Abstract #950

Preclinical Investigation of BDC-4182, a Claudin 18.2-targeting ISAC to Support Clinical Development

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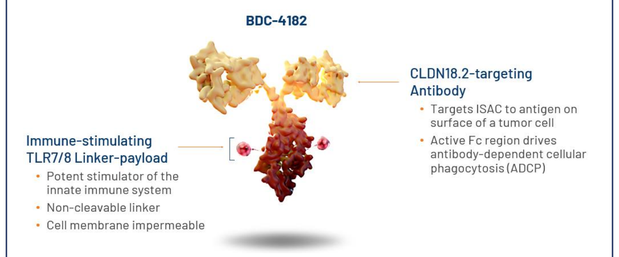
Background

BDC-4182 is a next-generation ISAC with significantly enhanced immune activating capability. It builds upon the clinical experience with first generation ISACs and consists of a CLDN18.2-targeting antibody covalently attached to a potent toll-like receptor (TLR)7/8 agonist via an intervening non-cleavable linker. The key features and proposed mechanism of action are described herein.

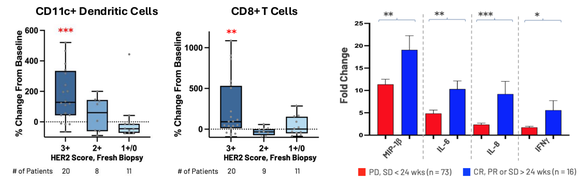
Briefly, BDC-4182 binds to CLDN18.2-expressing tumor cells and triggers antibody-dependent cellular phagocytosis (ADCP) by dendritic cells (DCs) and other antigen presenting cells (APCs). Following phagocytosis, BDC-4182 localizes to the endosomal TLRs, whereby agonism of TLR7/8 drives APC activation, upregulation of antigen presenting machinery, and secretion of proinflammatory cytokines. These cytokines help activate and recruit additional immune effector cells to the tumor. Activated APCs also process tumor-associated antigens and tumor neoantigens for cross-presentation to tumor-reactive T cells, which can result in epitope spreading beyond the target antigen and a durable adaptive anti-tumor immune response.

BDC-4182: Key Features



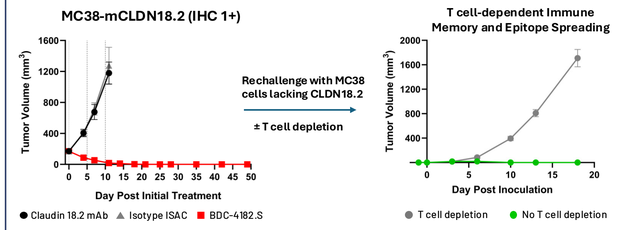
BDC-4182 Builds Upon 1st Generation ISACs

- BDC-1001
  - Clinical activity with 29% ORR at RP2D in HER2+ patients
  - Immune activity was most pronounced in HER2 IHC 3+ tumors
  - Increased immune activation in patients correlated with clinical benefit



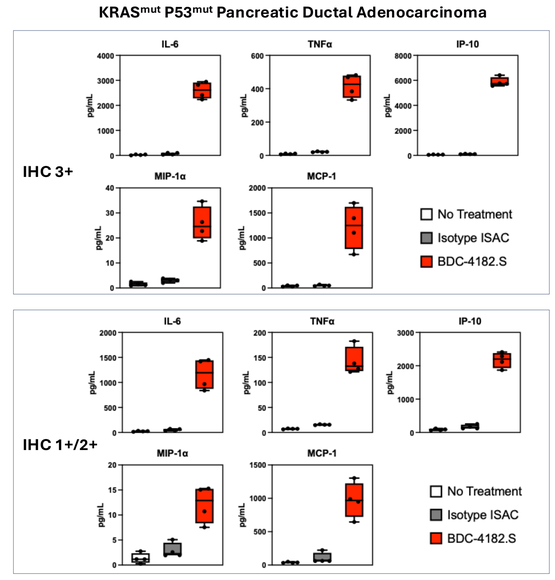
Enumeration in baseline and on-treatment biopsies following BDC-1001 monotherapy (left, middle). Fold increase in plasma cytokines in HER2+ patients treated with 8 to 20 mg/kg of BDC-1001 ± Nivolumab. Monotherapy showed similar trend (right). *p<0.05, **p<0.01, ***p <0.001

Immune Memory & Epitope Spreading Beyond Target Antigen



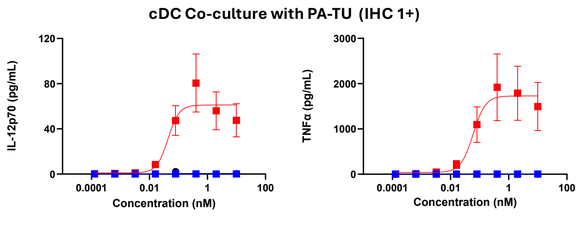
BDC-4182.S treated mice (5 mg/kg, q5dx3) with complete tumor regression for > 28 days following their last treatment were rechallenged with MC38-mCLDN18.2 cells (IHC1+ by H-score) on their right flank and parental MC38 cells on the left flank in the presence of absence of CD4 & CD8 T cell depletion (n=4 mice/group). Mice remained tumor free when challenged with MC38-mCLDN18.2 cells in the absence of T cell depletion (not shown).

On-Target & Tumor-Dependent Immune Activation



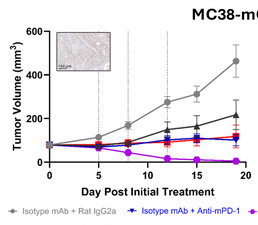
C57BL/6 mice bearing KPC-mCLDN18.2 tumors (IHC 3+ or IHC 1+/2+ by H-score) tumors were treated via IP injection with the indicated test articles at 5 mg/kg. Plasma cytokines and chemokines were measured 4 hours after dosing (n=4 per group). A separate study in tumor naïve mice showed low levels of the above cytokines following administration of 5 mg/kg of the indicated test articles.

Dramatically Enhanced Immune Activity with BDC-4182



Human cDCs were co-cultured with CLDN18.2-expressing PA-TU-8988S tumor cells (IHC 1+) and the indicated test articles for 18 hr (n=9).

Synergy with Checkpoint Blockade

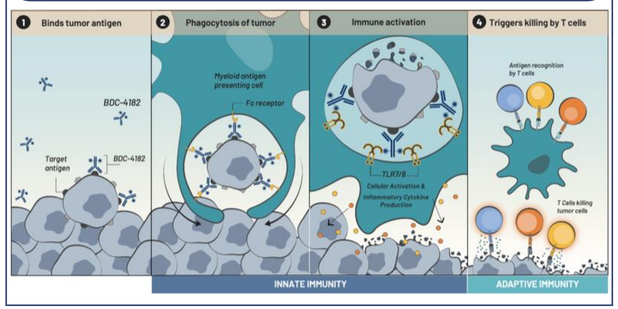


	IHC Score	% cells ≥ IHC 2+
MC38-mCLDN18.2	1+	11.7

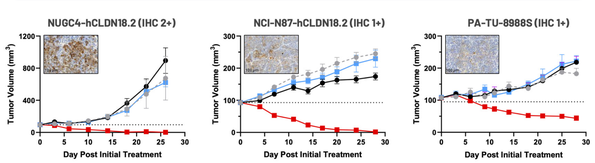
	mPD1	BDC-4182.S	BDC-4182.S + mPD-1
TGI	78%	74%	99%
Tumor Free	None	2 out of 8	7 out of 8

C57BL/6 mice bearing MC38-mCLDN18.2 tumors (IHC 1+ by H-score) were administered 2 mg/kg of the indicated test articles biweekly for 4 doses (dashed lines; n=8 mice per group). TGI was calculated on Day 19 relative to the Isotype ISAC; tumor free mice were recorded on Day 19.

Mechanism of Action



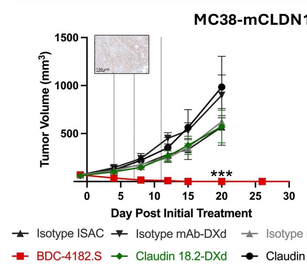
Translates to Efficacy in Low Antigen Density Models



	IHC Score	% cells ≥ IHC 2+	BDC-4182.S (TGI)	Tumor Free Mice
NUGC4-hCLDN18.2	2+	61.3	100%	8 out of 8
NCI-N87-hCLDN18.2	1+	15.0	99%	6 out of 8
PA-TU-8988S	1+	18.8	76%	None

SCID/beige mice with the indicated tumors were treated with BDC-4182.S at 5 mg/kg BIW (4 doses, n=8 per group). TGI was calculated on day 26 or 28 post initial treatment and the number of tumor free mice were recorded on the last day of the study.

Superior Preclinical Efficacy vs Topo1-based ADCs



	IHC Score	% cells ≥ IHC 2+
MC38-mCLDN18.2	1+	11.7

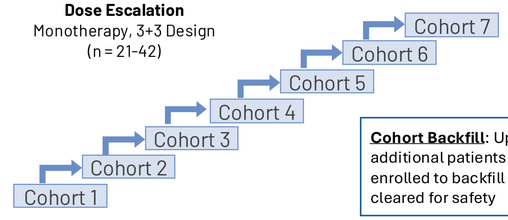
	BDC-4182.S	Claudin 18.2-DXd
TGI	100%	12%
Tumor Free	8 out of 8	0 out of 8

C57BL/6 mice bearing MC38-mCLDN18.2 tumors (IHC 1+ by H-score) were administered 5 mg/kg of the indicated test article biweekly for 4 doses (dashed lines; n=6 to 8 mice per group). TGI was calculated on Day 20 relative to the Isotype mAb; tumor free mice were recorded on Day 42.

Phase 1 Clinical Investigation

- Will enroll gastric or gastroesophageal cancer patients
- Enrollment in Australia, South Korea, and Taiwan (NCT06921837)

Dose Escalation
Monotherapy, 3+3 Design
(n = 21-42)



Cohort Backfill: Up to n=20 additional patients may be enrolled to backfill cohorts cleared for safety

Benefits of Targeting TLR7 & TLR8

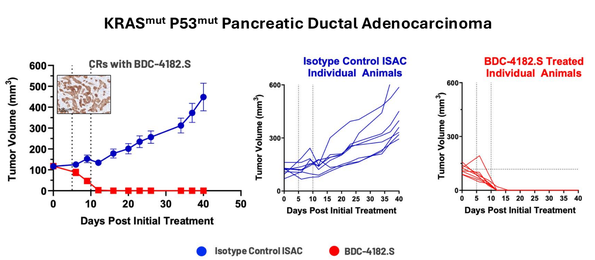
- TLRs are receptors that recognize specific foreign patterns/signatures (e.g., viral, bacterial, fungal)
- Stimulation of TLRs triggers a robust innate immune response and initiates adaptive immunity
- TLR7 and TLR8 are expressed intracellularly in the phagolysosome in a variety of immune cells:

TLR7	TLR7/8			TLR8
Plasmacytoid Dendritic Cells	Conventional Dendritic Cells	Monocytes	Macrophages	Neutrophils

Goal of TLR7 and TLR8 stimulation is anti-tumor activity

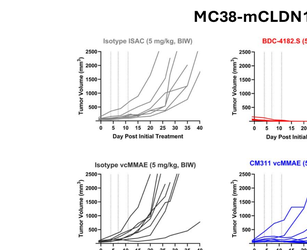
Stimulation produces IFNα	Stimulation produces cytokines such as TNFα and IL-12p70 and chemokines such as MIP-1β (recruits more myeloid cells) & IP-10 (recruits more T cells)

Complete Regression in Immunologically Cold Tumors



C57BL/6 mice bearing KPC tumors (CLDN18.2 IHC 3+) were treated via IP with the indicated test articles at 5 mg/kg when tumors reached ~100 mm3. Animals received three doses in total (dashed lines). Data are shown as mean with SEM from n=8 female mice per group.

Superior Preclinical Efficacy vs MMAE-based ADCs



C57BL/6 mice bearing MC38-mCLDN18.2 tumors (IHC 1+ H-score) were administered 2 or 5 mg/kg of the indicated test article biweekly for 4 doses (dashed lines; n=7 to 8 mice per group).

Summary

- BDC-4182 is a next-generation ISAC with significantly enhanced immune activating capability. It promotes tumor killing by several mechanisms, including antibody-dependent cellular phagocytosis by tumor-associated myeloid cells which can propagate additional killing by tumor-specific T cells.
- Preclinical studies indicate that the murine surrogate, BDC-4182.S, stimulates powerful immune responses that elicit complete regression and induces T cell-dependent memory that prevents the growth of CLDN18.2 antigen-loss variants.
- When compared to cytotoxic MMAE- or Topo1-based ADCs, BDC-4182.S elicits superior anti-tumor efficacy in syngeneic tumors with low levels of CLDN18.2 (IHC 1+).
- BDC-4182 is being investigated in a Phase 1/2 study in patients with 2L+ metastatic gastric or gastroesophageal cancer. Initial clinical data expected 3Q 2026.