Phase 2 study of novel HER2-targeting, TLR7/8 immune-stimulating antibody conjugate (ISAC) BDC-1001 ± pertuzumab in patients with HER2-positive metastatic breast cancer (MBC) previously treated with trastuzumab deruxtecan

ABSTRACT # 1575721

Mark D. Pegram[1], Carmen Calfa[2], Chris Chen[1], Alfonso Cortes Salgado[3], Arielle L. Heeke[4], Irene Kang[5], Barbara Pistilli[6], Paula Pohlmann[7], Hope Rugo[8], Cristina Saura[9], Cecile Vicier[10], Cecelia I. Pearson[11], Danlin Cai[11], Tai Yu[11], Michael N. Alonso[11], Edith A. Perez[11], Josh Drago[12]

[1]Stanford University, Stanford, CA, USA; [2]University of Miami, Miami, FL, USA; [3]Hospital Universitario Ramon y Cajal, Madrid, Spain; [4]Levine Cancer Institute, Atrium Heath, Charlotte, NC, USA; [5]City of Hope, Orange County, CA, USA; [6]Gustave Roussy, Villejuif, Paris, France; [7]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]University of California San Francisco (UCSF), San Francisco, CA, USA; [9]Vall d'Hebron University Hospital, Barcelona, Spain; [10]Institut Paoli-Calmette, Marseille, France; [11]Bolt Biotherapeutics, Redwood City, CA, USA; [12]Memorial Sloan Kettering Cancer Center, New York, NY, USA

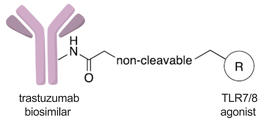
BACKGROUND

- Therapies to effectively manage patients with HER2+ metastatic breast cancer (MBC) have significantly improved over the years, but novel, more tolerable treatment options are needed for patients
- BDC-1001 is an immune-stimulating antibody conjugate (ISAC) consisting of a trastuzumab biosimilar conjugated to a TLR7/8 agonist with a non-cleavable linker
  - It is designed to be delivered systemically and act locally by targeting HER2-expressing tumors and related metastatic disease for destruction by the innate and adaptive immune systems
  - Preclinical studies 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]
- Preclinical studies demonstrated that the combination of a surrogate ISAC and pertuzumab significantly enhances efficacy in multiple HER2-expressing tumors, including those with lower HER2 expression[1,2]
  - Addition of pertuzumab lowered the dose of ISAC required for anti-tumor activity in the JIMT-1 HER2 IHC2+ preclinical model
  - Combination of pertuzumab with the ISAC significantly increased the cytokine and chemokine concentration in the tumor compared to monotherapy or antibody control, indicating enhanced myeloid activation in the tumor
- BDC-1001 was well tolerated in the phase 1 dose-escalation trial that enrolled patients with HER2-expressing solid tumors (NCT04278144)[3,4]
  - 131 patients with 16 different HER2-expressing solid tumors; 18 cohorts (0.5 – 20 mg/kg, q3w, q2w, q1w)
  - Well tolerated as monotherapy and in combination with nivolumab
  - Clinical activity observed across different HER2+ tumor types in a heterogenous, heavily pre-treated patient population
  - 20 mg/kg q2w selected as recommended phase 2 dose (RP2D) based on safety, clinical efficacy, and pharmacokinetics
  - Target serum exposure reached at RP2D
  - Chemokines and cytokines in plasma, tissue immunohistochemistry, and gene analysis consistent with the ISAC mechanism of action
- BBI-20231001 is a phase 2, randomized, open-label, multicenter trial evaluating BDC-1001 ± pertuzumab in patients with HER2-positive MBC previously treated with trastuzumab deruxtecan and at least 1 other prior anti-HER2 therapy (NCT05954143)

Proposed Mechanism of Action for Combination of BDC-1001 With Pertuzumab

Molecular Structure

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



Proposed Mechanism of Action

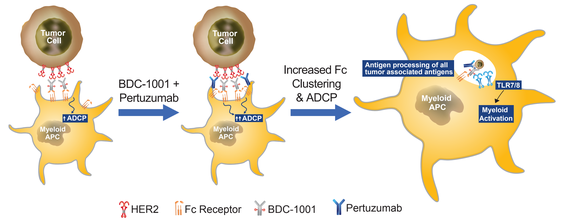
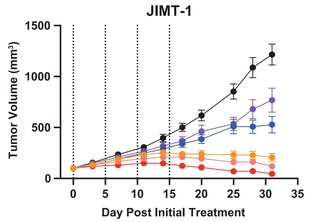


Figure 1. Combination of BDC-1001 with Pertuzumab. ISACs mediate activation of myeloid APCs via a three-factor mechanism: 1) tumor targeting, 2) tumor engulfment via antibody-dependent cellular phagocytosis, and 3) TLR7/8 activation. Addition of pertuzumab, which binds a distinct epitope of HER2, increases the number of bound antibodies to the tumor cell surface, increasing Fc clustering, which in turn increases Fc receptor-mediated phagocytosis. Schematic does not represent appropriate scale or binding dynamics.[2]

BDC-1001.S Combination With Pertuzumab Enhances Anti-Tumor Efficacy in HER2-Expressing Tumor Models



	%TGI Relative to Isotype
Isotype	–
Trastuzumab + Pertuzumab	25
BDC-1001.S (5 mg/kg)	38
BDC-1001.S (1 mg/kg) + Pertuzumab	61
BDC-1001.S (2 mg/kg) + Pertuzumab	68
BDC-1001.S (5 mg/kg) + Pertuzumab	82

Figure 2. SCID/beige mice bearing JIMT-1 tumors (n=6 per group) were treated systemically with the indicated test articles q5dx4 (dashed lines). BDC-1001.S was administered at 1, 2 or 5 mg/kg in combination with 5 mg/kg pertuzumab. Pertuzumab and trastuzumab were each administered at 5 mg/kg, while the isotype was administered at 10 mg/kg. BDC-1001.S monotherapy was co-administered with an isotype control antibody. Percentage of tumor growth inhibition (% TGI) is calculated on Day 20 relative to isotype. Data are shown as mean with standard error of the mean (SEM) from one experiment and are representative of three experiments.[2]

REFERENCES

1. Ackerman SE, et al. *Nat Cancer*. 2021;2(1):18-33.
2. Pearson C, et al. SITC 2023. Abstract#821.
3. Li BT, et al. *J Clin Oncol*. 2023;41(suppl 16):2538.
4. Li BT, et al. ESMO 2023. Presentation #657MO.

STUDY DESCRIPTION

Study Design

Eligibility

- Histologically confirmed HER2+ (ASCO/CAP) breast adenocarcinoma
- 2 or more prior anti-HER2-directed therapies
  - at least 1 in the metastatic setting
  - 1 prior therapy needs to be trastuzumab deruxtecan
- ECOG PS 0 or 1

Randomize 1:1

- **BDC-1001 (20 mg/kg q2w)**
- **BDC-1001 (20 mg/kg q2w) pertuzumab (840 mg/420 mg q3w)**

Independent Simon 2-stage design in each arm.
Not powered to compare the two arms statistically.

Eligibility

Key Inclusion Criteria

- Histologically confirmed HER2+ breast adenocarcinoma
- Have received 2 or more prior anti-HER2-directed therapies, at least 1 in the metastatic setting and 1 prior therapy needs to be trastuzumab deruxtecan
  - Prior neo-adjuvant or adjuvant therapy that resulted in relapse within 12 months of completion of therapy will be considered a line of treatment for metastatic disease
- ECOG PS 0 or 1
- Agree to have biopsy prior to enrollment, unless not safely accessible or clinically feasible
  - An archival tumor sample must be submitted in lieu of a freshly collected specimen

Key Exclusion Criteria

- History of treatment with a TLR7, TLR8, or a TLR7/8 agonist within 12 months prior to starting study treatment
- CNS metastases unless disease is asymptomatic, clinically stable, and has not required steroids for at least 28 days prior to starting study treatment

Biomarker Assessment

- Tissue biopsies will be collected at baseline and on-treatment if accessible and clinically feasible
- Potential association between circulating and tissue baseline biomarkers expression and BDC-1001 ± pertuzumab anti-tumor activity
- Pro-inflammatory cytokines and chemokines to be evaluated
- Additional exploratory biomarkers in tumor tissue and blood related to tumor and immune biology by such methods as gene expression profiling, mutational, protein and tissue image analysis

Study Objectives and Endpoints

Primary Objective and Endpoint

- Evaluate the preliminary anti-tumor activity of BDC-1001 ± pertuzumab as measured by objective response rate according to RECIST v1.1

Secondary Objectives and Endpoints

- Evaluate the preliminary anti-tumor activity of BDC-1001 ± pertuzumab as measured by duration of response, disease control rate, progression-free survival, and overall survival
- Determine the safety and tolerability of BDC-1001 ± pertuzumab by evaluating the incidence of treatment-emergent AEs and SAEs and changes in laboratory values and ECGs
- Evaluate pharmacokinetics of BDC-1001 ± pertuzumab as measured by C_{min} and C_{max}
- Evaluate the immunogenicity of BDC-1001 ± pertuzumab as measured by incidence of anti-drug antibodies

SUMMARY

- **Therapies to effectively manage patients with HER2+ MBC have significantly improved over the years, but novel, more tolerable treatment options are needed for patients**
- **BDC-1001 is an ISAC consisting of a trastuzumab biosimilar conjugated to a TLR7/8 agonist with a non-cleavable linker**
- **Preclinical studies demonstrate combination of a BDC-1001 surrogate and pertuzumab significantly enhances anti-tumor efficacy in multiple HER2-expressing tumor models providing, rationale for the combination of BDC-1001 and pertuzumab[2]**
- **BDC-1001 was well tolerated in the phase 1 dose-escalation trial that enrolled patients with HER2-expressing solid tumors. Clinical activity was observed across different HER2+ tumor types and in a heterogenous, heavily pretreated patient population: 29% response rate in HER2 evaluable HER2+ tumors at RP2D; multiple patients with long-term stable disease[3,4]**
- **BBI-20231001 is phase 2, randomized, open-label, multicenter trial evaluating BDC-1001 ± pertuzumab in patients with HER2-positive MBC previously treated with trastuzumab deruxtecan and at least 1 other prior anti-HER2 therapy (NCT05954143)**
- **Enrollment is ongoing in the United States, France, Italy, and Spain.**

For additional information, call: +1 650-434-8640 or email: clinicaltrials@boltbio.com