

# Phase 1/2 study of novel HER2-targeting, TLR7/8 immune-stimulating antibody conjugate (ISAC) BDC-1001 as a single agent and in combination with an immune checkpoint inhibitor in patients with advanced HER2-expressing solid tumors

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Ecaterina Ileana Dumbrava<sup>1</sup>, Manish R. Sharma<sup>2</sup>, Richard D. Carvajal<sup>3</sup>, Daniel Catenacci<sup>4</sup>, Leisha A. Emens<sup>5</sup>, Shirish M. Gadgeel<sup>6</sup>, Glenn J. Hanna<sup>7</sup>, Dejan Juric<sup>8</sup>, Bob T. Li<sup>9</sup>, Kathleen Moore<sup>10</sup>, Mark D. Pegram<sup>11</sup>, Paula R. Pohlmann<sup>12</sup>, Drew Rasco<sup>13</sup>, Alexander Spira<sup>14</sup>, Antionette R. Tan<sup>15</sup>, Shelley Ackerman<sup>16</sup>, Heidi LeBlanc<sup>16</sup>, David Dornan<sup>16</sup>, Marcin Kowanetz<sup>16</sup>, Michael N. Alonso<sup>16</sup>, and Edith A. Perez<sup>16</sup>

<sup>1</sup>The University of Texas MD Anderson Cancer Center, Houston, TX; <sup>2</sup>START Midwest, Grand Rapids, MI; <sup>3</sup>Columbia University Medical Center, New York, NY; <sup>4</sup>University of Chicago, Chicago, IL; <sup>5</sup>UPMC Hillman Cancer Center, Pittsburgh, PA; <sup>6</sup>Henry Ford Cancer Institute/Henry Ford Hospital, Detroit, MI; <sup>7</sup>Dana-Farber Cancer Institute, Boston, MA; <sup>8</sup>Massachusetts General Hospital, Boston, MA; <sup>9</sup>Memorial Sloan Kettering Cancer Center, New York, NY; <sup>10</sup>Stephenson Cancer Center, Oklahoma City, OK; <sup>11</sup>Stanford University, Stanford, CA; <sup>12</sup>Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; <sup>13</sup>START, San Antonio, TX; <sup>14</sup>Virginia Cancer Specialists, Fairfax, VA; <sup>15</sup>Levine Cancer Institute, Atrium Health, Charlotte, NC;

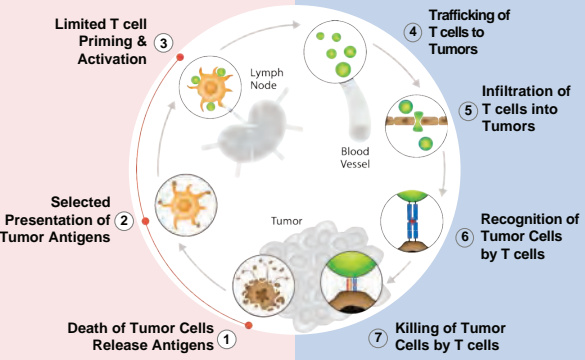
<sup>16</sup>Bolt Biotherapeutics, Redwood City, CA

## BACKGROUND

- In spite of advances made in the management of patients with human epidermal growth factor receptor 2 (HER2)-expressing or -driven solid tumors, there remains a significant unmet need for novel approaches to improve patient outcomes.
- Intratumoral delivery of antitumor antibodies and immunostimulatory adjuvants such as toll-like receptor (TLR)7/8 agonists has been shown to activate tumor resident antigen-presenting cells (APCs), driving uptake, processing, and presentation of tumor neoantigens to T cells that mediate antitumor immunity.
- BDC-1001 is delivered systemically and has demonstrated superior preclinical biology. This novel ISAC consists of an investigational biosimilar of the humanized monoclonal antibody trastuzumab chemically conjugated to a TLR7/8 agonist with a non-cleavable linker. BDC-1001 activates human myeloid APCs in addition to retaining antibody-mediated effector functions such as antibody-dependent cellular cytotoxicity/phagocytosis (ADCC/ADCP).
- Studies in trastuzumab-resistant xenograft models and syngeneic tumor models indicate that HER2-targeted ISACs elicit potent and durable immune-mediated antitumor efficacy, leading to complete tumor regression in a TLR- and Fc receptor-dependent manner.<sup>1,2</sup>
- Importantly, BDC-1001 did not induce interstitial lung disease, cytokine release syndrome, or thrombocytopenia in non-human primate studies.
- A four-part phase 1/2, first-in-human study has been initiated that evaluates BDC-1001 with or without (+/-) an immune checkpoint inhibitor targeting PD-1 in patients with HER2-expressing or HER2-amplified advanced/metastatic solid tumors.

## Traditional Immunotherapies Focus on an Adaptive Immune System

### “Traditional” dysfunctional immune response



### T cell Targeted Therapies

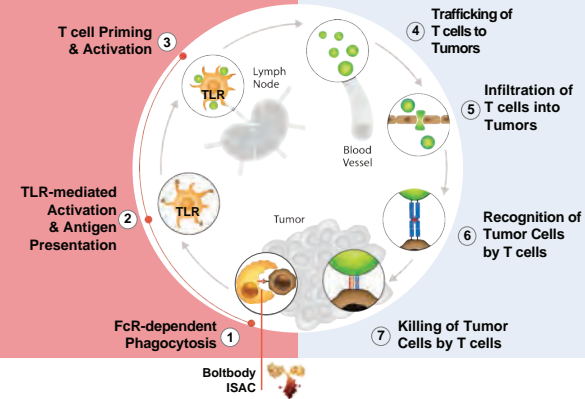
- Rely on dysfunctional/narrow immune response.
- Risk of T cell exhaustion.
- Some approaches require complex manufacturing/personalization.

### Myeloid biology contributes to productive cancer immunity cycle

- Use innate immunity to create new antitumor immune responses.
- Amplify antitumor immune response
- Convert “cold” tumors to “hot.” response to additional neoantigens.
- Expand antitumor T cell response & killing.

## Boltbody ISACs Act at Different Steps of the Cancer Immunity Cycle

### Boltbody ISACs initiate new immune response



Boltbody ISACs initiate an entirely new immune response.

### Boltbody ISACs combine:

- Precise antibody targeting.
- Activation of innate immunity.
- Triggering adaptive immune response.

All within a single therapeutic.

Boltbody ISACs enhance the antigen presentation capability of immunosuppressed APCs, driving a robust new antitumor immune response that can recognize additional neoantigens.

## OBJECTIVES

### PRIMARY OBJECTIVES

- The dose-escalation phase will define safety and tolerability and determine the recommended phase 2 dose of BDC-1001 as monotherapy and in combination with an immune checkpoint inhibitors.
- The dose-expansion portion of the trial will evaluate preliminary antitumor activity of BDC-1001 alone and in combination with an immune checkpoint inhibitor.

### SECONDARY OBJECTIVES

- Secondary objectives will evaluate pharmacokinetic (PK) parameters and pharmacodynamic (PD) biomarkers in tumor tissue and in peripheral blood associated with drug exposure.

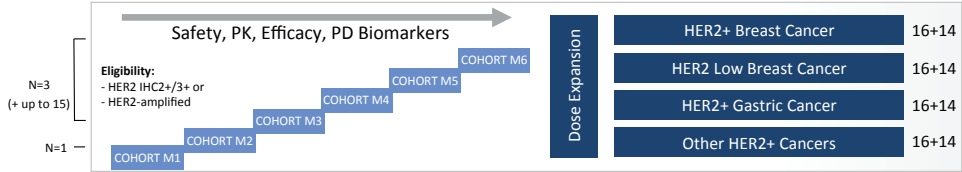
### EXPLORATORY OBJECTIVES

- Evaluate exploratory pharmacodynamic biomarkers and potential baseline biomarkers associated with biological activity.

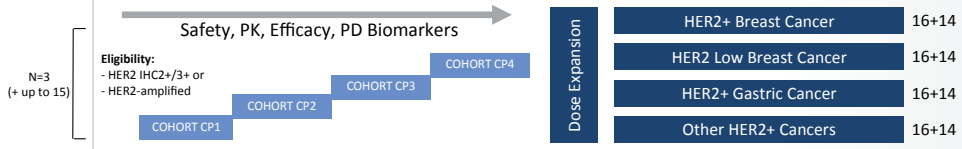
## STUDY DESIGN

- This dose-escalation and dose-expansion study is enrolling up to 390 patients with HER2-expressing advanced solid tumors.
- BDC-1001 is administered IV by syringe pump over 60 minutes (±15 minutes) every 3 weeks.

### Monotherapy - Parts 1 and 3



### Combination Therapy with Checkpoint Inhibitor - Parts 2 and 4



## ENDPOINTS

### Parts 1 and 2

- Incidence of adverse events and serious adverse events graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Incidence and nature of dose-limiting toxicities within a 3+3 design. Changes from baseline in clinical safety laboratory values and vital signs. Incidence of potential-immune related toxicities.
- The maximum tolerated dose (MTD) or a tolerated dose below MTD (if MTD is not reached).
- PK variables (eg, C<sub>max</sub>, C<sub>min</sub>, AUC<sub>0-4</sub>, AUC<sub>0-inf</sub>, CL, Vz, t<sub>1/2</sub>).
- Incidence of anti-drug antibodies (ADAs).

### Additional Endpoints for Parts 3 and 4

- Overall response rate using RECIST v1.1 and iRECIST, disease control rate of confirmed complete response, partial response, lasting 4 or more weeks following the initiation of BDC-1001, duration of response, progression-free survival, and overall survival.
- Antitumor activity in tumors with different levels of HER2 and PD-L1 expression.

## ELIGIBILITY

### HER2 Inclusion Criteria

#### Dose Escalation Cohorts for Parts 1 and 2

- HER2+ in any solid tumor with IHC3+ or IHC2+ (including HER2 low) or gene amplification.

#### Dose Expansion Cohorts for Part 3 and 4

- For HER2+ breast, gastric, or other HER2+ solid tumors IHC3+ or gene amplification.
- For HER2 low breast cancer HER2 IHC2+ and negative gene amplification.

### Exclusion Criteria

- History of treatment with a TLR7, TLR8, or a TLR7/8 agonist.
- Use of another investigational agent or anticancer therapy within 4 weeks prior to C1D1 or within 5 estimated elimination half-lives, whichever is shorter.
- Use of another anti-HER2 based therapy within 4 weeks prior to C1D1.
- History of severe hypersensitivity to any ingredient of the study drug(s), including trastuzumab.

#### Anti-PD1 Combination Therapy Exclusions

- Patient has a history of immune-mediated colitis.
- Patient has an active autoimmune disease with the exception of autoimmune endocrinopathies that are stable on hormone replacement therapy.
- Hypersensitivity to pembrolizumab or particular excipients that are used for formulation.

## BIOMARKER ASSESSMENTS

- Assess PD biomarkers to demonstrate that BDC-1001 is biologically active, and support dose selection.
  - Focus on TLR7/8 pathway, myeloid cell, and T cell activation.
    - Mandatory paired pre-/on-tx biopsies in both escalation and expansion cohorts
    - Serial blood collections for all patients.
- Evaluate potential predictive biomarkers of response to BDC-1001.
  - HER2 status and biomarkers related to immune biology.
    - Baseline (archival or freshly collected) tumor sample, and blood mandated for all patients.
- Changes in TLR7/8 pathway activation, myeloid, and T cell content, and activation status by gene expression profiling, and tissue image analysis.

## STATUS Q1

Status: Phase 1/2 Trial Initiated Q1 2020; Currently in Dose Escalation

- Enrollment in monotherapy dose-escalation phase is proceeding well.
- No unexpected adverse events have been observed to date.
- Anticipate combination dose-escalation to start Q1 2021.

### Expected Upcoming Milestones:

- Complete phase 1/2 dose escalation portion in Q1 2021.
- Initiate phase 2 dose expansions in Q1 2021.
- Phase 1/2 data anticipated to provide clinical proof of concept.

ClinicalTrials.gov (NCT04278144)

## REFERENCES

- Ackerman S, et al. TLR7/8 immune-stimulating antibody conjugates elicit robust myeloid activation leading to enhanced effector function and anti-tumor immunity in pre-clinical models. *Cancer Res.* 2019;79 [13 Suppl].
- Ackerman S, et al. HER2-targeting TLR7/8 immune-stimulating antibody conjugates elicit robust myeloid activation and anti-tumor immune responses in a TLR- and FcR- dependent manner. *J Immunother Cancer.* 2019;7:283.