent with the hypothesis that LGR5 is a functional CSC target in CRC.
- LGR5 has also been reported to be expressed on regenerating pancreatic stem cells and to be upregulated in pancreatic cancer, providing a strong rationale to investigate efficacy of BNC101 in pre-clinical models of pancreatic cancer.

Results and Conclusion

- Using qPCR and/or RNAscope, LGR5 found to be highly expressed in a number of pancreatic (PANC) PDX samples including JH109.
- Additionally, we screened LGR5 expression in a series of pancreatic cancer cell lines and identified both high-LGR5 expressing lines (ASPC1 and PANC1) and an LGR5-negative line (BxPc3).
- *In vivo* debulking of JH109 tumors with standard of care (SOC; combination of Gemcitabine and Abraxane) followed by treatment with BNC101 caused complete tumor regression in 43% (3/7) of mice compared to SOC control (0/7) group.
- BNC101 monotherapy partially inhibited tumor growth in ASPC1 and PANC1 models. In combination with Gemzar, however, BNC101 significantly inhibited tumor growth in both models.
- In contrast, BNC101 had no anti-tumor activity (as single agent or in combination with chemotherapy) in the LGR5^{negative} BxPc3 xenograft tumors.
- Using qPCR, LGR5 expression was upregulated in chemo-treated tumors, suggesting that BNC101-chemo combination activity was efficacious due to greater LGR5 target availability.
- IHC analysis showed an increase in CA19 and Alcian blue expression, consistent with the hypothesis that BNC101 targets CSCs and induces terminal differentiation.
- Treatment with BNC101 in two orthotopic PANC PDX models, resulted in a significant reduction in the frequency of LGR5+HLA+ circulating-tumor-cells (CTCs) in the peripheral blood, providing a pharmacodynamic (PD) biomarker of target engagement to further evaluate in clinical studies.
- Altogether, the data support further evaluation of BNC101 in the clinic for the treatment of pancreatic cancer.

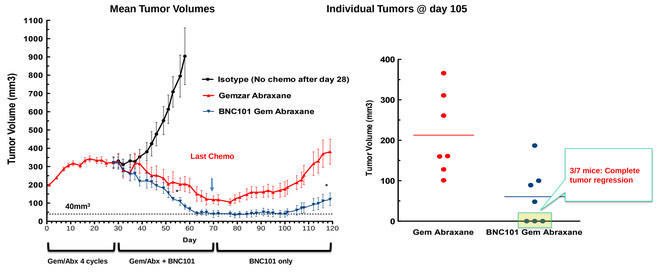
Results

LGR5 is differentially expressed in primary or metastatic PANC Tumors



Combination of BNC101 and standard of care (Gemzar and Abraxane) significantly inhibit tumor growth in JH109 pancreatic PDX model

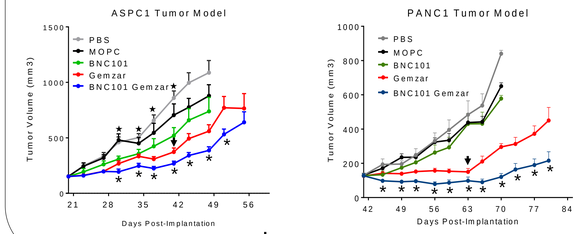
JH109: Progressive ductal adenocarcinoma (T3N1M0); Stage IIB with multiple (4) lines of chemo, radiation and targeted Rx



* P < 0.05: Gem/Abx vs BNC101 Gem/Abx day 56 to day 120, with the exception of d65 and d72

Results

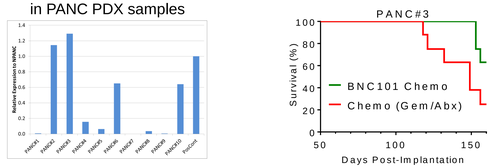
Combination of BNC101 and Gemzar significantly inhibits tumor growth in ASPC1 and PANC1 cancer cell lines



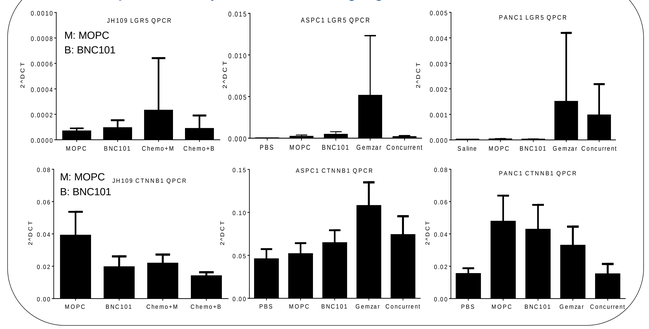
★ p<0.05 when comparing BNC101 vs. PBS ↓: Last dose of chemo * p<0.05 when comparing Gemzar vs. Combination

Combination of BNC101 and standard of care (Gemzar and Abraxane) improves overall survival in a pancreatic PDX model

LGR5 qPCR expression in PANC PDX samples



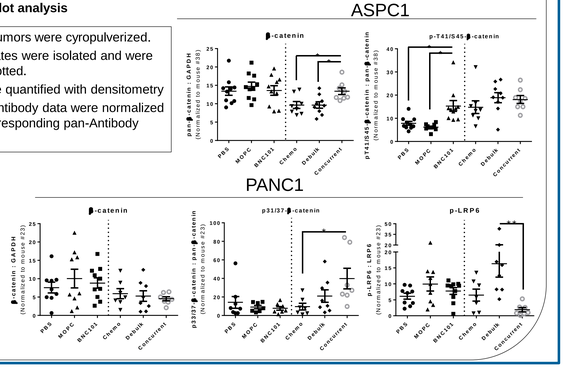
LGR5 and β-Catenin expression is trending higher in chemo-treated tumors



BNC101 treatment modulates expression of Wnt pathway proteins in ASPC1 and PANC1 tumors

Western blot analysis

- Individual tumors were cyropulverized.
- Protein lysates were isolated and were Western blotted.
- Bands were quantified with densitometry
- Phospho-Antibody data were normalized against corresponding pan-Antibody

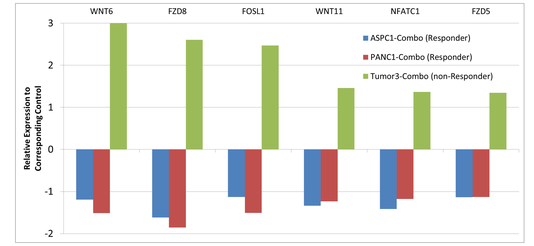


Results

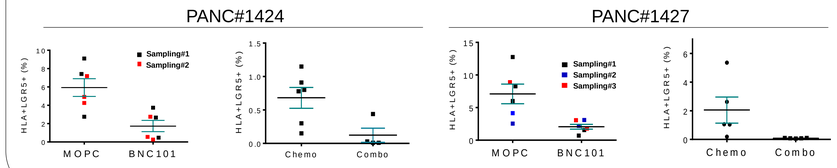
Candidate Wnt gene expression pattern associated with response to BNC101 in PANC tumors

Overview of Study Design

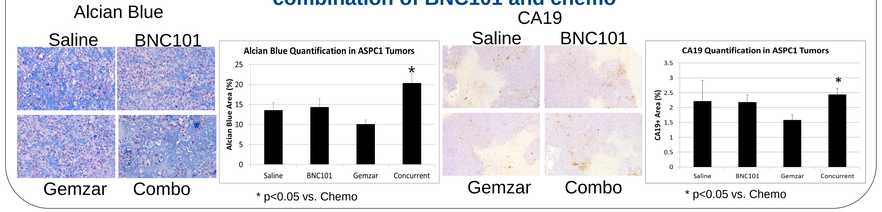
Pooled (n=10) cDNA from Chemo or Combo treated PANC tumors → QPCR in Wnt Plates Containing Primers for 84 genes → Data Analyses



Reduction of LGR5+ CTCs in BNC101 Pancreatic Orthotopic PDX Mice



Induction of expression of Alcian and CA19 in ASPC1 tumors treated with combination of BNC101 and chemo



* p<0.05 vs. Chemo * p<0.05 vs. Chemo

Conclusions and Future Plans

- LGR5 displays a wide range of expression in pancreatic PDX tumors and cell lines.
- BNC101 treatment in combination with Gemzar + Abraxane significantly inhibited tumor growth and or survival in PANC tumors including two PDX models and cancer cell lines.
- LGR5 and CTNNB1 expressions are trending higher in chemo treated tumors providing a rationale for combination of BNC101 and chemotherapy.
- Early biomarker investigations indicate that BNC101 treatment is affecting expression of Wnt pathway proteins and transcripts in both pancreatic and CRC tumors.
- Further efforts are currently underway to identify predictive biomarkers by investigating expression of Wnt pathway genes.
- BNC101 mAb treatment may significantly extend patient survival in CRC, TNB, SCLC and also Pancreatic cancers.
- Future investigations will be focused on identification and validation of a set of biomarkers to stratify patient population in the near future clinical trials.