Preliminary results from a Phase 1/2 study of BDC-1001, a novel HER2 targeting TLR7/8 immune-stimulating antibody conjugate (ISAC), in patients (pts) with advanced HER2-expressing solid tumors

Poster 2549

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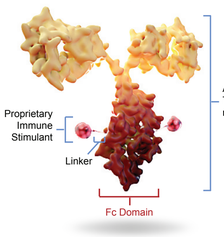
Background

BDC-1001 Has a Targeted IO Approach to Stimulate and Bridge the Innate and Adaptive Immune Systems

Boltbody ISAC



IO, immuno-oncology; mAb, monoclonal antibody

Systemic Delivery, Local Effect

- Systemically-delivered, tumor-targeting therapeutics
- Antibody against a tumor antigen directs Boltbody ISACs to the tumor
- Proprietary immune stimulant activates myeloid antigen-presenting cells
- Myeloid cells kill tumor cells, create a “hot” tumor microenvironment, & initiate an innate & adaptive anti-tumor immune response[1]

Promising Anti-tumor Activity in Preclinical Models[2-4]

Robust single-agent anti-tumor activity and elimination of established tumors in preclinical models demonstrating:

- Activity on resistant tumors
- Immunological memory
- Epitope spread

Off-the-Shelf Product

Potential for the patient’s own immune system to determine the relevant neoantigen-specific T cells to mobilize for tumor destruction to deliver a personalized therapeutic outcome

BDC-1001 is a novel ISAC consisting of an investigational biosimilar of the humanized monoclonal antibody trastuzumab chemically conjugated to a TLR7/8 agonist with a non-cleavable linker

Study Objectives

Primary Objectives

- Define safety and tolerability and determine the recommended phase 2 dose (RP2D) of BDC-1001 as monotherapy and in combination with an immune checkpoint inhibitor
- Evaluate preliminary anti-tumor activity of BDC-1001 alone and in combination with an immune checkpoint inhibitor

Secondary & Exploratory Objectives

- Evaluate pharmacokinetic (PK) parameters and pharmacodynamic biomarkers associated with drug exposure in tumor tissue and in peripheral blood
- Evaluate exploratory pharmacodynamic biomarkers associated with biological activity and potential baseline biomarkers

Study Assessments

Safety (primary clinical endpoint for dose escalation)

- Incidence of adverse events (AEs), serious adverse events (SAEs), and dose-limiting toxicities (DLTs) using NCI-CTCAE criteria version v5.0
- Incidence of potential-immune related toxicities
- Maximum tolerated dose (MTD) or a tolerated dose below MTD (if MTD is not reached)

Efficacy (primary clinical endpoint for dose expansion)

- Tumor assessments using RECISTv1.1

Pharmacokinetics

- PK variables (eg, C_{max}, C_{min}, AUC_{0-t}, AUC_{0-inf}, CL, Vz, $t_{½}$)

Exploratory Biomarker Analyses

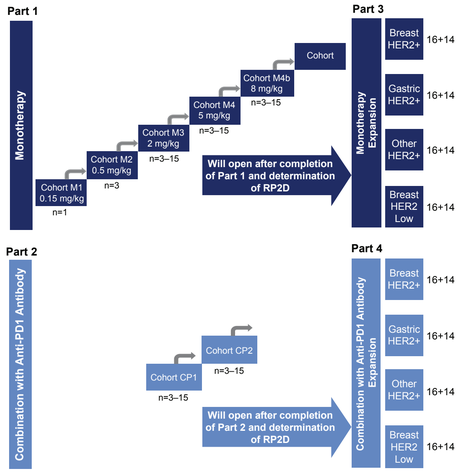
- Changes in TLR7/8 pathway activation, myeloid, and T cell content, and activation status in plasma and tumor tissue by measures of cytokines and chemokines as well as gene expression profiling, and tissue image analysis
- Evaluate potential predictive biomarkers of response to BDC-1001

Study Design

- This first-in-human, dose-escalation and dose-expansion study (NCT04278144) is enrolling up to 390 patients with HER2-expressing advanced solid tumors[5]

Key Inclusion Criteria

- Patients with advanced/metastatic solid tumors
- HER2 IHC2+/3+ or HER2 amplified
- ECOG PS 0-1
- Adequate hematologic, renal, cardiac, and hepatic function as defined in the protocol
- No symptomatic or untreated brain metastases



ECOG PS, Eastern Cooperative Oncology Group performance status

Demographics and Baseline Characteristics

	All patients (N=20)
Median age, years (range)	66 (45, 84)
Sex, n (%)	
Female	14 (70%)
Male	6 (30%)
ECOG PS at baseline, n (%)	
0	6 (30%)
1	14 (70%)
Number of prior therapies, median (range)	4 (1, 7)
HER2 categories*, n (%)	
HER2 IHC3+	10 (50%)
HER2 IHC2+/ISH+	1 (5%)
HER2 amplified – NGS or ISH	12 (60%)
Tumor types, n (%)	
Gastroesophageal	6 (30%)
Colorectal	5 (25%)
Uterus	3 (15%)
Breast	1 (5%)
Cervix	1 (5%)
Lung	1 (5%)
Pancreas	1 (5%)
Salivary duct	1 (5%)
Urinary bladder	1 (5%)

*In 3 cases, tumors were reported as both IHC+ and NGS HER2 amplified
IHC, immunohistochemistry; ISH, in-situ hybridization; NGS, next-generation sequencing

Data cut-off date Jan 29, 2021

Overall Safety Summary

	All TEAEs (N=20)	Treatment-related TEAEs (N=20)
All Grades	20 (100%)	13 (65%)
Grade ≥3	10 (50%)	1 (5%)
Serious adverse event (SAE)	8 (40%)	0
Leading to treatment discontinuation	1 (5%)	0
Leading to death	2 (10%)	0

- No DLTs observed to date, and the MTD has not been reached
- The single Grade 3 treatment-related event was anemia (patient had Grade 2 anemia at screening)
- No Grade 5 treatment-related events
- Treatment-emergent adverse events (TEAEs) that led to treatment discontinuation included 1 patient with a serious adverse event (SAE) of urinary tract infection who went on hospice shortly after the event
- Of the treatment-related AEs, a mild decrease in left-ventricular ejection fraction ocurred in 1 patient, and infusion-related reactions (IRRs) occurred in 4 patients on cohort M4 (5 mg/kg)
  - All IRRs were grades 1 or 2 and did not require interruption to the infusion
  - Two patients received subsequent infusions with non-steroid premedication and no further IRRs; the other 2 patients went off study prior to subsequent infusions

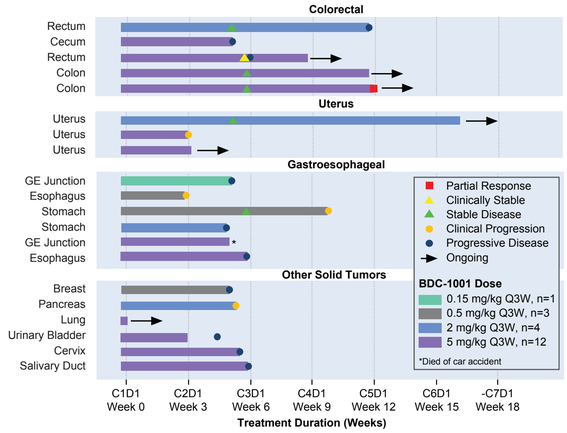
Overview of Most Common* TEAEs

	All TEAEs (N=20)		Treatment-related TEAEs (N=20)	
Preferred term, n (%)	**All Grades***	**≥ Grade 3**	**All Grades**	**≥ Grade 3**
Fatigue	8 (40%)	1 (5%)	2 (10%)	0
Arthralgia	4 (20%)	0	2 (10%)	0
Infusion related reaction	4 (20%)	0	4 (20%)	0
Pyrexia	4 (20%)	0	2 (10%)	0
Nausea	3 (15%)	1 (5%)	1 (5%)	0
Abdominal pain	3 (15%)	1 (5%)	1 (5%)	0
Dyspnea	3 (15%)	1 (5%)	0	0
Aspartate aminotransferase increased	3 (15%)	0	1 (5%)	0
Diarrhea	3 (15%)	0	3 (15%)	0
Urinary tract infection	3 (15%)	1 (0%)	0	0
Vomiting	3 (15%)	1 (0%)	0	0

* Occurring >10% in all patients

Data cut-off date Jan 29, 2021

Swimmer Plot of Study Treatment Period, Best Response, and Progression (as of Jan 29, 2021)

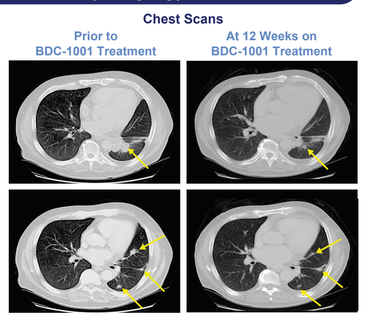


Patient with Metastatic CRC and Partial Response in Cohort M4 (5 mg/kg)

66-year-old Male with Metastatic Adenocarcinoma of the Colon

- Tumor HER2+ (IHC3+, amplified FMI); microsatellite stable, KRASwt
- Previous treatments include chemotherapy, radiation therapy, biologic therapies and immunotherapy with progression on most recent checkpoint inhibitor
- ECOG PS =1
- Metastatic disease in the lung
- Medical history: hypertension, hypercholesterolemia, anemia, diverticulosis

Chest Scans



Data cut-off date Jan 29, 2021

Preliminary Pharmacokinetics and Pharmacodynamics

- Early pharmacokinetic data demonstrate that C_{max} levels are consistent with those predicted in non-human primate (NHP) models
- Elevations in exploratory pharmacodynamic biomarkers were observed with a trend towards greater magnitude in patients with increasing dose level. These included biomarkers associated with TLR7/8 activation, myeloid cell activation and T cell activation (eg, TNFα, IP-10, MCP-1, MIP-1α, MIP-1β, IFNγ)
  - The plasma cytokine and chemokine data are consistent with preclinical data and with the proposed mechanism of action of BDC-1001, including markers of myeloid cell and TLR activation

Conclusions

- The novel ISAC BDC-1001 has been well-tolerated to date (ie, Jan 29th, 2021 clinical cut-off date) with evidence of early clinical anti-tumor activity in advanced HER2-expressing solid tumors
  - No DLTs or drug-related SAEs have been reported
  - Mild infusion-related reactions were reported in 4 patients among the early cohort at the 5 mg/kg dose level, but no subsequent IRRs have been seen in subsequent patients enrolled on the same dose
  - Other TEAEs are consistent with those reported across phase 1 trials in patients with advanced solid tumors
- The MTD has not been reached, and the study continues to enroll patients in the monotherapy dose-escalation phase
- Early pharmacokinetic data demonstrate that C_{max} levels are consistent with that predicted in non-human primate (NHP) models
- More details and data on pharmacodynamic biomarkers in blood and tumor are anticipated to be presented at a future meeting in 2021
- The checkpoint inhibitor combination and dose-expansion parts are planned to start after completion of monotherapy dose escalation later in 2021

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