Abstract #CT154

BDC-3042, a first-in-class Dectin-2 agonist, in patients with advanced malignancies: Results from the first-in-human dose-escalation study

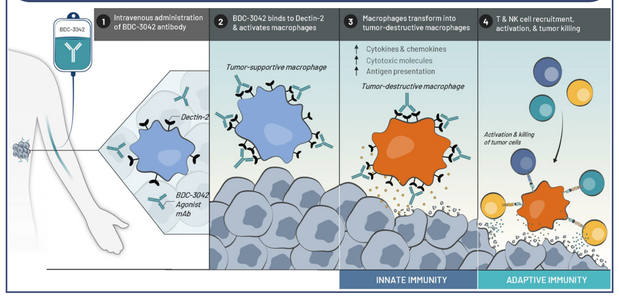
Ecaterina E. Dumbrava[1], Ildefonso Ismael Rodriguez[3], M. Adham Salkeni[4], Antonio Giordano[5], Chris Chen[6], Sheena Sahota[2], Edith A. Perez[7], Tai Yu[7], Katherine Rosenthal[7], Samara Violet[7], Kristi Balacy[7], Danlin Cai[7], Jason Ptacek[7], Lu Xu[7], Dawn Colburn[7], Shelley E. Ackerman[7], Michael N. Alonso[7], Justin A. Kenkel[7], Andrae Vandross[2]

1. The University of Texas MD Anderson Cancer Center, Houston, TX; 2. Next Oncology, Austin, TX; 3. Next Oncology, San Antonio, TX; 4. Next Oncology, Fairfax, VA, 5. Dana-Farber Cancer Institute, Boston, MA; 6. Stanford Cancer Institute, Stanford, CA; 7. Bolt Biotherapeutics, Redwood City, CA

Background

- Tumor-associated macrophages (TAMs) play a key role in establishing the immunosuppressive tumor microenvironment (TME) and are believed to limit the efficacy of immune checkpoint inhibitors and other therapies
- TAMs are phenotypically plastic with the potential to be reprogrammed into immunostimulatory cells that enhance innate and adaptive anti-tumor immune responses
- BDC-3042 is a novel agonistic antibody targeting an immune-activating receptor expressed on TAMs known as Dectin-2 (CLEC6A)[1]
- Dectin-2 is a C-type lectin receptor best known for its role in pathogen recognition and induction of protective immune responses against fungi and other microbes
- Nonclinical studies with BDC-3042 have demonstrated its ability to reprogram TAMs and elicit anti-tumor activity as a novel immunotherapeutic approach for diverse human cancers[2]

BDC-3042 Mechanism of Action



Study Design

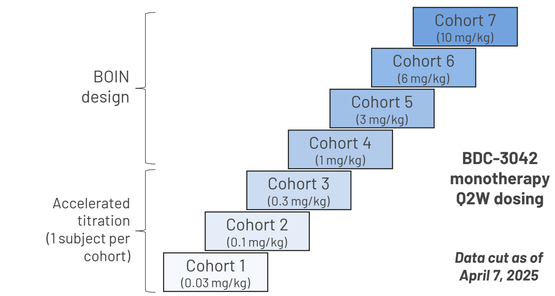
Overview

- We report on the first-in-human dose-escalation trial evaluating BDC-3042 in patients with metastatic or unresectable triple-negative breast cancer (TNBC), clear cell renal cell carcinoma (ccRCC), colorectal cancer (CRC), head and neck cancer, melanoma, non-small cell lung cancer (NSCLC), or ovarian cancer (NCT06052852)

Objectives

- Primary: Characterize the safety and tolerability and define the RP2D of BDC-3042 in subjects with advanced malignancies
- Secondary: Evaluate the pharmacokinetics, immunogenicity, and preliminary anti-tumor activity of BDC-3042
- Exploratory: Assess baseline and pharmacodynamic biomarkers in blood and tumor tissue to define their association with the biological activity, efficacy, or safety of BDC-3042

Dose Escalation Schema



BDC-3042 monotherapy Q2W dosing

Data cut as of April 7, 2025

Demographics

Heterogeneous & heavily pretreated population (n=17) including 8 CRC patients

- 6 tumor types across 7 dose cohorts; median of 4 prior lines of therapy

	Cohort 1 0.03 mg/kg N=1	Cohort 2 0.1 mg/kg N=1	Cohort 3 0.3 mg/kg N=1	Cohort 4 1 mg/kg N=4	Cohort 5 3 mg/kg N=4	Cohort 6 6 mg/kg N=3	Cohort 7 10 mg/kg N=3	Total N=17
Mean age, years (range)	61.0 (61, 61)	53.0 (53, 53)	78.0 (78, 78)	62.0 (52, 83)	55.8 (51, 63)	68.7 (59, 75)	68.0 (65, 72)	63.1 (51, 83)
Sex, n (%)								
Female	0	1 (100%)	1 (100%)	2 (50%)	1 (25%)	1 (33.3%)	2 (66.7%)	8 (47.1%)
Male	1 (100%)	0	0	2 (50%)	3 (75%)	2 (66.7%)	1 (33.3%)	9 (52.9%)
Prior lines of therapies, Mean (range)	5 (5, 5)	2 (2, 2)	4 (4, 4)	4.8 (3, 8)	3.3 (2, 5)	6.0 (4, 8)	4 (4, 4)	4.3 (2, 8)
Prior immune therapy, n (%)	0 (0%)	0 (0%)	1 (100%)	1 (25%)	0 (0%)	2 (66.7%)	3 (100%)	7 (41.2%)
Tumor types, n (%):								
Colorectal	1 (100%)	1 (100%)	0 (0%)	2 (50%)	3 (75%)	1 (33.3%)	0 (0%)	8 (47.1%)
NSCLC	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	2 (66.7%)	3 (17.6%)
Ovarian	0 (0%)	0 (0%)	0 (0%)	1 (25%)	1 (25%)	1 (33.3%)	0 (0%)	2 (11.8%)
ccRCC	0 (0%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	1 (33.3%)	0 (0%)	2 (11.8%)
TNBC	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5.9%)
Uveal Melanoma	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (33.3%)	1 (5.9%)

Safety

BDC-3042 was well tolerated up to 10 mg/kg Q2W

- No DLTs or drug-related SAEs
- No drug-related grade 4 or grade 5 AEs
- One drug-related infusion related reaction (grade 1)
- Most frequent drug-related AEs were fatigue (12%), flatulence (12%), and nausea (12%)
- No drug-related treatment discontinuations
- No overarching trends identified in safety profile

Summary of treatment-related TEAEs

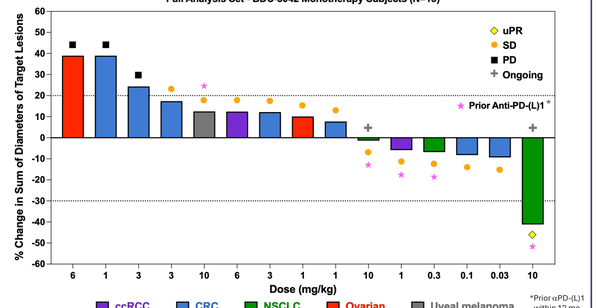
	Cohort 1 0.03 mg/kg N=1	Cohort 2 0.1 mg/kg N=1	Cohort 3 0.3 mg/kg N=1	Cohort 4 1 mg/kg N=4	Cohort 5 3 mg/kg N=4	Cohort 6 6 mg/kg N=3	Cohort 7 10 mg/kg N=3	Total N=17
All grades (%)	0	1 (100%)	1 (100%)	2 (50%)	2 (50%)	1 (33.3%)	1 (33.3%)	8 (47.1%)
Grade ≥ 3 (%)	0	0	0	2 (50%)	0	0	0	2 (11.8%)
Serious adverse events (%)	0	0	0	0	0	0	0	0
Leading to tx discontinuation	0	0	0	0	0	0	0	0
Leading to tx interruption	0	0	0	0	0	0	0	0
Leading to death	0	0	0	0	0	0	0	0

Related grade 3 TEAEs: increased amylase/lipase (Cohort 4), muscle weakness (Cohort 4)

Efficacy

PR (unconfirmed) in NSCLC patient at 10 mg/kg with treatment ongoing

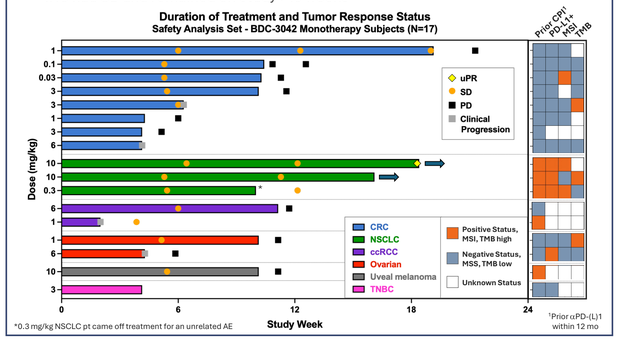
- 3/3 (100%) NSCLC patients & 4/5 (80%) patients with progression on prior anti-PD-(L)1 therapy had SD or better with some reduction in tumor size
- 12/15 (80%) evaluable patients had SD or better as best response



Efficacy

Signs of disease control in 3/3 NSCLC patients and 2/3 patients at 10 mg/kg

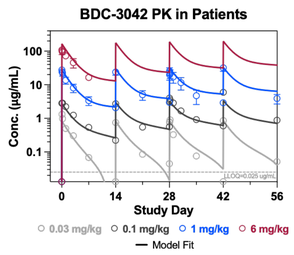
- All patients with NSCLC had SD or better for ≥12 weeks, with a uPR in one 10 mg/kg patient observed at 18 weeks
- All patients with NSCLC had progressed on multiple (≥2) prior lines of CPI therapy
- One MSS CRC patient with 8 prior lines of therapy and high Dectin-2 expression by IHC had SD and remained on study >18 weeks



Pharmacokinetics

Favorable PK profile conducive to Q2W, Q3W, or Q4W dosing

- Typical mAb PK characteristics
- Clearance in linear dose range: 4.4 mL/day/kg
- Prominent distribution phase typical of mAb with high isoelectric point (pI)
- $t_{1/2}$ in linear dose range: 20 days
- Drug accumulation observed at ≥ 0.1 mg/kg
- No evidence of ADA formation to date



Dectin-2 Expression & Prevalence Across Tumor Types

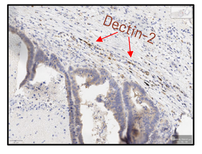
5 out of 5 patient samples* assessed by IHC had detectable Dectin-2 staining

Dectin-2 IHC Results

Dose	Indication	Treatment Duration (wks)	% Tumor Area Dectin-2+	% Macrophages Dectin-2+
0.1 mg/kg	CRC	10.4	8%	40%
1 mg/kg	CRC	19.1	20%	80%
	Ovarian‡	10.1	2%	20%
	CRC	4.3	2%	5%
3 mg/kg	CRC	6.3	5%	30%

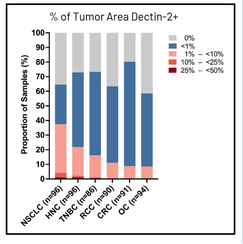
* Available biopsy samples less than 5 years old
‡ Fresh baseline biopsy; all others were archival samples

CRC Patient at 1 mg/kg
20% Tumor Area Dectin-2+



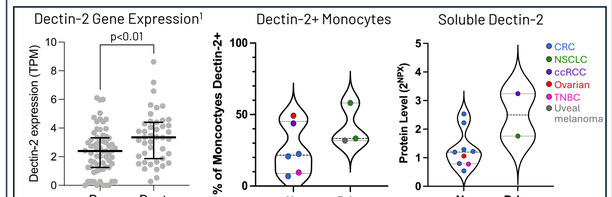
Tissue Microarray (TMA) and whole tissue sections commercially sourced show Dectin-2 is expressed across tumor types

- All whole tissue sections had detectable Dectin-2 (n=137 across 6 indications evaluated with TMAs plus melanoma)
  - Small size of TMA cores likely underestimates Dectin-2 expression
- ~40 % of NSCLC TMA samples and 50% of NSCLC whole tissue sections had ≥1% tumor area positive for Dectin-2



Dectin-2 Expression is Elevated Following αPD-(L)1 Treatment

- Prior reports found increased Dectin-2 gene expression in tumor biopsies following pembrolizumab[1] and nivolumab[2] treatment
- In the present study, patients with recent prior αPD-(L)1 treatment had:
  - Higher frequency of Dectin-2+ monocytes in peripheral blood
  - Elevated levels of soluble Dectin-2 in serum samples
  - No biopsies taken after αPD-(L)1 therapy were available for Dectin-2 IHC evaluation



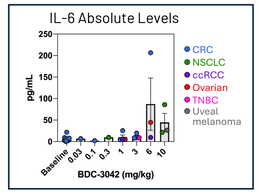
¹Cindy Yang et al., Nat. Commun. 2021. Plot shows all pre- (n=65) and post- (n=43) treatment samples analyzed by unpaired t-test. ²Bi et al., Cancer Cell 2021.

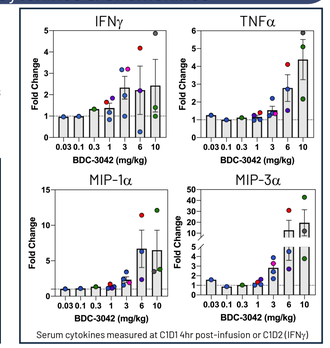
Dectin-2 expression on monocytes at baseline from patients at 3 – 10 mg/kg

Soluble Dectin-2 Normalized Protein eXpression (NPX) at baseline from patients at 0.03 – 3 mg/kg

BDC-3042 Elicits Dose-Dependent Increases in Proinflammatory Cytokines & Chemokines

- Serum cytokine responses are dose-dependent and induced over multiple cycles
- IL-6 concentrations were below levels associated with CRS, consistent with BDC-3042 being well tolerated





Serum cytokines measured at C1D1 4hr post-infusion or C1D2 (IFNγ)

Summary

Conclusions

- BDC-3042 was safe and well tolerated at all doses tested in a heterogeneous and heavily pretreated patient population
- BDC-3042 exhibited favorable PK providing ample exposure and flexibility to widen the dosing interval
- BDC-3042 showed biological activity, with evidence of target engagement and immunostimulatory effects consistent with Dectin-2 agonism
- Single-agent BDC-3042 demonstrated preliminary antitumor activity in NSCLC patients who progressed on prior immunotherapies, including a uPR in one patient treated at the highest dose level (10 mg/kg)

Future Directions

- Emerging efficacy data support further investigation in NSCLC and/or post αPD-(L)1 setting
- Favorable safety profile supports combination with immune checkpoint inhibitors and other potentially synergistic therapies

Acknowledgements

- The authors are grateful to the patients and their caregivers for their support as well as the investigators and their study teams for their contributions
- This presentation is the intellectual property of Bolt Biotherapeutics, Inc. and can be found online at boltbio.com

References:

1. Kenkel JA, et al. *Cancer Research*. 2023; 83(suppl 7):2964.
2. Kenkel JA, et al. *Journal for Immuno Therapy of Cancer.* 2021;9(suppl2):A903