# 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)

<sup>1</sup>Memorial Sloan Kettering Cancer Center, New York, NY, USA; <sup>2</sup>Stanford University Bundang Hospital, Seongnam, South Korea; <sup>4</sup>START-Midwest, Grand Rapids, MI, USA; <sup>-1</sup>Memorial Sloan Kettering Cancer Center, New York, NY, USA; <sup>2</sup>Stanford, CA, USA; <sup>3</sup>Seoul National University Bundang Hospital, Seongnam, South Korea; <sup>4</sup>START-Midwest, Grand Rapids, MI, USA; <sup>-1</sup>Memorial Sloan Kettering Cancer Center, New York, NY, USA; <sup>4</sup>Stanford, CA, USA; <sup>4</sup>Stanford, C <sup>5</sup>Samsung Medical Center, Seoul, South Korea; <sup>6</sup>Virginia, Fairfax, VA, USA; <sup>7</sup>Dana-Farber Cancer Institute, Boston, MA, USA; <sup>8</sup>Asan Medical Center, Seoul, South Korea; <sup>9</sup>START, San Antonio, TX, USA; <sup>1</sup> <sup>10</sup>Stephenson Cancer Center, Oklahoma City, OK, USA; <sup>12</sup>Bolt Biotherapeutics, Redwood City, CA, USA; <sup>13</sup>The University of Texas MD Anderson Cancer Center, Houston, TX, USA

## INTRODUCTION

## Novel, First-in-Class Boltbody<sup>™</sup> 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)** 



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**

not reached with q3w

Dose escalation now completed (Feb 2023)

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

#### **Dose-escalation Schema**



	q3w n=52	qi n =
Median age, years (range)	64.0	6
	(30, 84)	(42
Sex, n(%): Female	33(63.5)	12 (
Male	19(36.5)	10 (4
ECOG, n (%): 0	16(30.8)	5(2
1	36(69.2)	17 (
Prior lines of systemic treatment,	4(0,12)	3(
median (range)		
Prior anti-HER2 therapy, n(%)	43 (82.7)	8(3
Prior immune therapy, n (%)	16(30.8)	5(2
HER2 categories from screening, n (%):		
HER2+(IHC3+ or gene amplification)	51(98.1)	18 (
HER2 low (IHC2+ and no gene amplification)	1(1.9)	4(1
Tumor types, n (%): Colorectal	10 (19.2)	10 (4
Gastroesophageal	16(30.8)	<b>4(</b> 1
Breast	9(17.3)	1(4
Endometrial	6(11.5)	0(
Others*	11(21.2)	7(3
*Other tumor types include (monotherapy and combination c and one each of head and neck, intestinal ampulla, liver, prost	ombined): n=6 c ate, and urinary	ovary, n / bladde

#### Safety

with Nivolumab

- dose(MTD) not reached
- One DLT of supraventricular tachycardia (grade 3) at 8 mg/kg BDC-1001 q1w in combination with nivolumab

- 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

All grades (%)
Grade≥3(%)
Serious adverse events (%
Leading to treatment disc
Leading to treatment inter
Leading to death
Safety graded by CTCAE v5; TEAE, t Definition of treatment-related TEA

# Pharmacokinetics of BDC-1001

- 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<sub>min</sub> with q2w and q1w dosing At 20 mg/kg g2w,  $C_{min}$  increase from first dose to steady state: ~ 12 to 29 µg/mL
- steady state: ~ 34 to 68 µg/mL Virtually no accumulation was observed with
- q3w dosing
- BDC-1001

ADA, anti-drug antibody; SD, standard deviation Note: g1w samples were not collected at Weeks 5 and 7

## Bob T. Li,<sup>1</sup> Mark D. Pegram,<sup>2</sup> Keun-Wook Lee,<sup>3</sup> Manish R. Sharma,<sup>4</sup> Jeeyun Lee,<sup>5</sup> Alexander Spira,<sup>6</sup> Glenn J. Hanna,<sup>7</sup> Yoon-Koo Kang,<sup>8</sup> Drew Rasco,<sup>9</sup> Kathleen Moore,<sup>10</sup> Benjamin A. Weinberg,<sup>11</sup> Michael N. Alonso,<sup>12</sup> Jason Ptacek,<sup>12</sup> Ming Yin,<sup>12</sup> Coya Tapia,<sup>12</sup> Lu Xu,<sup>12</sup> Edith A. Perez,<sup>12</sup> Ecaterina E. Dumbrava<sup>13</sup>

### **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 M	onotherapy	,	BDC-	1001 + Nivolu	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
	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)
	33(63.5)	12 (54.5)	11(55.0)	56 (59.6)	13 (76.5)	14 (70.0)	27(73.0)	83(63.4)
	19(36.5)	10(45.5)	9(45.0)	38(40.4)	4(23.5)	6(30.0) 10(E0.0)	10(27.0)	48(36.6)
	36 (69.2)	5(22.7) 17(77.3)	8(40.0) 12(60.0)	29(30.9) 65(69.1)	7 (41.2) 10 (58.8)	10 (50.0) 10 (50.0)	17 (45.9) 20 (54.1)	46(35.1) 85(64.9)
tment,	4(0,12)	3 (1, 11)	4(1,9)	4(0,12)	5(1,10)	5(2,13)	5 (1, 13)	4(0,13)
(%)	43 (82.7)	8(36.4)	11(55.0)	62(66.0)	12 (70.6)	16 (80.0)	28(75.7)	90 (68.7)
) ()	16(30.8)	5(22.7)	8(40.0)	29(30.9)	4(23.5)	5(25.0)	9(24.3)	38(29.0)
ening, n (%): olification) ene 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)
ectal	10 (19.2)	10 (45.5)	4(20.0)	24(25.5)	3 (17.6)	7(35.0)	10(27.0)	34(26.0)
oesophageal	16(30.8)	4(18.2)	4(20.0)	24(25.5)	2(11.8)	2(10.0)	4(10.8)	28(21.4)
t	9(17.3)	1(4.5)	5(25.0)	15(16.0)	2(11.8)	8(40.0)	10(27.0)	25(19.1)
netrial	6(11.5)	0(0.0)	1(5.0)	7(7.4)	2(11.8)	1(5.0)	3(8.1)	10(7.6)
×	11(21.2)	7(31.8)	6(30.0)	24(25.5)	8(47.0)	2(10.0)	10(27.0)	34(26.0)
erapy 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.								

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

BDC-1001 has a wide therapeutic window, up to 20 mg/kg q1w with maximum-tolerated

- 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)

Summary of Treatment-related TEAEs										
	BI	DC-1001 M	lonothera	ру		BDC-1001 + Nivolumab				
	Treatment-related TEAEs				Treatm	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	q2w n = 17	q1w n = 20	Total n = 37
	30 (57.7)	11(50.0)	17(85.0)	58(61.7)	11(64.7)	14(70.0)	25(67.6)	5(29.4)	12(60.0)	17(45.9)
	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)
<b>()</b>	3(5.8)	0	0	3(3.2)	1(5.9)	1(5.0)	2(5.4)	0	1(5.0)	1(2.7)
ontinuation	3(5.8)	1(4.5)	0	4(4.3)	0	1(5.0)	1(2.7)	0	1(5.0)	1(2.7)
rruption	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)
	0	0	0	0	0	0	0	0	0	0
reatment-emergent adverse event										

Es = an AE considered as related to with unknown/missing relationship to study drug Data cut-off: March 24, 2023

Serum Target Exposure > 10  $\mu$ g/mL Achieved with q2w and q1w Dosing, Not with q3w

Population mean clearance 1.6 L/day and

- At 20 mg/kg q1w,  $C_{min}$  increase from first dose to
- Presence of nivolumab did not impact PK of
- Low incidence of BDC-1001 ADA formation (4.2%) with no impact on PK, safety, or efficacy



Time (Week)

### 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  $\ge$  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
- colorectal, endometrial, gastric, lung, salivary, skin (melanoma), and ovarian cancer

#### Clinical Efficacy in <u>All</u> 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 $\geq$ 6 weeks, n(%)	5(71%)	6(75%)	11(73%)
Disease control rate $\geq$ 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 no 4 HER2-low tumors (2 each from BDC-1001 monotherapy and	n-evaluable patient included in combination) are excluded.		Data cut-off: March 24, 2023

#### Clinical Efficacy in <u>All</u> 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 $\geq$ 6 weeks, n(%)		1(14%)	5(71%)	2(29%)	6(75%)	
Disease control rate $\geq$ 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 d 5 HER2-low tumors are excluded (1 at 12 m	ata cutoff; **One non-e ng/kg and 4 at 20 mg/kg	valuable patient included J			Data cut-off: March 24, 2023	

#### Meaningful Anti-tumor Activity in <u>Evaluable</u> 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

# 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
	Colorectal, HER2+	84	4	No	Yes	MSS	5 mg/kg q3w
	Biliary tract cancer, HER2+	36	2	No	No	MSS	20 mg/kg q2w
Partial	Salivary gland, HER2+	48+	2	No	No	MSI	20 mg/kg q2w
Response	<b>Ovarian cancer, HER2+</b>	24	12	Yes	No	MSS	20 mg/kg q2w + nivolumab
Response	Colorectal, HER2+	48	5	Yes	No	MSS	20 mg/kg q2w + nivolumab
	Colorectal, HER2+	12+	5	Yes	No	MSS	12 mg/kg q1w + nivolumab
	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
Durable	Gastric cancer, HER2+	48+	2	Yes	No	No data	12 mg/kg q2w
Stable	Colorectal, HER2+	60+	2	No	No	MSI	20 mg/kg q2w
Disease	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 t	Bold: patients treated at RP2D Data cut-off: March 24, 2023						

## RESULTS

Tumor shrinkage observed in a variety of tumor types including biliary, breast, cervical,

Monotherapy (n=7)

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

### ombination 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



# **Confirms MOA and Safety Profile**





![](_page_0_Picture_116.jpeg)