Preliminary results from a phase 1/2 study of BDC-1001, a novel HER2 targeting TLR7/8 immune-stimulating antibody conjugate (ISAC), in patients (pts) with advanced HER2-expressing solid tumors

ABSTRACT 164P

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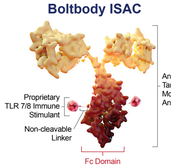
BACKGROUND

BDC-1001 is a novel ISAC consisting of an investigational biosimilar of the humanized monoclonal antibody trastuzumab chemically conjugated to a TLR7/8 agonist with a non-cleavable linker

Boltbody ISAC



Systemic Delivery, Local Effect

- Intravenously delivered, tumor-targeting therapeutic
- Antibody against a tumor antigen directs Boltbody ISACs to the tumor
- Novel immune stimulant activates myeloid antigen-presenting cells
- Myeloid cells kill tumor cells, create a "hot" tumor microenvironment, & initiate an innate & adaptive anti-tumor immune response

Anti-tumor Activity in Preclinical Models[1]

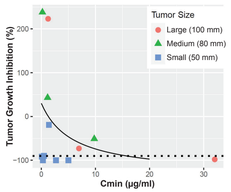
Robust single agent anti-tumor activity and elimination of established tumors in preclinical models demonstrating:

- Activity on trastuzumab resistant tumors
- Immunological memory
- Epitope spreading

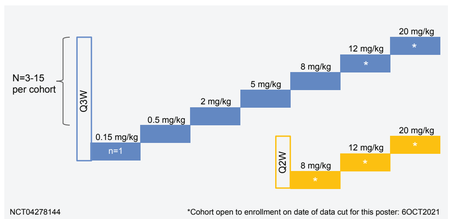
BDC-1001 Harnesses a Targeted Immuno-Oncology Approach to Stimulate and Bridge the Innate and Adaptive Immune Systems

Preclinical Data Demonstrate Importance of Exposure Threshold for Effective Anti-tumor Activity

- Dose range finding preclinical studies for efficacy determined a minimal exposure threshold of approximately 16 µg/ml in serum was required for optimal efficacy
- >15 treatment regimens were assessed in xenograft and syngeneic models
  - Overall, C_{min} and C_{mean} were well correlated with tumor growth inhibition (TGI)
  - In larger tumor models, exposure levels including C_{min} of 10-20 µg/ml are required for efficacy
- Goal: achieve highest safe exposure and C_{min} in phase 1 clinical trial, then test efficacy hypothesis in phase 2 portion of the study



BDC-1001 Monotherapy Dose Escalation Schema in Ongoing Phase 1/2[2]



NCT04278144 *Cohort open to enrollment on date of data cut for this poster: 6OCT2021

Primary Objectives	Safety and tolerability; recommended Phase 2 dose (RP2D) selection
Other Objectives	Pharmacokinetics, preliminary anti-tumor activity, plasma and tissue biomarkers to explore proof of mechanism
Key Eligibility	Any HER2-expressing solid cancer: • HER2 IHC2+/3+ or • HER2-amplified

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ACKNOWLEDGMENTS

The authors would like to acknowledge the patients and their caregivers for their support, as well as the investigators and their study teams for their contributions.

RESULTS

Demographics and Baseline Characteristics

	All Subjects (N=57)
Median age, years (range)	64 (30, 84)
Sex, n (%)	
Female	33 (58)
Male	24 (42)
ECOG PS at baseline, n (%)	
0	17 (30)
1	40 (70)
Number of prior anti-cancer regimens, median (range)	4 (1, 11)
Subjects with prior anti-HER2 therapy (%)	45 (79)
HER2 categories, n (%)	
HER2 IHC3+	31 (54)
HER2 IHC2+	13 (23)
IHC2+ & ISH- or unknown	5
HER2 amplified* (ISH or NGS)	22 (39)
Tumor types, n (%)	
Gastroesophageal	18 (32)
Colorectal (CRC)	13 (23)
Breast	9 (16)
Endometrial	6 (10.5)
Cervix	2 (3.5)
Ovarian	2 (3.5)
Salivary duct	2 (3.5)
Other (Bladder, Biliary, Lung, Pancreas, Melanoma)	1 ea (9)

*Some subjects' tumors are both IHC 2+ or 3+ and NGS amplified Data cut 6OCT2021

Overall Safety Summary

- No DLTs observed to date; MTD has not been reached up to 20 mg/kg q3w dose level
- Data reported inclusive of all q3w dose cohorts and q2w dose cohorts 8 and 12 mg/kg
- Two treatment related SAEs, both of which led to treatment discontinuation
  - Grade 3 ejection fraction decrease (>20%) after 4 cycles of therapy in an anti-HER2 therapy naïve subject
  - Grade 4 bronchopulmonary hemorrhage in a subject who had a lung biopsy 5d prior to treatment
- No Grade 5 drug-related AEs
- Grade 1/2 infusion-related reactions (IRRs) occurred in 11 subjects
  - No IRRs were reported below 5 mg/kg q3w dosing; non-steroid pre-medication was introduced at the 8 mg/kg dose level
  - All subjects were re-challenged and 1 experienced IRRs at repeated infusions
  - **No AEs consistent with cytokine release syndrome (CRS) were reported**

	All TEAEs (N=57)	Treatment-related TEAEs (N=57)
All Grades	50 (87.7%)	30 (52.6%)
Grade ≥3	24 (42.1%)	3 (5.3%)
Serious adverse event (SAE)	19 (33.3%)	2 (3.5%)
Leading to treatment discontinuation	3 (5.3%)	2 (3.5%)
Leading to death	4 (7.0%)[a]	0

[a]Three related to disease progression and one motor vehicle accident Data cut 6OCT2021
TEAEs, treatment emergent adverse events

Overview of TEAEs Occurring in >10% of All Subjects

	All TEAEs (N=57)		Treatment-related TEAEs (N=57)	
Preferred Term, n (%)	All Grades	≥ Grade 3	All Grades	≥ Grade 3
Fatigue	16 (28.1)	4 (7.0)	4 (7.0)	0
Infusion related reaction	11 (19.3)	0	11 (19.3)	0
Nausea	10 (17.5)	1 (1.8)	3 (5.3)	0
Abdominal pain	9 (15.8)	1 (1.8)	1 (1.8)	0
Pyrexia	9 (15.8)	1 (1.8)	5 (8.8)	0
Arthralgia	7 (12.3)	0	3 (5.3)	0
Constipation	7 (12.3)	0	0	0
Anemia	6 (10.5)	5 (8.8)	1 (1.8)	1 (1.8)
Diarrhea	6 (10.5)	0	5 (8.8)	0
Dyspnea	6 (10.5)	2 (3.5)	0	0
Vomiting	6 (10.5)	1 (1.8)	1 (1.8)	0

TEAEs, treatment emergent adverse events Data cut 6OCT2021

BDC-1001 Clinical Activity Seen in 13 of 40 Tumor Evaluable Subjects* Across Tumor Types and Dose Levels (2-20 mg/kg)

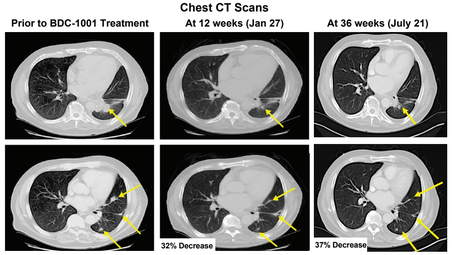
- Disease control rate 33% (13/40; 95% CI 18.6%, 49.1%) for 2-20 mg/kg cohorts

Tumor Response	Site of Primary Tumor	Duration of Disease Control (PR or SD) in Wks	Cohort
Partial response (>36 weeks)	Colorectal	36[§]	5 mg/kg q3w
Long-term stable disease (>12 weeks)	Endometrial	24	2 mg/kg q3w
	Cervix	23+	5 mg/kg q3w
	Breast	15+	8 mg/kg q3w
	Melanoma	13+	8 mg/kg q3w
	Colorectal	19+	8 mg/kg q2w
	Colorectal	13+	8 mg/kg q2w
Stable disease at week 6 scan	Gastro-esophageal	10+	12 mg/kg q3w
	Ovarian	6	20 mg/kg q3w
	Colorectal	6	2 mg/kg q3w
	Colorectal	6	5 mg/kg q3w
	Bile duct	6	8 mg/kg q3w
	Gastro-esophageal	7+	8 mg/kg q3w

*Defined as subjects with baseline and at least one post baseline tumor scan available as of the data cutoff date
[§]Subject continued with PR at 52 weeks without any subsequent therapies
+Denotes subjects are still on treatment Data cut 6OCT2021

Subject with Metastatic CRC Confirmed PR at 36 Weeks, with 37% Reduction in Sum of Longest Diameter of Target Lesions, and Maintained Through 52 Weeks

Chest CT Scans



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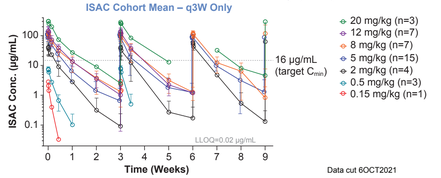
66-Year-Old Male with Metastatic Adenocarcinoma of the Colon

- Tumor HER2+ (IHC3+, amplified; MSS, KRAS wt)
- Previous treatments include chemotherapy regimens +/- bevacizumab, anti-PD-1 and anti-LAG3 combination therapy
- BDC-1001 discontinued after 4 doses due to asymptomatic grade 3 decrease in LVEF, which has improved with follow up
  - Persistent PR while no anti-cancer therapy since Jan 2021

BDC-1001 PK and Anti-drug Antibody (ADA) Results

ISAC Cohort Mean – q3W Only



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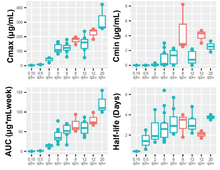
- Starting from 5 mg/kg, PK reached linearity, ie, overcomes target mediated drug disposition
- ADA results: 53 subjects have been evaluated for the presence of antibodies to BDC-1001, of which 2 (3.8%) were found to have pre-existing antibodies reactive to BDC-1001, and none developed antibodies to BDC-1001 after treatment was initiated

BDC-1001 PK Parameters Show Increase with Ascending Dose Levels

PK Parameters vs Dose (mg/kg)



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Summary of PK Data

- C_{max} increases proportionally with dose
- Observed exposure levels to date are lower than those predicted based on NHP (non-human primate) modeling data; BDC-1001 does not follow the presumed allometric scaling regarding clearance
- C_{min} levels seen in clinical PK data to date are lower than levels for optimal efficacy indicated by preclinical studies (C_{min} of approximately 16 µg/ml)[1,3]
- Clinical PK modeling suggests that higher sustained trough levels of >16 µg/mL can be achieved in humans

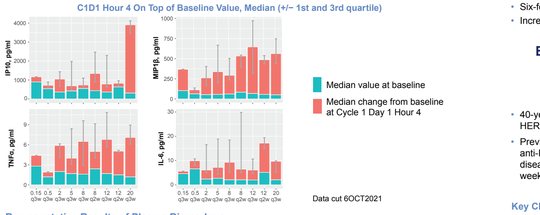
Updated Modeling of BDC-1001 PK Predicts Higher Exposure and C_{min} with More Frequent Dosing

	Median AUCs over 3 weeks (µg*day/mL)[4]	CL (mL/day/kg)[5,6]	Median $C_{max,SS}$ (µg/mL)[4]	Median $C_{min,SS}$ (µg/mL)[4]	Median Half Life (days)[5,6]
Trastuzumab (8 then 6 mg/kg q3w)	1600	3.8	178	29	25-30
BDC-1001 @ 20 mg/kg q3w	828	25	335	1.4	3
BDC-1001 @ 20 mg/kg q2w	1242	25	362	7.0	3
BDC-1001 @ 8 mg/kg q1w	1010	25	151	14.6	3
BDC-1001 @ 12 mg/kg q1w	1510	25	227	21.9	3
BDC-1001 @ 20 mg/kg q1w	2520	25	379	36.6	3

SS, steady state Data cut 6OCT2021

BDC-1001 Phase 1/2 Study Plasma Cytokines/Chemokines: Increases Observed from Baseline by Dose Cohort

C1D1 Hour 4 On Top of Baseline Value, Median (+/− 1st and 3rd quartile)



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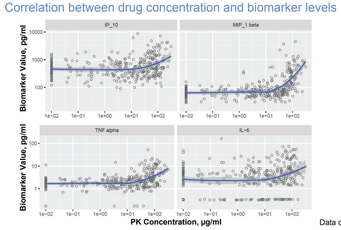
Representative Results of Plasma Biomarkers

Observed increases in multiple biomarkers consistent with mechanism of action and peaked at four hours after infusion initiation

- Myeloid cell activation signals: IP10, MIP1β show increase over baseline with highest levels noted at 20 mg/kg doses (median values: IP10=3913 pg/ml, MIP1β=647 pg/ml)
- TLR7/8 activation signals: TNFα shows increase with dose and highest levels with 20 mg/kg dose levels (median value of 7 pg/ml)
- Observed increase in IL-6, a marker of inflammatory response, at levels well below those seen in CRS (ie, <80 pg/ml)

Time-matched PK Concentration vs Plasma Biomarker Levels

Correlation between drug concentration and biomarker levels



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- Increasing plasma cytokine/chemokine levels were observed at higher drug concentration levels and have not reached a plateau

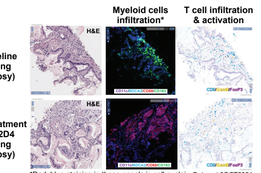
BDC-1001 Induces Changes in the Tumor Microenvironment Consistent with MOA as Seen in Paired Tissue Biopsies from Ongoing Clinical Trial

- Representative tissue biomarkers investigated with IHC:
  - Myeloid cell infiltration: CD11c, CD68, BDCA-2 (pDC), CD163 (M2s)
  - T cell infiltration and activation: CD8, Granzyme B
  - Overall immune infiltration: Stromal TILs
  - Baseline samples at screening, on-treatment biopsy at C2D4 (q3w dosing), C3D4 (q2w dosing), N=22 paired samples to date
  - Twelve paired biopsies across dose levels have been analyzed for all markers, analyses of additional samples are ongoing
  - Two representative paired biopsies are shown in the panels below
- Following BDC-1001 administration, percent of tumor CD11c and CD68 cells trend higher in some samples suggesting that BDC-1001 may be inducing changes in the tumor cellular microenvironment
- Results, whilst exploratory and based on a small number of samples, support further collection of serial biopsies to confirm the observed trends

Evidence of Activated Tumor Immunity in Paired Tissue Biopsies Example 1

Clinical trial subject with cervical cancer on BDC-1001 5 mg/kg q3w

- 29-year-old female with recurrent metastatic endocervical cancer, HER2 amplified, MSS, PD-L1 negative
- Previously treated with surgical resection as well as multiple systemic regimens including cisplatin, carboplatin, paclitaxel, bevacizumab, ZW49
- On BDC-1001 5 mg/kg q3w with stable disease for 23+ weeks and ongoing



*Dark blue staining in these panels is cell nuclei Data cut 6OCT2021

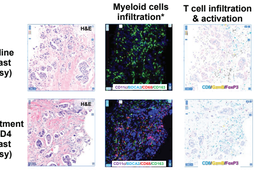
Key Changes:

- ~Four-fold increase in classic dendritic cells (cDC, CD11c+) and two-fold increase in plasmacytoid dendritic cells (pDC, BDCA2+) infiltration
- Six-fold increase in M1 (CD68+CD163-) and slight decrease in M2 (CD163+) macrophage infiltration
- Increase in dendritic cell (DC) infiltration and M1/M2 ratio on BDC-1001 treatment (vs baseline)

Evidence of Activated Tumor Immunity in Paired Tissue Biopsies Example 2

Clinical trial subject with breast cancer on BDC-1001 8 mg/kg q3w

- 40-year-old female with metastatic HER2+ (IHC3+) breast cancer
- Previously treated with multiple anti-HER2 therapies with stable disease on BDC-1001 as of week 12 scan and ongoing



*Dark blue staining in these panels is cell nuclei Data cut 6OCT2021

Key Changes:

- Four-fold increase in cDC (CD11c+) infiltration
- Seven-fold increase in M1 (CD68+CD163-) and decrease in M2 (CD163+) macrophage infiltration
- Two-fold increase in CD8+ T cell infiltration and activation on BDC-1001 treatment (vs baseline)
- Observations suggest an overall increase in DC and T cell infiltration, increase in M1/M2 ratio

CONCLUSIONS AND NEXT STEPS

Favorable Safety Profile

- The novel ISAC BDC-1001 has favorable safety and tolerability to date without DLTs at dose levels up to 20 mg/kg q3w and no indication of cytokine release syndrome (CRS)
- MTD has not been reached; dose escalation enrollment continues

PK: Target Serum Exposure Not Yet Reached

- Modeling predicts that weekly dosing may achieve target plasma concentrations

PD: Plasma and Tumor Biomarker Changes Seen Consistent with BDC-1001 Proposed Mechanism of Action

Early Signs of Clinical Disease Control

- Noted in this ongoing dose escalation trial despite still being below target exposure level
- Early signs of disease control in 13/40 evaluable subjects across multiple tumor types
  - One durable partial response and 6 durable stable diseases (>12 weeks)

Increasing Exposure is Warranted Based on Preclinical and Clinical Data

- The safety, PK, and PD findings to date support continued optimization of dose and schedule and the initiation of combination therapy with nivolumab (PD-1 inhibitor)
  - BDC-1001's novel mechanism of action provides opportunity to combine with checkpoint inhibitor in order to harness two independent mechanisms of action