Abstract # 30

Key Learnings From BDC-1001 Phase 1 FIH Dose Escalation Trial Inform Next-Generation ISACs

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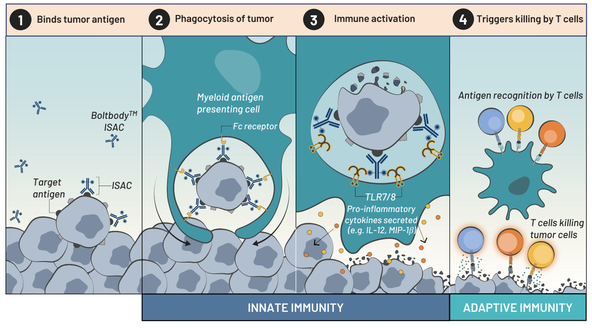
BBI-20201001 Trial Overview and Translational Questions

- Phase 1 dose escalation completed & RP2D selected[1]
  - 18 cohorts with 16 different HER2-expressing[2] solid tumor types
    - Doses: 0.5 - 20 mg/kg IV; schedules: q3w, q2w, q1w
  - BDC-1001 was well tolerated up to 20 mg/kg q1w as monotherapy and in combination with nivolumab at 240 mg q2w (no MTD identified)
  - Clinical activity across all cohorts in a heterogenous, heavily pre-treated patient population: 1 CR, 5 PRs, 14 SDs ≥ 24 weeks
- Translational questions that we answered
  - What is the immune activity of BDC-1001 in both blood and tumor tissue?
    - Does BDC-1001 induce recruitment of myeloid cells and T cells into tumors?
    - Does BDC-1001 activate innate and adaptive immune pathways in tumors?
  - What patient groups are most responsive to BDC-1001 immune activity?

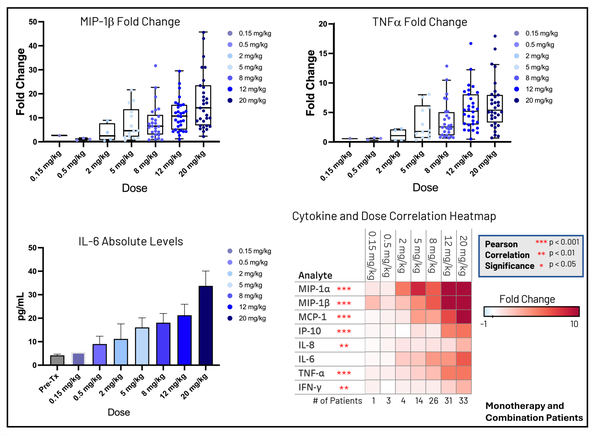
[1]Li B, et al. Ann Oncol. 2023;34(suppl_2):S458-S497 (ESMO, 2023)
[2]HER2-expressing: Either HER2+ (IHC 3+ or HER2 gene amplification) or HER2 Low (IHC 2+ without gene amplification)
RP2D = Recommended Phase 2 Dose, MTD = Maximum Tolerated Dose, IV = Intravenous

Boltbody™ Immune-Stimulating Antibody Conjugate (ISAC)



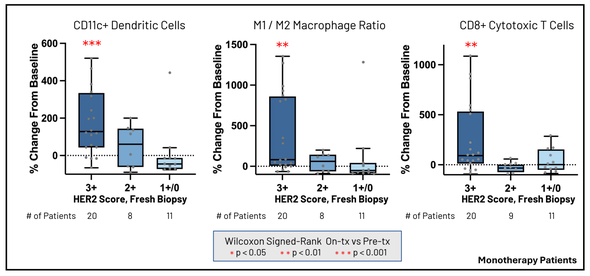
BDC-1001 Elicits Proinflammatory Cytokines

- Peripheral cytokines were measured at multiple timepoints
- Fold change in biomarkers significantly correlated to dose at Cycle 1 Day 1, 4 hours post-infusion
  - MIP-1β and TNFα exemplify these dose relationships
- IL-6 levels were low and transient, well below those observed with cytokine release syndrome



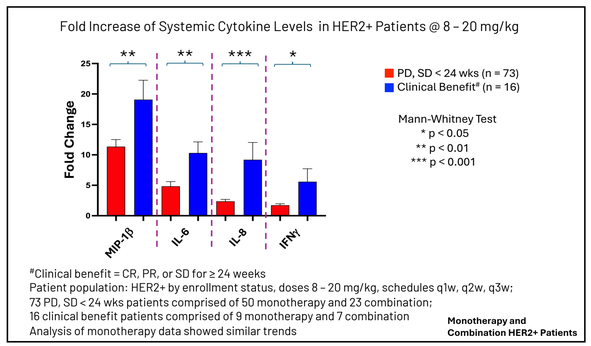
BDC-1001 Monotherapy Drives Immune Cell Infiltration and Increased Immune-related Gene Expression in HER2 IHC 3+ Tumors

- Multiplex IHC assays and RNAseq transcriptomic analysis were utilized to enumerate immune populations and gene signatures in baseline and on-treatment biopsies collected at 4 weeks after first dose
- BDC-1001 shows the potential to alter the tumor microenvironment by recruiting dendritic cells, CD68+CD163- M1 macrophages, and cytotoxic T cells
- Activation of TLR, innate and adaptive immunity pathways were observed from on-treatment tumor biopsies
- These changes were statistically significant in HER2 IHC 3+ tumors only
  - Analysis of blended monotherapy and combination data showed similar trends



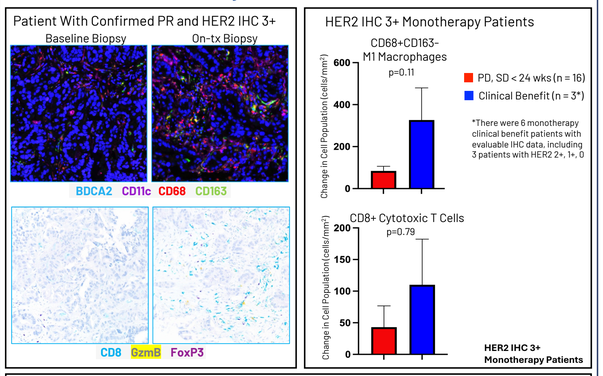
Stronger Peripheral Immune Activation Observed in Patients Achieving Clinical Benefit

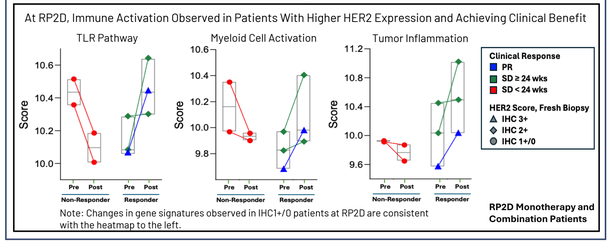
- Higher peripheral blood cytokine levels are associated with clinical benefit



Clinical Benefit in HER2 IHC 3+ Patients Trends with Enhanced Immune Cell Infiltration

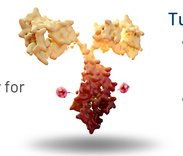
- In HER2 IHC 3+ tumors, clinical benefit patients trended higher in myeloid and cytotoxic T cells
- The small sample size limits sensitivity, but the trend indicates that BDC-1001 functions through immune activation





Next-Generation ISACs Designed For Stronger Activity Against Tumors With Lower Antigen Density

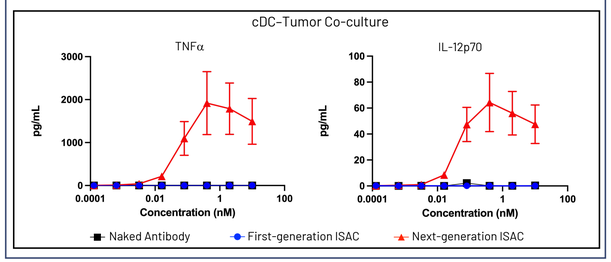
Immune-stimulating Payload
- Enhanced potency
- Tailored TLR specificity for key biology
- Optimized conjugation chemistry with non-cleavable linkers



Tumor-targeting Antibody
- Geo-locates ISAC to antigen on surface of a tumor cell
- Active Fc region triggers phagocytosis

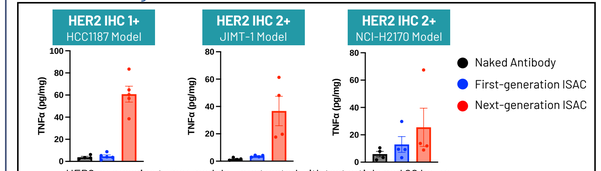
Next-Generation ISACs Show Enhanced Immune Activation *In Vitro* in Preclinical Models With Lower Antigen Levels

- *In vitro* activity of next-gen ISACs outperforms first-gen ISAC in cDC–tumor co-culture with low (IHC 1+) CLDN18.2 expressing PA-TU-8988S tumor cells
- Next-generation CLDN18.2 ISAC was tolerated in NHP at the highest dose evaluated

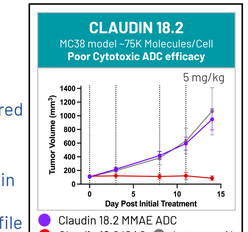


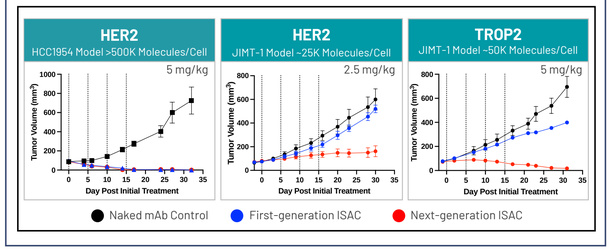
Next-Generation ISACs Outperform First-Generation ISACs and Cytotoxic ADC in Models With Lower Tumor Antigen Expression

- Next-generation ISAC produced greater levels of proinflammatory cytokines across all tumor models
- The advantage of the next-generation ISAC was particularly noticeable in lower-antigen tumor models



- Multiple tumor antigens with varying expression levels were evaluated with different ISACs
- Next-gen ISACs show greater tumor growth inhibition across models compared to first-gen ISACs and cytotoxic ADC
- For additional data, see Abstract #1052, Preclinical Activity of BDC-4182, a Claudin 18.2-Targeting ISAC with Enhanced Potency and an Encouraging Safety Profile





Summary

- First-generation ISAC BDC-1001 demonstrated immunological activity, particularly in patients with higher HER2 antigen expression
  - Stimulates the production of chemokines and cytokines that mobilize immune cells and promote immune cell activation
  - Recruits dendritic cells, macrophages and cytotoxic T cells to the tumor microenvironment
  - Activates gene expression pathways related to TLR signaling, innate immunity, antigen presentation, and IFN and T cell inflamed signatures
  - Trend of greater increases in patients achieving clinical benefit
- Next-generation ISACs have shown superior immunological activity and efficacy in tumors with lower antigen density in preclinical models
- These enhanced next-generation ISACs outperform ADCs in preclinical studies and merit clinical advancement to assess their potential in transforming cancer treatment paradigms

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