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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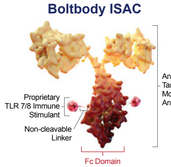
BACKGROUND

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]

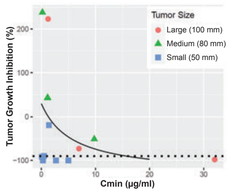
Robust single agent anti-tumor activity and elimination of established tumors in preclinical models demonstrating:

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

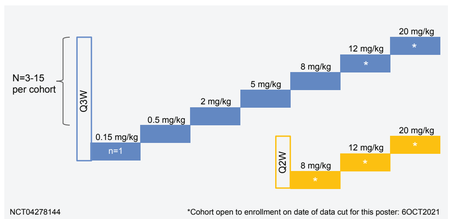
BDC-1001 Harnesses a Targeted Immuno-Oncology Approach to Stimulate and Bridge the Innate and Adaptive Immune Systems

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_{max} 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]



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*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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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

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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

TEAEs, treatment emergent adverse events

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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

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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

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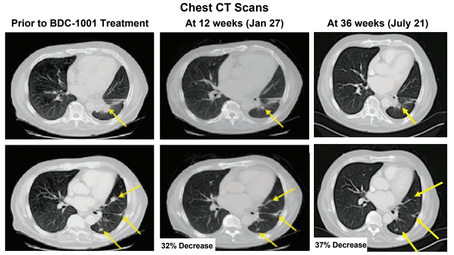
Subject with Metastatic CRC Confirmed PR at 36 Weeks, with 37% Reduction in Sum of Longest Diameter of Target Lesions, and Maintained Through 52 Weeks

Chest CT Scans



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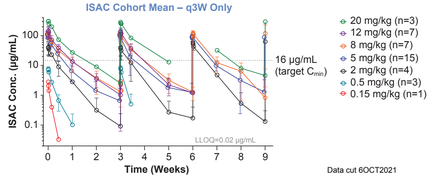
66-Year-Old Male with Metastatic Adenocarcinoma of the Colon

- 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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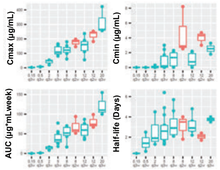
- Starting from 5 mg/kg, PK reached linearity, ie, overcomes target mediated drug disposition
- ADA results: 53 subjects have been evaluated for the presence of antibodies to BDC-1001, of which 2 (3.8%) were found to have pre-existing antibodies reactive to BDC-1001, and none developed antibodies to 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)[3,4]	Median $C_{max,SS}$ (µg/mL)[4]	Median $C_{min,SS}$ (µg/mL)[4]	Median Half Life (days)[3,4]
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

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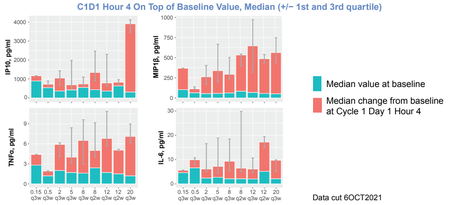
BDC-1001 Phase 1/2 Study Plasma Cytokines/Chemokines: Increases Observed from Baseline by Dose Cohort

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



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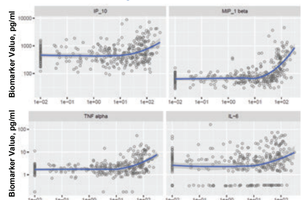
Representative Results of Plasma Biomarkers

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

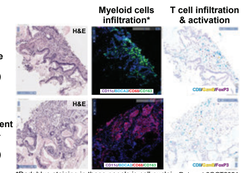
BDC-1001 Induces Changes in the Tumor Microenvironment Consistent with MOA as Seen in Paired Tissue Biopsies from Ongoing Clinical Trial

- 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

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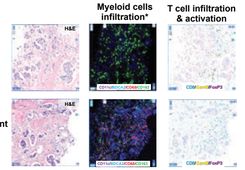
Key Changes:

- ~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

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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