A Phase 1/2 Study of a First-in-Human Immune-Stimulating Antibody Conjugate (ISAC) BDC-1001 in Patients with Advanced HER2-Expressing Solid Tumors (NCT04278144)

ABSTRACT 2538

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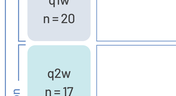
INTRODUCTION

Novel, First-in-Class Boltbody™ Immune-Stimulating Antibody Conjugate (ISAC)

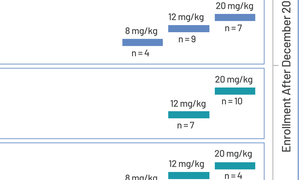
Molecular Structure

- BDC-1001 consists of
  - Trastuzumab biosimilar
  - Payload: TLR7/8 agonist
  - Linker: non-cleavable
- BDC-1001 linker-payload is cell membrane-impermeable



Proposed Mechanism of Action (MOA)

- Intravenous administration
- Local activation of the innate immune system
- Generates a durable tumor-targeted adaptive immune response



Ackerman SE, et al. *Nature Cancer*. 2021;2(1):18-33.

METHODS

Single Agent and Combination with Nivolumab

Key Eligibility

- HER2-expressing solid tumors:
  - HER2 IHC3+ or gene amplified by ISH or NGS (HER2+)
  - HER2 IHC2+ and no gene amplification (HER2-low)
- Prior anti-HER2 and/or checkpoint inhibitor therapy allowed

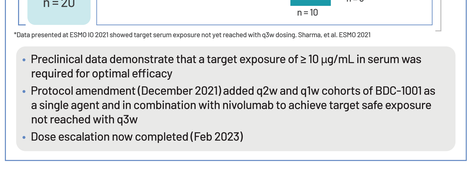
Primary Objectives

- Safety and tolerability; recommended phase 2 dose (RP2D) selection

Exploratory Objectives

- Pharmacokinetics, preliminary anti-tumor activity, plasma and tissue biomarkers to explore proof of mechanism

Dose-escalation Schema



*Data presented at ESMO IO 2021 showed target serum exposure not yet reached with q3w dosing. Sharma, et al. ESMO 2021

- Preclinical data demonstrate that a target exposure of ≥ 10 µg/mL in serum was required for optimal efficacy
- Protocol amendment (December 2021) added q2w and q1w cohorts of BDC-1001 as a single agent and in combination with nivolumab to achieve target safe exposure not reached with q3w
- Dose escalation now completed (Feb 2023)

RESULTS

Demographics and Baseline Characteristics

Heterogenous and Heavily Pretreated Patient Population with 16 Different Tumor Types
Majority of Patients Had HER2+ Tumors and Prior Anti-HER2 Therapy

		BDC-1001 Monotherapy				BDC-1001 + Nivolumab			All Patients
		q3w n = 52	q2w n = 22	q1w n = 20	Total n = 94	q2w n = 17	q1w n = 20	Total n = 37	Total n = 131
Median age, years (range)		64.0 (30, 84)	62.5 (42, 80)	63.0 (33, 85)	64.0 (30, 85)	65.0 (34, 71)	55.0 (31, 81)	57.0 (31, 81)	62.0 (30, 85)
Sex, n (%):	Female	33 (63.5)	12 (54.5)	11 (55.0)	56 (59.6)	13 (76.5)	14 (70.0)	27 (73.0)	83 (63.4)
	Male	19 (36.5)	10 (45.5)	9 (45.0)	38 (40.4)	4 (23.5)	6 (30.0)	10 (27.0)	48 (36.6)
ECOG, n (%):	0	16 (30.8)	5 (22.7)	8 (40.0)	29 (30.9)	7 (41.2)	10 (50.0)	17 (45.9)	46 (35.1)
	1	36 (69.2)	17 (77.3)	12 (60.0)	65 (69.1)	10 (58.8)	10 (50.0)	20 (54.1)	85 (64.9)
Prior lines of systemic treatment, median (range)		4 (0, 12)	3 (1, 11)	4 (1, 9)	4 (0, 12)	5 (1, 10)	5 (2, 13)	5 (1, 13)	4 (0, 13)
Prior anti-HER2 therapy, n (%)		43 (82.7)	8 (36.4)	11 (55.0)	62 (66.0)	12 (70.6)	16 (80.0)	28 (75.7)	90 (68.7)
Prior immune therapy, n (%)		16 (30.8)	5 (22.7)	8 (40.0)	29 (30.9)	4 (23.5)	5 (25.0)	9 (24.3)	38 (29.0)
HER2 categories from screening, n (%): HER2+ (IHC3+ or gene amplification) HER2 low (IHC2+ and no gene amplification)		51 (98.1) 1 (1.9)	18 (81.8) 4 (18.2)	16 (80.0) 4 (20.0)	85 (90.4) 9 (9.6)	15 (88.2) 2 (11.8)	18 (90.0) 2 (10.0)	33 (89.2) 4 (10.8)	118 (90.1) 13 (9.9)
Tumor types, n (%):	Colorectal	10 (19.2)	10 (45.5)	4 (20.0)	24 (25.5)	3 (17.6)	7 (35.0)	10 (27.0)	34 (26.0)
	Gastroesophageal	16 (30.8)	4 (18.2)	4 (20.0)	24 (25.5)	2 (11.8)	2 (10.0)	4 (10.8)	28 (21.4)
	Breast	9 (17.3)	1 (4.5)	5 (25.0)	15 (16.0)	2 (11.8)	8 (40.0)	10 (27.0)	25 (19.1)
	Endometrial	6 (11.5)	0 (0.0)	1 (5.0)	7 (7.4)	2 (11.8)	1 (5.0)	3 (8.1)	10 (7.6)
	Others*	11 (21.2)	7 (31.8)	6 (30.0)	24 (25.5)	8 (47.0)	2 (10.0)	10 (27.0)	34 (26.0)

*Other tumor types include (monotherapy and combination combined): n=6 ovary, n=5 salivary gland, n=4 cervix, n=4 lung, n=4 pancreatic, n=2 biliary tract, n=2 skin, n=2 small intestine, and one each of head and neck, intestinal ampulla, liver, prostate, and urinary bladder.

Safety

BDC-1001 was Well Tolerated Up to 20 mg/kg q1w Monotherapy and in Combination with Nivolumab

- BDC-1001 has a wide therapeutic window, up to 20 mg/kg q1w with maximum-tolerated dose (MTD) not reached
  - One DLT of supraventricular tachycardia (grade 3) at 8 mg/kg BDC-1001 q1w in combination with nivolumab
  - One grade 4 and no grade 5 drug-related AEs
- Most frequent (29.0%) drug-related AEs were low grade (grade 1 and grade 2) infusion-related reactions (IRRs)
- One drug-related cytokine release syndrome (grade 1) at 12 mg/kg BDC-1001 q1w
- Left ventricular ejection fraction (LVEF) decrease
  - 6 patients with ejection fraction decrease (grade 2 [n=4], grade 3 [n=2])
    - 4 received BDC-1001 q1w
      - Monotherapy: 1 patient at 12 mg/kg, 2 at 20 mg/kg; combination: 1 at 8 mg/kg + nivolumab
    - 2 received BDC-1001 q3w or q2w
      - Monotherapy: 1 patient at 5 mg/kg q3w and 1 at 8 mg/kg q2w
- 2 patients discontinued therapy due to LVEF decrease
  - 5 mg/kg BDC-1001 q3w, 8 mg/kg BDC-1001 q2w

Safety graded by CTCAE v5; AE, adverse event; DLT, dose limiting toxicity

Details of Safety Profile of BDC-1001 Monotherapy and in Combination with Nivolumab

Summary of Treatment-related TEAEs

	BDC-1001 Monotherapy				BDC-1001 + Nivolumab			
	Treatment-related TEAEs				BDC-1001 Treatment-related TEAEs			BDC-1001 + Nivolumab Treatment-related TEAEs
	q3w n = 52	q2w n = 22	q1w n = 20	Total n = 94	q2w n = 17	q1w n = 20	Total n = 37	q1w n = 20	Total n = 37
All grades (%)	30 (57.7)	11 (50.0)	17 (85.0)	58 (61.7)	11 (64.7)	14 (70.0)	25 (67.6)	5 (25.4)	12 (60.0)	17 (45.9)
Grade ≥ 3 (%)	5 (9.6)	1 (4.5)	1 (5.0)	7 (7.4)	0	2 (10.0)	2 (5.4)	0	1 (5.0)	1 (2.7)
Serious adverse events (%)	3 (5.8)	0	0	3 (3.2)	1 (5.9)	1 (5.0)	2 (5.4)	0	1 (5.0)	1 (2.7)
Leading to treatment discontinuation	3 (5.8)	1 (4.5)	0	4 (4.3)	0	1 (5.0)	1 (2.7)	0	1 (5.0)	1 (2.7)
Leading to treatment interruption	5 (9.6)	2 (9.1)	2 (10.0)	9 (9.6)	1 (5.9)	1 (5.0)	2 (5.4)	0	1 (5.0)	1 (2.7)
Leading to death	0	0	0	0	0	0	0	0	0	0

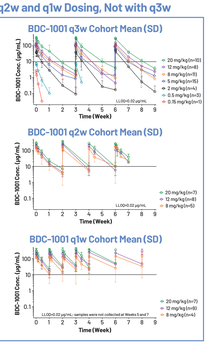
Safety graded by CTCAE v5; TEAE, treatment-emergent adverse event
Definition of treatment-related TEAEs = an AE considered as related to with unknown/missing relationship to study drug

Data cut-off: March 24, 2023

Pharmacokinetics of BDC-1001

Serum Target Exposure > 10 µg/mL Achieved with q2w and q1w Dosing, Not with q3w

- Population mean clearance 1.6 L/day and terminal $T_{1/2}$ of 4.3 days
  - Faster clearance at dose levels lower than 5 mg/kg exhibits TMDD (target-mediated drug disposition)
- Two-fold accumulation observed in median C_{min} with q2w and q1w dosing
  - At 20 mg/kg q2w, C_{min} increase from first dose to steady state: ~ 12 to 29 µg/mL
  - At 20 mg/kg q1w, C_{min} increase from first dose to steady state: ~ 34 to 68 µg/mL
  - Virtually no accumulation was observed with q3w dosing
- Presence of nivolumab did not impact PK of BDC-1001
- Low incidence of BDC-1001 ADA formation (4.2%) with no impact on PK, safety, or efficacy



ADA, anti-drug antibody; SD, standard deviation
Note: q1w samples were not collected at Weeks 5 and 7

Efficacy

Most Clinically Meaningful Efficacy Observed at 20 mg/kg q2w (RP2D)

- Six patients had PRs
  - 3 colorectal, 1 ovarian, 1 biliary, 1 salivary
  - 4 at 20 mg/kg q2w (2 mono, 2 combo)
    - 3 were MSS (mono or combo) and 1 was MSI (mono)
  - 1 at 12 mg/kg q1w (combo) in MSS tumor
  - 1 at 5 mg/kg q3w (mono) in MSS tumor
- Twelve patients had SD ≥ 24 weeks
  - 4 colorectal, 1 melanoma, 1 endometrial, 2 gastric, 1 salivary gland, 2 cervical, 1 ovarian
  - 3 of 12 at 20 mg/kg q2w with colorectal, salivary gland, and ovarian cancer
- Tumor shrinkage observed in a variety of tumor types including biliary, breast, cervical, colorectal, endometrial, gastric, lung, salivary, skin (melanoma), and ovarian cancer

Clinical Efficacy in All Patients with HER2+ Tumors Treated with 20 mg/kg q2w (RP2D)

BDC-1001 Monotherapy or in Combination with Nivolumab

		BDC-1001 20 mg/kg + (n = 7) 4 Tumor Types	BDC-1001 20 mg/kg + Nivolumab (n = 8)** 5 Tumor Types	All (n = 15) 7 Tumor Types
Response assessment, n (%):	PR	2* (29%)	2 (25%)	4 (27%)
	SD	3 (43%)	4 (50%)	7 (47%)
	PD	2 (29%)	1 (13%)	3 (20%)
	Not evaluable	0	1 (13%)	1 (7%)
Overall response rate, n (%)		2 (29%)	2 (25%)	4 (27%)
Disease control rate ≥ 6 weeks, n (%)		5 (71%)	6 (75%)	11 (73%)
Disease control rate ≥ 24 weeks, n (%)		3 (43%)	4 (50%)	7 (47%)
Tumor shrinkage, n (%)		4 (57%)	5 (63%)	9 (60%)

*One PR confirmed post March 24, 2023 data cutoff; **One non-evaluable patient included
4 HER2-low tumors (2 each from BDC-1001 monotherapy and in combination) are excluded.

Data cut-off: March 24, 2023

Clinical Efficacy in All Patients with HER2+ Tumors Was Greater with 20 mg/kg Compared to 12 mg/kg q2w

Data fairly comparable for BDC-1001 Monotherapy or in Combination with Nivolumab

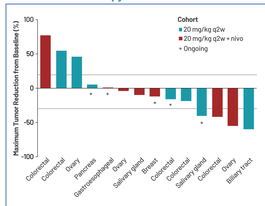
		BDC-1001		BDC-1001 + Nivolumab	
		12 mg/kg (n = 7) 5 Tumor Types	20 mg/kg (n = 7) 4 Tumor Types	BDC-1001 12 mg/kg (n = 7) 6 Tumor Types	BDC-1001 20 mg/kg (n = 8)** 5 Tumor Types
Response assessment, n (%):	PR	0	2* (29%)	0	2 (25%)
	SD	1 (14%)	3 (43%)	2 (29%)	4 (50%)
	PD	4 (57%)	2 (29%)	4 (57%)	1 (13%)
	Not evaluable	2 (29%)	0	1 (14%)	1 (13%)
Overall response rate, n (%)		0	2 (29%)	0	2 (25%)
Disease control rate ≥ 6 weeks, n (%)		1 (14%)	5 (71%)	2 (29%)	6 (75%)
Disease control rate ≥ 24 weeks, n (%)		1 (14%)	3 (43%)	0	4 (50%)
Tumor shrinkage, n (%)		1 (14%)	4 (57%)	2 (29%)	5 (63%)

*One PR confirmed post March 24, 2023 data cutoff; **One non-evaluable patient included
5 HER2-low tumors are excluded (1 at 12 mg/kg and 4 at 20 mg/kg)

Data cut-off: March 24, 2023

Meaningful Anti-tumor Activity in Evaluable Heterogeneous HER2+ Tumor Population at 20 mg/kg q2w (RP2D)

BDC-1001 Monotherapy and Combination with Nivolumab



HER2+ either assessed by protein or gene analysis determined at enrollment
RECIST v1.1 assessment criteria

Monotherapy (n=7)

- 29% achieved PR
- 43% had disease control ≥24w
- 57% achieved tumor shrinkage
  - Tumor types: colorectal, salivary gland, and biliary tract

Combination with Nivolumab (n=7)

- 29% achieved PR
- 57% had disease control ≥24w
- 71% achieved tumor shrinkage
  - Tumor types: breast, colorectal, ovary, and salivary gland

Data cut-off: March 24, 2023

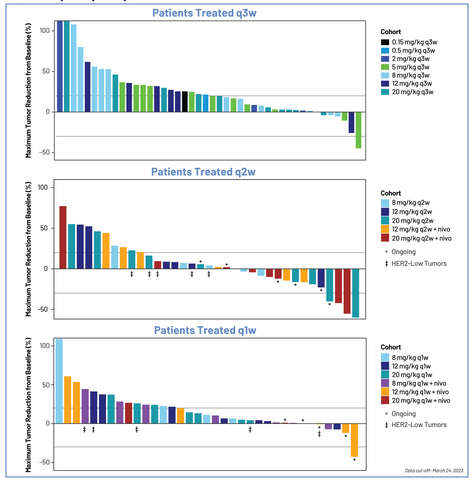
Clinical Activity: 6 PRs and 12 Long-lasting SDs (≥ 24 Weeks) Observed in 8 Tumor Types, Particularly in 20 mg/kg q2w Dose Cohorts

Best Response	Site of Primary Tumor, HER2 Status	Duration of Disease Control (PR or SD) in Wks	Prior Lines of Therapy	Prior Anti-HER2 Therapy	Prior Checkpoint Inhibitor	MSS/ MSI	Dose Cohort
Partial Response	Colorectal, HER2+	84	4	No	No	MSS	5 mg/kg q3w
	Biliary tract cancer, HER2+	**36**	**2**	**No**	**No**	**MSS**	**20 mg/kg q2w**
	Salivary gland, HER2+	**48+**	**2**	**No**	**No**	**MSI**	**20 mg/kg q2w**
	Ovarian cancer, HER2+	**24**	**12**	**Yes**	**No**	**MSS**	**20 mg/kg q2w + nivolumab**
	Colorectal, HER2+	**48**	**5**	**Yes**	**No**	**MSS**	**20 mg/kg q2w + nivolumab**
	Colorectal, HER2+	12+	5	Yes	No	MSS	12 mg/kg q1w + nivolumab
Durable Stable Disease	Endometrial cancer, HER2+	36	3	Yes	No	No data	2 mg q3w
	Cervical cancer, HER2+	60	3	Yes	No	No data	5 mg/kg q3w
	Melanoma, HER2+	24	1	No	Yes	MSS	8 mg/kg q3w
	Colorectal, HER2+	36	11	Yes	No	MSS	20 mg/kg q3w
	Colorectal, HER2+	24+	2	No	No	MSS	8 mg/kg q2w
	Gastric cancer, HER2+	48+	2	Yes	No	No data	12 mg/kg q2w
	Colorectal, HER2+	**60+**	**2**	**No**	**No**	**MSI**	**20 mg/kg q2w**
	Salivary gland cancer, HER2+	**24**	**8**	**Yes**	**Yes**	**MSS**	**20 mg/kg q2w + nivolumab**
	Ovarian cancer, HER2+	**36**	**4**	**Yes**	**No**	**MSI**	**20 mg/kg q2w + nivolumab**
	Colorectal, HER2+	36	1	No	No	MSS	8 mg/kg q1w
	Cervical cancer, HER2+	24	5	Yes	Yes	MSS	12 mg/kg q1w
	Gastric cancer, HER2+	24	2	Yes	No	No data	12 mg/kg q1w

Bold: patients treated at RP2D

Data cut-off: March 24, 2023

Waterfall Plots for All Patients (HER2+ and HER2-Low Tumors) Treated q3w, q2w, q1w



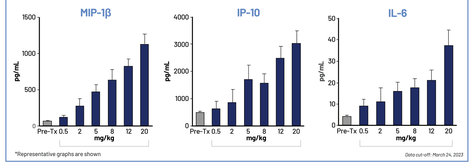
Data cut-off: March 24, 2023

Peak Increase in Plasma Myeloid Activation Markers at 4 Hours

Confirms MOA and Safety Profile

- Plasma samples for cytokines and chemokines obtained from all patients
- Dose-dependent peak increases in Cycle 1 were observed in multiple cytokines and chemokines*
  - Similar responses observed for MIP-1α, IFNγ, TNFα and eotaxin

Average IL-6 levels were low at all doses (< 50 pg/mL)

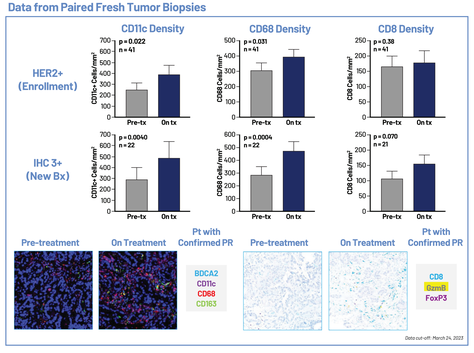


*Representative graphs are shown

Data cut-off: March 24, 2023

BDC-1001 Drives Myeloid and T Cell Infiltration in HER2+ Tumors

Data from Paired Fresh Tumor Biopsies

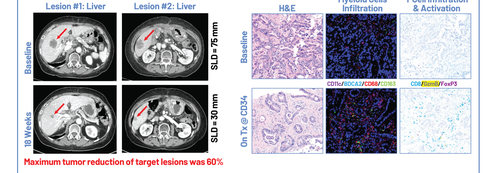


Data cut-off: March 24, 2023

CT Imaging and Biomarker Data in a Patient with PR

Patient with HER2+ by NGS, MSS biliary tract carcinoma
- No prior anti-HER2 or immunotherapy

Fresh matched (pre- and on-Tx) biomarker data



Maximum tumor reduction of target lesions was 60%

Key observations:

- cDC (CD11c) increased by 16% and pDC (BDCA2) decreased by 70%
- 62% increase in M1 (CD68+CD163-) macrophage, 161% increase in monocyte-derived DCs (CD11c+CD163+), and 16% increase in cDC (CD11c+CD163-)
- 500% increase in CD8+ T cell infiltration and 400% increase in CD8+Granzyme B+ T cell activation

CT= Computerized tomography; SLD=Sum of Longest Diameter

Data cut-off: March 24, 2023

CONCLUSIONS

Results demonstrate encouraging evidence of safety, anti-tumor efficacy, and biomarker changes consistent with MoA of ISAC technology

- BDC-1001 was well-tolerated at all doses and dosing frequencies up to 20 mg/kg q1w
  - In a heterogeneous (16 different tumor types in 18 cohorts) and heavily pretreated (median 4 prior lines of systemic treatment) patient population
- Target exposure established in preclinical models achieved at higher dose and increased frequency of administration
  - C_{min} above 10 µg/mL achieved at q2w and q1w schedules
  - Improved efficacy observed with q2w compared to q3w or q1w
- Clinical activity of BDC-1001 observed alone and in combination with nivolumab, particularly in the 20 mg/kg q2w cohorts
- Pharmacodynamic responses in both plasma and tissue consistent with ISAC MOA
  - Responses of myeloid and T cell activation and infiltration not anticipated with trastuzumab treatment alone
- Selection of 20 mg/kg q2w as RP2D based on the totality of safety, efficacy, PK, and biomarkers
- Results support Phase 2 development of BDC-1001 as a single agent and in combination strategies

FUTURE DIRECTION

Two multi-arm Phase 2 studies in four HER2+ solid tumor types

- Phase 2 portion of the BDC-1001 Phase 1/2 Trial (BBI-20201001) will enroll patients with HER2+ colorectal, gastroesophageal, and endometrial cancers evaluating BDC-1001 as single agent and in combination with nivolumab*
- A new Phase 2 trial (BBI-20231001) will evaluate BDC-1001 as single agent and in combination with pertuzumab** in patients with HER2+ metastatic breast cancer previously treated with trastuzumab deruxtecan
- Tumor selection based on unmet patient need, evolving therapeutic landscape, accrued clinical data, regulatory path, and strategic collaborations
- Studies to expand globally in 2023 to include Spain, Italy, and France, in addition to the U.S. and South Korea
- Continue Phase 1 patient follow-up and conduct gene analysis of tumor samples

*Provided by BMS; **provided by Roche

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- This presentation is the intellectual property of Bolt Biotherapeutics, Inc. and can be found on boltbio.com