Phase 1/2 study of novel HER2-targeting, TLR7/8 immune-stimulating antibody conjugate (ISAC) BDC-1001+/- nivolumab in patients with advanced HER2+ colorectal (CRC), endometrial, and gastroesophageal (GE) and breast (BC) cancers

ABSTRACT # 716

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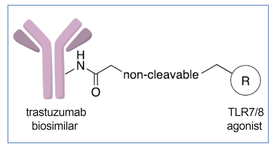
BDC-1001: Novel, First-in-Class Boltbody™ Immune-Stimulating Antibody Conjugate (ISAC)[1]

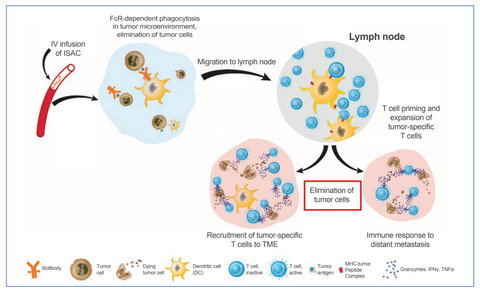
Molecular Structure

- 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 (MOA)

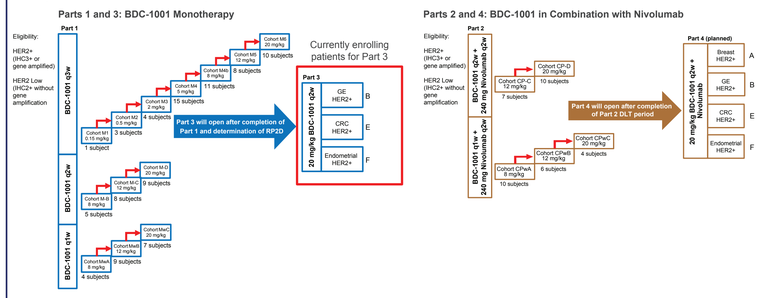
- Local activation of the innate immune system
- Generates a durable tumor-targeted adaptive immune response



BBI-20201001 Trial Study Design
Currently Enrolling Patients in Part 3 BDC-1001 Monotherapy

NCT 04278144

Total patients enrolled in the completed dose escalation part: n=131



BC, breast cancer; CRC, colorectal cancer; GE, gastroesophageal cancer.

Results from Dose-Escalation Presented at ASCO 2023 Abstract #2538[2]

- 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
- Data from the dose-escalation support Phase 2 development of BDC-1001 as a single agent and in combination strategies
- Updated results from dose escalation presented at ESMO 2023 #657MO

Trial Design and Statistical Considerations (Dose Expansions Parts 3 and 4)

Study Number	BBI-20201001
NCT	04278144
EudraCT	2021-006812-10
Design	Phase 1/2 open-label, dose escalation, and dose expansion
Target Population	Advanced HER2+ CRC, GE, endometrial cancer, and BC (part 4 only) with measurable disease
Treatment Schedule	BDC-1001 20 mg/kg q2w as monotherapy or in combination with nivolumab
Statistical Considerations	Simon 2 stage design for each tumor cohort with 30% ORR efficacy target. The combination cohort with nivolumab (Part 4) will be opened to enrollment only if the clinical activity is observed in the monotherapy cohorts (Part 3).

Primary and Secondary Objectives & Endpoints: Dose Expansion Part 3 (Monotherapy) & Part 4 (Combination with Nivolumab)

Primary Objectives	Primary Endpoints
• To evaluate preliminary anti-tumor activity of BDC-1001 as monotherapy (Part 3) and in combination with nivolumab (Part 4)	• ORR • DoR of confirmed CR/PR • DCR of confirmed CR/PR, or SD lasting 4 or more weeks following the initiation of BDC-1001 • PFS • OS
Secondary Objectives	**Secondary Endpoints**
• Safety and tolerability of BDC-1001 as monotherapy (Part 3) or in combination with nivolumab (Part 4) • Verify the exposure of BDC-1001 • Evaluate immunogenicity of BDC-1001 as monotherapy (Part 3) or in combination with nivolumab (Part 4)	• Incidence of AEs/SAEs according to CTCAE v5.0 • PK variables may include: – C_{max} – C_{min} – AUC • Incidence of ADAs against BDC-1001
Exploratory Objectives	**Exploratory Endpoints**
• Preliminary anti-tumor activity of BDC-1001 as monotherapy (Part 3) and in combination with nivolumab (Part 4) assessed using iRECIST version 1.1 • Evaluate pharmacodynamic biomarkers of BDC-1001 biological activity as monotherapy (Part 3) or in combination with nivolumab (Part 4) in tumor tissue and in peripheral blood • Explore potential baseline biomarkers associated with BDC-1001 biologic activity as monotherapy (Part 3) or in combination with nivolumab (Part 4)	• iORR, iDOR, iDCR, iPFS • Changes in TLR7/8 pathway activation, myeloid and T-cell content and activation status by gene expression profiling and tissue image analysis • Evaluation of changes in 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 • Evaluation of the potential association between baseline HER2/ PD-L1 expressions and BDC-1001/BDC-1001 + nivolumab activity • Evaluation of the potential association between baseline biomarkers and BDC-1001 activity by such methods as gene expression profiling, mutational, protein, and tissue image analysis

ADA, anti-drug antibodies; AE, adverse event; AUC, area under the curve; C_{max}, maximum concenration; C_{min}, minimum concentration; CR, complete response; DCR, disease control rate; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmakokinetic; PR, partial response; SAE; serious adverse event

Key Eligibility

Key Inclusion Criteria

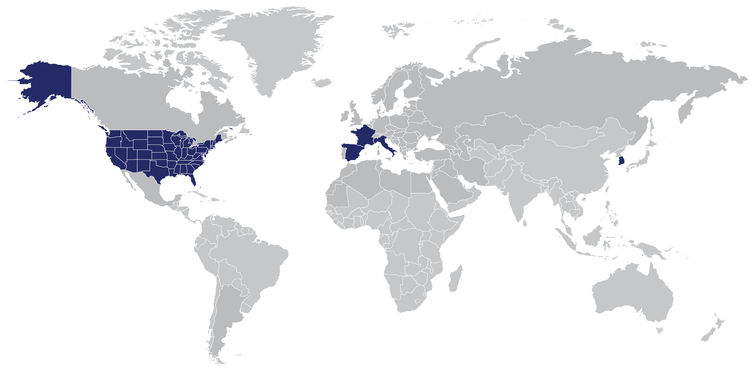
- Advanced, HER2+*, CRC, GE, endometrial cancer, and BC (Part 4 only)
- Mandatory baseline biopsies if clinically safe
- Measurable disease according to RECIST v1.1
- ECOG PS 0-1
- Prior anti-HER2 therapy for GE and BC

Key Exclusion Criteria

- No limit on prior lines of therapy
- No prior TLR7, TLR8, or TLR7/8 agonist
- No cardiac or hepatic disease
- Autoimmune disease other than controlled type 1 diabetes, hypothyroidism, selected skin disorder
- Not exceeding 10 mg/day prednisone or equivalent dose

*HER2+ defined as IHC 3+ or HER2 gene amplification

Study in Progress: Number of Selected Sites and Locations for the Phase 2 Dose Expansion



Site Activation Status

	Confirmed Sites	Active Sites
United States	11	10
France	6	0
Spain	8	4
South Korea	3	3
Italy	3	0
Total	31	17

As of 27Sept2023

Correlative Studies Planned for Part 3 and Part 4

- Serum biomarkers including cytokines and chemokines before and at the end of infusion
- Evaluations of the tumor and tumor microenvironment regarding myeloid and T-cell subsets before and after treatment using baseline and matched on treatment biopsies
- Protein and gene analyses of pathways related to the mechanisms of action of BDC-1001

SUMMARY

- The phase 2 dose expansion with BDC-1001 monotherapy at the RP2D of 20 mg/kg q2w (Part 3) for patients with HER2+ CRC, GE and endometrial cancer is open for enrollment
- Multiple sites are active for enrollment across the USA, Spain and South Korea
- Additional sites will be activated in Europe (France and Italy) in October 2023
- The first patient in the dose expansion with BDC-1001 monotherapy at RP2D was treated in August 2023
- Phase 2 dose expansion combination will open according to evolving data from the monotherapy (Part 3)
- Additional biomarker analyses are planned to elucidate further the mechanism of action of BDC-1001

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