Phase 1/2 study of a novel HER2 targeting TLR7/8 immune-stimulating antibody conjugate (ISAC), BDC-1001, alone and in combination with anti-PD1 antibody in patients (pts) with HER2-expressing advanced solid tumors

Abstract Number: CT218

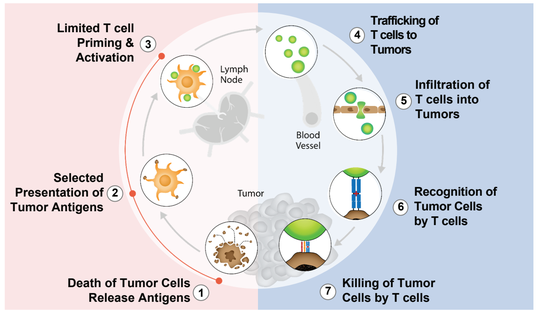
Manish R. Sharma[1], Richard D. Carvajal[2], Daniel Catenacci[3], Leisha A. Emens[4], Glenn J. Hanna[5], Dejan Juric[6], Yoon-Koo Kang[7], Jeeyun Lee[8], Keun-Wook Lee[9], Bob T. Li[10], Kathleen Moore[11], Mark D. Pegram[12], Paula R. Pohlmann[13], Drew Rasco[14], Alexander Spira[15], Arielle L. Heeke[16], Ding Wang[17], Lawrence Garbo[18], Sudhir Manda[19], Jasgit Sachdev[20], Shelley E. Ackerman[21], Heidi LeBlanc[21], David Dornan[21], Marcin Kowanetz[21], Michael N. Alonso[21], Amreen Husain[21], Edith A. Perez[21], and Ecaterina Ileana Dumbrava[22]

[1]START Midwest, Grand Rapids, MI; [2]Columbia University Medical Center, New York, NY; [3]University of Chicago, Chicago, IL; [4]UPMC Hillman Cancer Center, Pittsburgh, PA; [5]Dana-Farber Cancer Institute, Boston, MA; [6]Massachusetts General Hospital, Boston, MA; [7]Asan Medical Center, Seoul, Korea, Republic of; [8]Samsung Medical Center, Seoul, Korea, Republic of; [9]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea, Republic of; [10]Memorial Sloan Kettering Cancer Center, New York, NY; [11]Stephenson Cancer Center, Oklahoma City, OK; [12]Stanford University, Stanford, CA; [13]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC; [14]START, San Antonio, TX; [15]Virginia Cancer Specialists, Fairfax, VA; [16]Levine Cancer Institute, Atrium Health, Charlotte, NC; [17]Henry Ford Cancer Institute/Henry Ford Hospital, Detroit, MI; [18]New York Oncology Hematology, Albany, NY; [19]Arizona Oncology, Tucson, AZ; [20]HonorHealth Research Institute, Scottsdale, AZ; [21]Bolt Biotherapeutics, Redwood City, CA; [22]The University of Texas MD Anderson Cancer Center, Houston, TX

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.[1,2]
- 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.

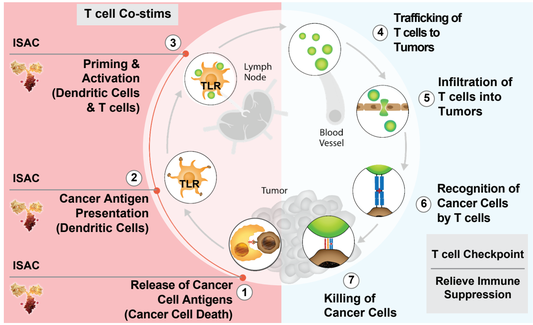
"Traditional" Immunotherapies Focus on the Adaptive Immune System



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 the cancer immunity cycle and merits further exploration in order to:
- Use innate immunity to create new antitumor immune responses.
- Amplify antitumor immune response
- Convert "cold" tumors to "hot."
- Expand antitumor T cell response & killing.

Boltbody ISACs Initiate New Immune Responses



Boltbody™ ISACs act to initiate an entirely new immune response and avoids shortcomings of other IO approaches

Engagement of biology encompassing innate and adaptive immunity within a single therapeutic

Neoantigen recognition: enhancing or antigen presentation capability of immunosuppressed APCs drives a robust new anti-tumor immune response

OBJECTIVES

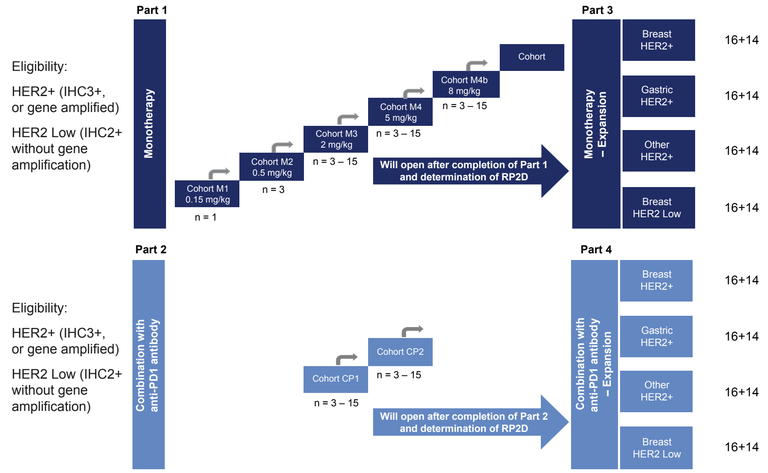
PRIMARY OBJECTIVES
- The dose-escalation phase will define safety and tolerability and determine the recommended phase 2 dose of BDC-1001 as monotherapy and in combination with an immune checkpoint inhibitors.
- The dose-expansion portion of the trial will evaluate preliminary antitumor activity of BDC-1001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



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_{max}, C_{min} $AUC_{0\text{-}t}$ $AUC_{0\text{-}inf}$ CL, Vz, $t_{½}$).
- 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
- IHC3+ or IHC2+ 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 anti-PD1 antibodylizumab or particular excipients that are used for formulation.

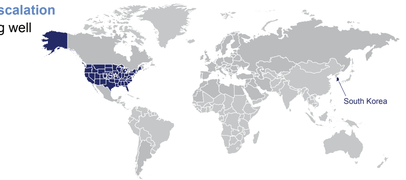
BIOMARKER ASSESSMENTS

- 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.
    - → Paired pre-/on-treatment 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

Status: Phase 1/2 Trial Initiated Q1 2020; Currently in Dose Escalation
- Enrollment in monotherapy dose-escalation phase is proceeding well (currently enrolling in the United States and South Korea)
- No unexpected adverse events have been observed to date.

Expected Upcoming Milestones:
- Complete monotherapy dose-escalation portion and initiate dose expansions in 2021.
- Phase 1/2 data anticipated to provide clinical proof of concept.



ClinicalTrials.gov (NCT04278144)

REFERENCES

1. Ackerman S, et al. Immune-stimulating antibody conjugates elicit robust myeloid activation and durable antitumor immunity. *Nature Cancer*. 2021;2:18–33.
2. Ackerman S, et al. 603 Covalent attachment of a TLR7/8 agonist to tumor-targeting antibodies drives potent anti-tumor efficacy by synergistically activating FcgR- and TLR- signaling and enables safe systemic administration. *J Immunother Cancer*. 2020;8:doi: 10.1136/jitc-2020-SITC2020.0603.
3. LeBlanc H, et al. 605 Systemically administered HER2-targeted ISACs provoke a rapid, local response that engages the innate and adaptive arms of the immune system to eradicate tumors in preclinical models. *J Immunother Cancer*. 2020;8: doi: 10.1136/jitc-2020-SITC2020.0605