MADRID 2023 ESMO congress

Recommended phase 2 dose (RP2D) selection and pharmacodynamic data of the first-in-human immune-stimulating antibody conjugate (ISAC) BDC-1001 in patients with advanced HER2-expressing solid tumors

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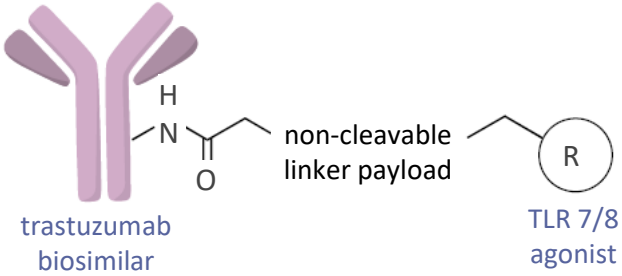
DECLARATION OF INTERESTS

Commercial Interests	Nature of Relationship
Amgen, AstraZeneca, Boehringer Ingelheim, BOLT Biotherapeutics, Daiichi Sankyo, Genentech, Lilly	Consultant/Advisor (uncompensated)
Amgen, MORE Health	Academic Travel Support
Karger Publishers, Shanghai Jiao Tong University Press	Intellectual Property as Book Author
Amgen, AstraZeneca, BOLT Biotherapeutics, Daiichi Sankyo, Genentech, Jiangsu Hengrui Pharmaceuticals, Lilly, MORE Health, Resolution Bioscience, Revolution Medicines	Institutional Research Support

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

Molecular Structure

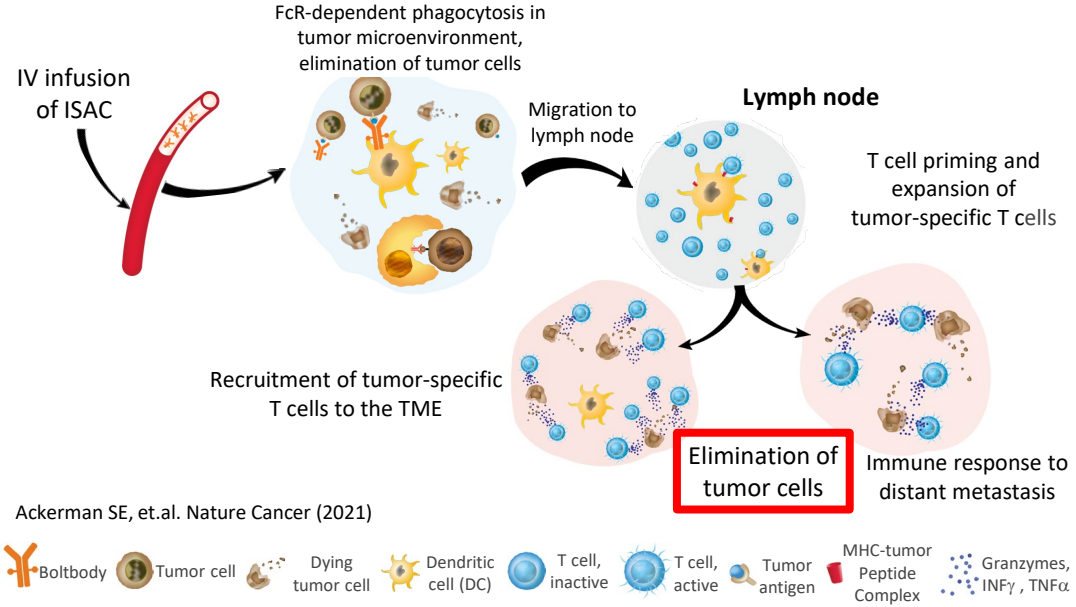
- BDC-1001 consists of
  - Antibody: trastuzumab biosimilar
  - Payload: TLR 7/8 agonist
  - Linker: non-cleavable
- BDC-1001 linker-payload is cell membrane-impermeable



TLR = toll like receptor

Proposed Mechanism of Action (MOA)

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



Ackerman SE, et.al. Nature Cancer (2021)

Trial Overview and Data Update Since ASCO 2023[1]

Phase 1 dose escalation results & RP2D selected

- 131 patients with 16 different HER2-expressing solid tumor types; 18 cohorts (doses: 0.5 – 20 mg/kg IV; schedules: q3w, q2w, q1w)
- BDC-1001 well tolerated up to 20 mg/kg q1w as monotherapy and in combination with nivolumab
- Clinical activity across all cohorts in a heterogenous, heavily pre-treated patient population: 1 CR, 5 PRs, 14 SDs ≥ 24 weeks
- BDC-1001 20 mg/kg q2w (as monotherapy or with nivolumab) selected as RP2D based on safety, clinical efficacy, and PK

Safety for BDC-1001 Monotherapy and Combination with Nivolumab

	BDC-1001 Related-TEAEs Grade ≥ 3 n (%)	LVEF Decrease Grade ≥ 3[3] n (%)	IRR n (%)
q3w[2] (N=52)	5 (9.6)	1 (1.9)	12 (23.1)
q2w (N=39)	1 (2.6)	1 (2.6)	11 (28.2)
q1w (N=40)	4 (10.0)	3 (7.5)	16 (40.0)
Total (N=131)	10 (7.6)	5 (3.8)	39 (29.8)

[2]q3w included monotherapy only; [3]Derived per CTCAE v5.0, Grade 3 is defined as 'Resting ejection fraction (EF) 39 - 20% OR ≥20% drop from baseline'. Grade 4 is defined as 'Resting ejection fraction (EF) <20%'.

- Of 10 patients with grade ≥ 3 BDC-1001-related TEAEs, 1 grade 4
- 5 patients with grade ≥ 3 LVEF, all grade 3
- No grade ≥ 3 IRR was observed
- No increase in nivolumab toxicity in combination with BDC-1001
- Nivolumab did not increase toxicity of BDC-1001

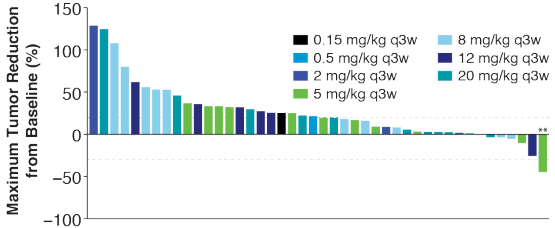
PK and Biomarkers

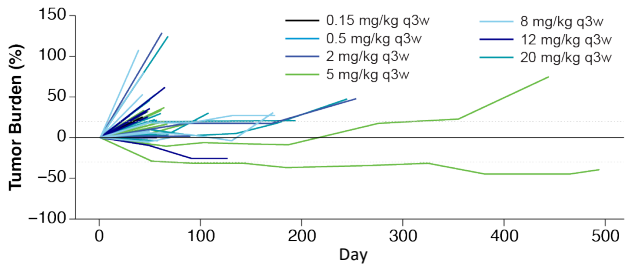
- Median target serum exposure of at least 10 μg/mL reached at RP2D; BDC-1001 half-life is 4.8 days
- No clinically significant ADA formation observed (6.3% incidence with very low titers, without impact on PK)
- Dose-dependent increases of multiple plasma cytokines/chemokines, including low IL-6 levels observed
- Increases of myeloid and T cell infiltrations observed in paired tumor biopsies by IHC

[1]Li B, et al. J Clin Oncol 41, 2023 (suppl 16; abstr 2538); ADA=anti-drug antibody, CR = complete response, IHC = immunohistochemistry, IRR = infusion related reaction, LVEF = left ventricular ejection fraction, PR = partial response, PK = pharmacokinetics, RP2D = recommended phase 2 dose, SD = stable disease, TEAE = treatment-emergent adverse event

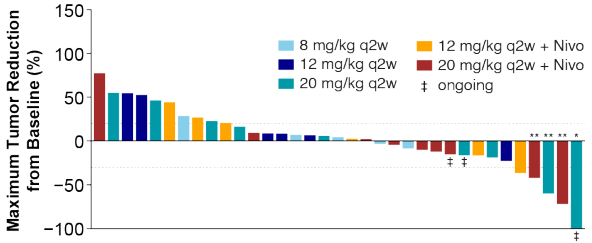
Improved BDC-1001 Efficacy Since ASCO:[1] 1 New CR, 2 Additional Long-Term SDs, and 3 Patients Have Now Received Therapy ≥ 1 Year

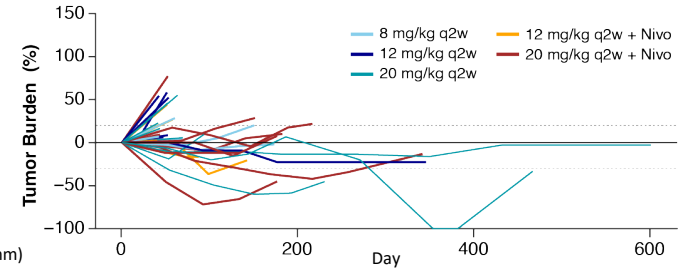
q3w (N = 44)[2]





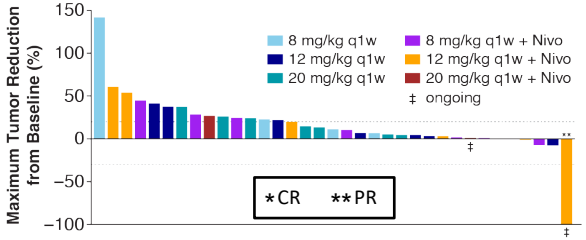
q2w (N = 35)[2]



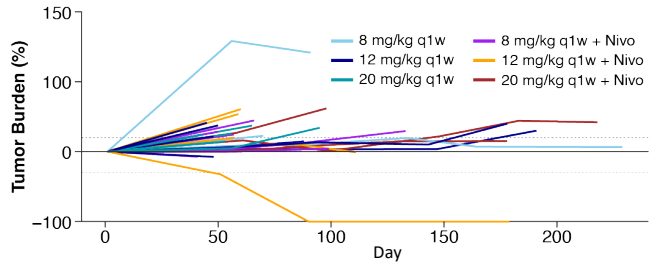


* CR patient had target lesion in lymph nodes (CR per RECIST v1.1 in lymph node is <10 mm)

q1w (N = 35)[2]



**PR patient with persistent non-target lesions



Efficacy at RP2D, 20 mg/kg q2w, in evaluable HER2+ tumors

- Monotherapy (n=7)
  - 1 CR, 1 PR (ORR = 29%)
  - 43% had disease control ≥24 weeks
  - 57% achieved tumor shrinkage
    - Tumor types: biliary tract, colorectal, salivary gland
  - 2 patients received therapy for ≥1 year
- Combination with nivolumab (n=7)
  - 2 PRs (ORR = 29%)
  - 57% had disease control ≥24 weeks
  - 71% achieved tumor shrinkage
    - Tumor types: breast, colorectal, ovary, salivary gland

Overall, 3 patients have now received therapy for ≥1 year

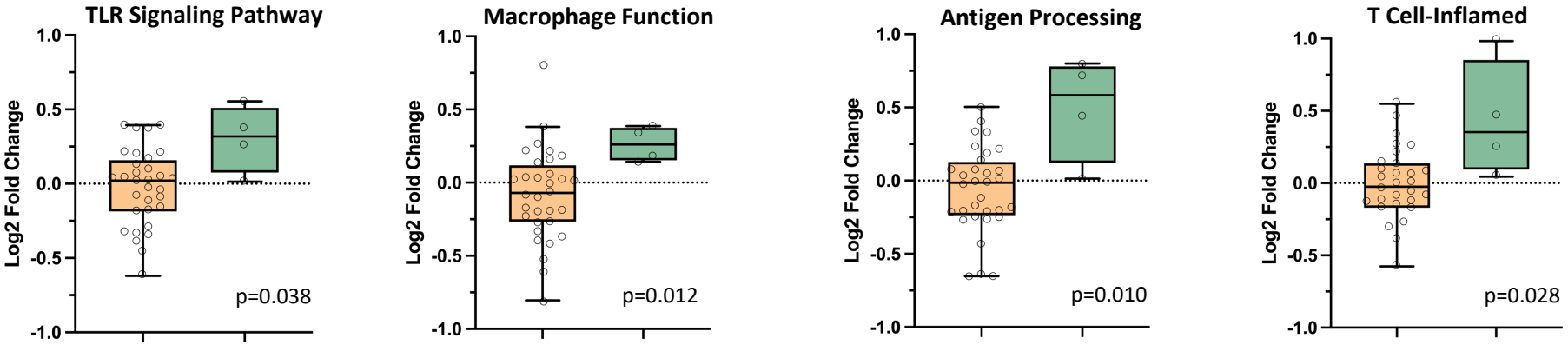
- 2 at 20 mg/kg q2w (RP2D)
- 1 at 5 mg/kg q3w

[1]Li B, et al. J Clin Oncol 41, 2023 (suppl 16; abstr 2538), [2]patients with ≥1 tumor assessment post-dose

Data cut-off: 11Aug2023

BDC-1001 Upregulates TLR Signaling, Myeloid, and T Cell Pathways in Clinical Responders, Consistent with MOA

Innate Immunity | **Adaptive Immunity**



PR or SD ≥ 24 weeks (n=4)

PD or SD < 24 weeks (n=32)

Dose (mg/kg)	BDC-1001			BDC-1001 + Nivolumab	
	q3w	q2w	q1w	q2w	q1w
5*	5	0	0	0	0
8	3	1	0	0	1
12	5	1	3	3	0
20	5	1	5	4	0

*1 patient missing response assessment

Methods

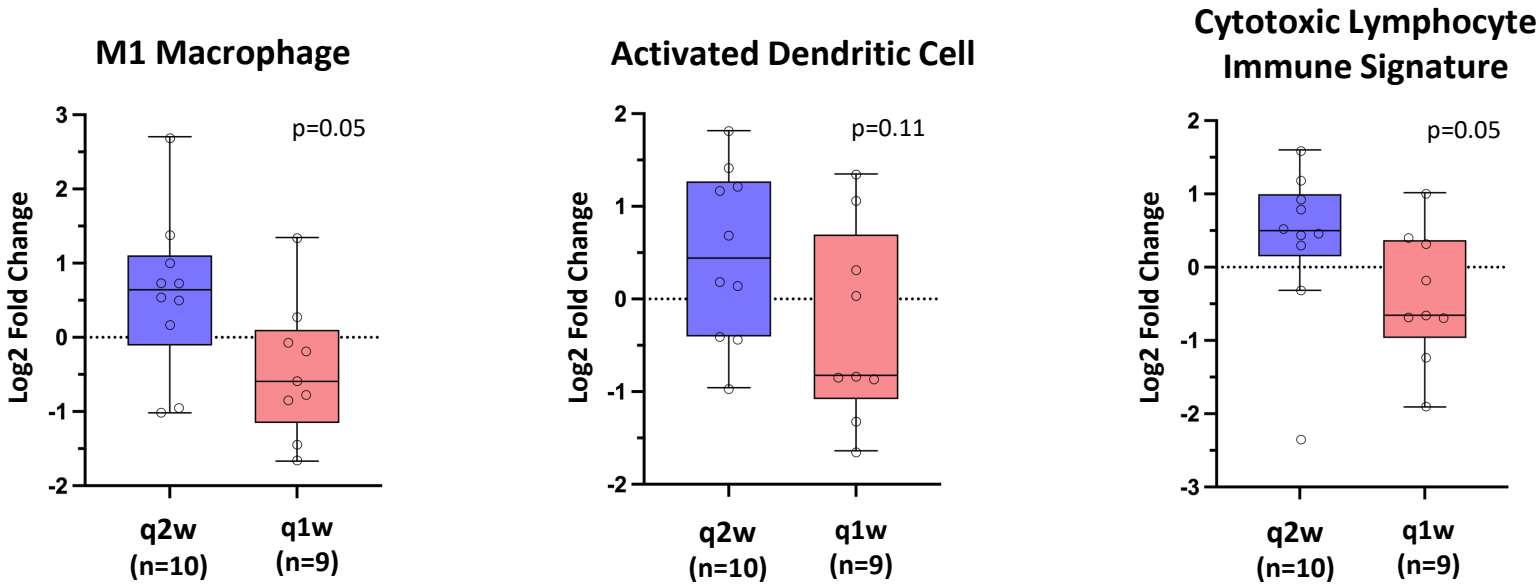
- Matched tumor biopsies obtained at baseline and approximately 4 weeks
- Gene expression analyzed by RNAseq and displayed as fold change relative to baseline
- 37 patients had paired and evaluable gene expression data (q3w, q2w, q1w)
  - 1 patient missing response assessment

Results

- Statistically significant[1] upregulation of TLR signaling pathway gene signature, innate immunity gene signatures, and T cell-inflamed phenotype[2] was observed in the 4 patients with clinical benefit

[1]MOA-driven evaluation of key signatures (Bolt Biotherapeutics; Nature Cancer 2021) assessed using Mann Whitney U test
[2]TLR Signaling Pathway - KEGG database; Macrophage Function & Antigen Processing - NanoString; T Cell-Inflamed Signature - Ayers M 2017

Increases in Select Innate Immune and Adaptive Immune Signatures Were Observed in Patients in the q2w Cohorts, but Not in q1w Cohorts



Dose (mg/kg)	BDC-1001		BDC-1001 + Nivolumab	
	q2w	q1w	q2w	q1w
5	0	0	0	0
8	1	0	0	1
12	1	3	3	0
20	1	5	4	0

Methods

- Gene expression data were generated by RNAseq
- 10 patients in q2w cohorts and 9 patients in q1w cohorts had paired and evaluable gene expression data

Results

- Upregulation of select innate and adaptive immune signatures[1] were observed in q2w cohorts, but not q1w

[1]M1, activated DC and cytotoxic lymphocyte immune signatures – Jones WD 2020

Summary and Next Steps

BDC-1001, a novel ISAC targeting HER2, is well tolerated with encouraging clinical activity

- Clinical activity across all cohorts (n=131): 1 CR, 5 PRs, and 14 SDs ≥ 24 weeks
- At RP2D, 20 mg/kg q2w (n=14[1]): 1 CR, 3 PRs (29% ORR), and 4 SDs ≥ 24 weeks
- No drug-related alopecia, interstitial lung disease, or grade ≥3 infusion-related reaction

Gene expression analysis demonstrates

- Upregulation of TLR signaling, myeloid, and T cell pathways in clinical responders, consistent with mechanism of action
- Increases in innate immune and adaptive immune signatures were observed in patients in the q2w cohorts, but not q1w

BDC-1001 is the first ISAC to advance to phase 2 trials

- Dose expansion phase of BDC-1001 monotherapy and with nivolumab[2] in HER2+ colorectal, gastroesophageal, and endometrial cancers (NCT04278144)
- New trial of BDC-1001 monotherapy with or without pertuzumab[3] in HER2+ metastatic breast cancer following prior treatment with trastuzumab deruxtecan (NCT05954143)

[1]HER2+ evaluable, BDC-1001 as monotherapy and with nivolumab; [2]provided by BMS; [3]provided by Roche

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Thank you to the patients and all the Investigators and their teams

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