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

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Author Disclosures and Funding

Jason Ptacek is an employee of Bolt Biotherapeutics.

Nivolumab was provided by Bristol Myers Squibb.

This study is funded by Bolt Biotherapeutics (NCT 04278144).

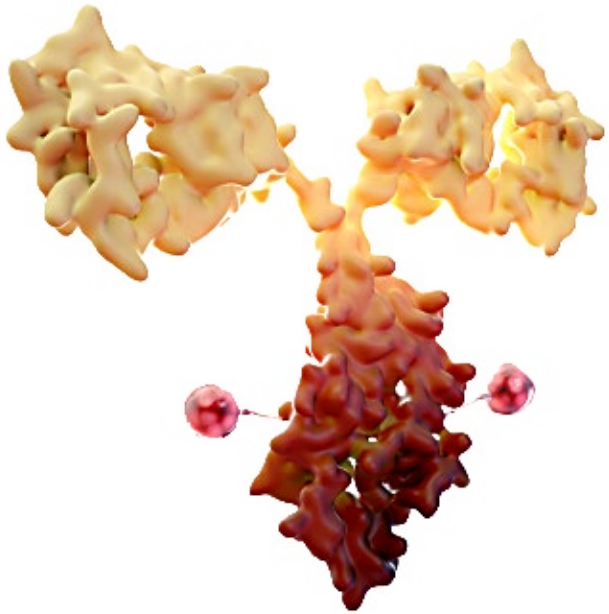
Boltbody™ Immune-Stimulating Antibody Conjugate (ISAC)

First-Generation ISAC

- Monoclonal antibody geo-locates ISAC to HER2 antigen on surface of a tumor cell
- Non-cleavable, cell-impermeable TLR7/8 agonist payload

Outcome in FIH Trial

- Evidence of immunological activity
- Safe and well-tolerated
- 29% ORR at RP2D (evaluable patients)



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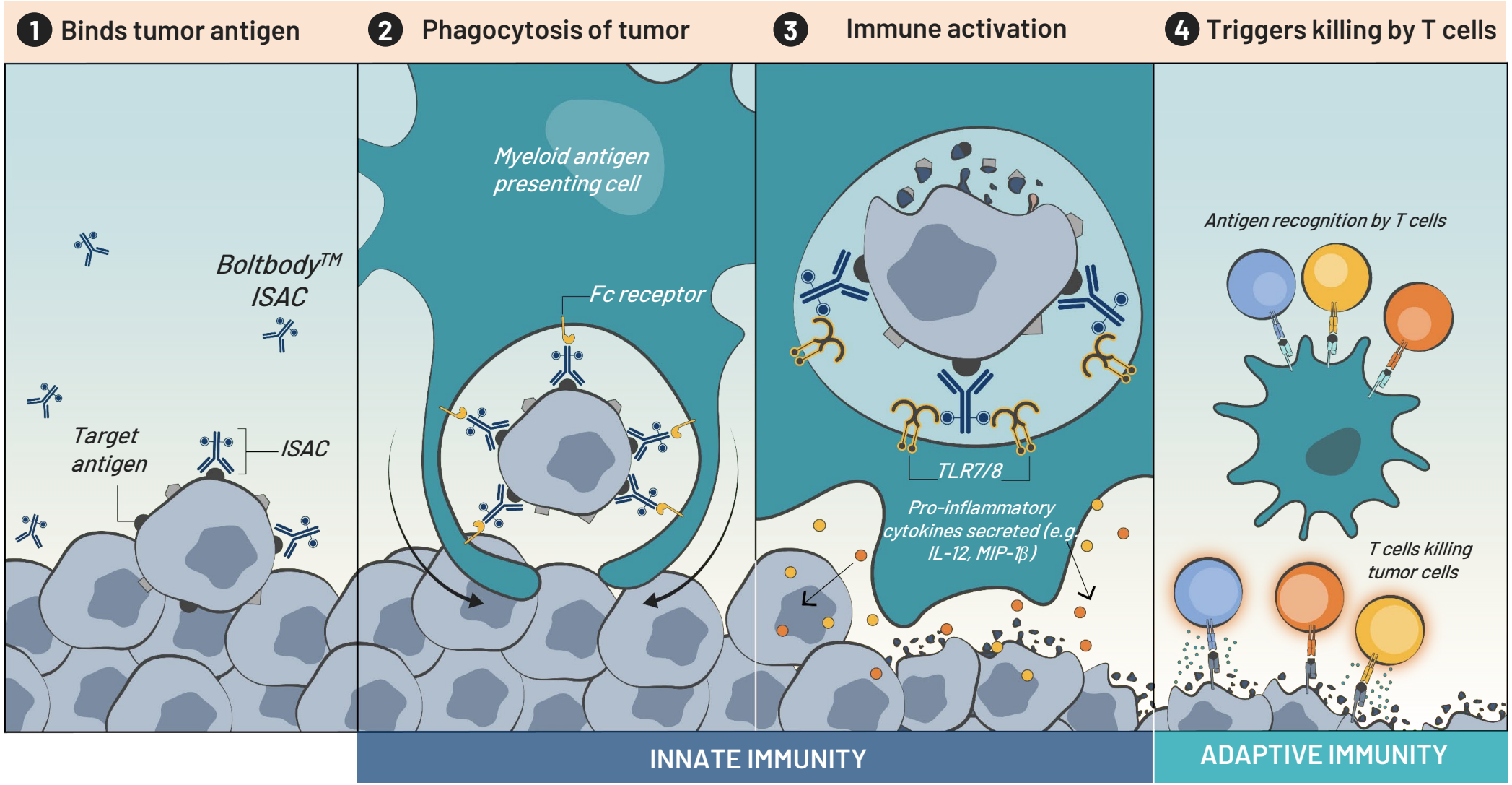


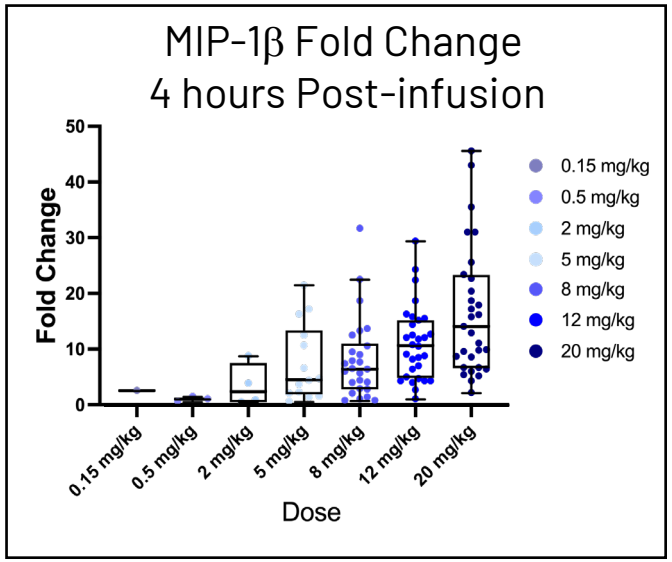
BBI-20201001 Trial Overview and Translational Questions

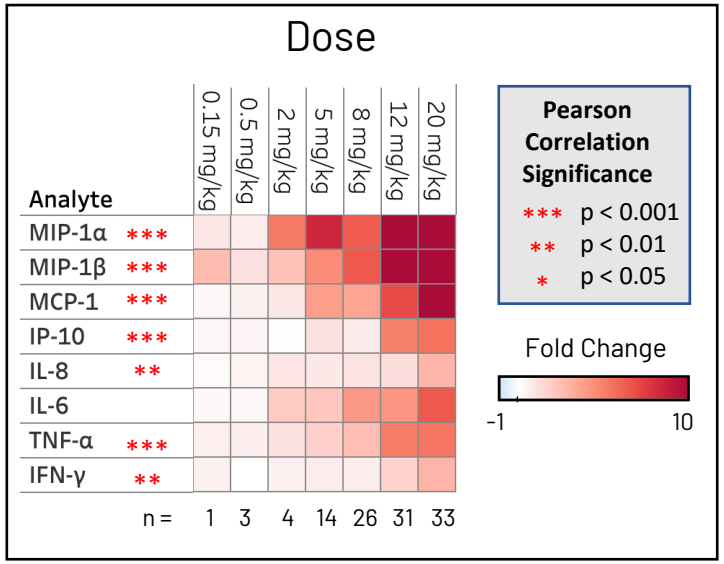
- Phase 1 dose escalation completed & RP2D selected[1]
  - 18 cohorts with 16 different HER2-expressing[2] solid tumor types
    - doses: 0.5 – 20 mg/kg IV; schedules: q3w, q2w, q1w
  - BDC-1001 well tolerated up to 20 mg/kg q1w as monotherapy and in combination with nivolumab at 240 mg q2w (no MTD identified)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

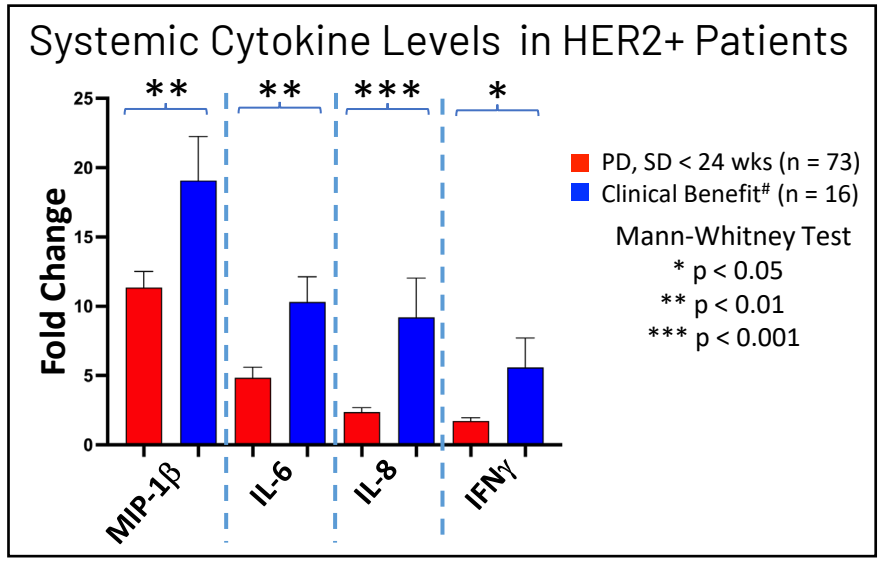
[1]Li B, et al. Ann Oncol. 2023;34(suppl_2):S458-S497 (ESMO, 2023)
[2]HER2-expressing: Either HER2+ (IHC 3+ or HER2 gene amplification) or HER2 Low (IHC 2+ without gene amplification)
RP2D = Recommended Phase 2 Dose, MTD = Maximum Tolerated Dose, IV = Intravenous

BDC-1001 Elicits Proinflammatory Cytokines, Associated With Clinical Benefit

- Fold change in biomarkers significantly correlated to dose
- Higher peripheral blood cytokine levels are associated with clinical benefit



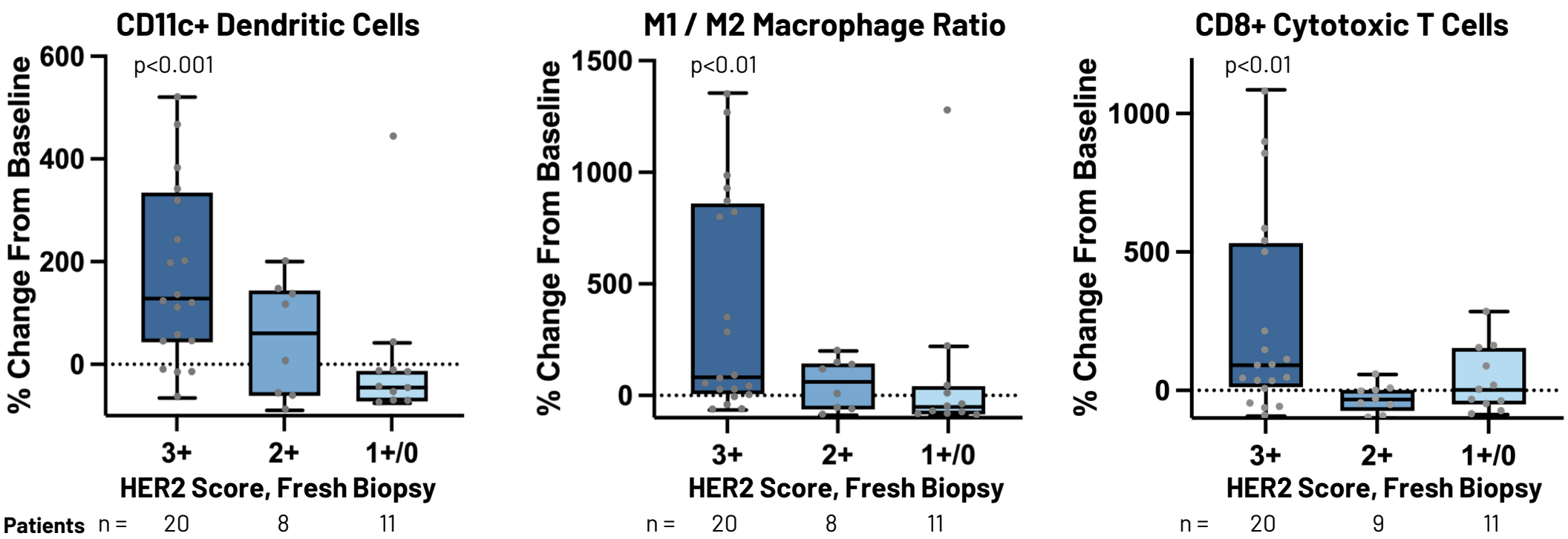




#Clinical benefit = CR, PR, or SD for ≥ 24 weeks
Patient population: HER2+ by enrollment status, doses 8 – 20 mg/kg, schedules q1w, q2w, q3w; 73 PD, SD < 24 wks patients comprised of 50 monotherapy and 23 combination; 16 clinical benefit patients comprised of 9 monotherapy and 7 combination

BDC-1001 Monotherapy Drives Immune Cell Infiltration in HER2 IHC 3+ Tumors

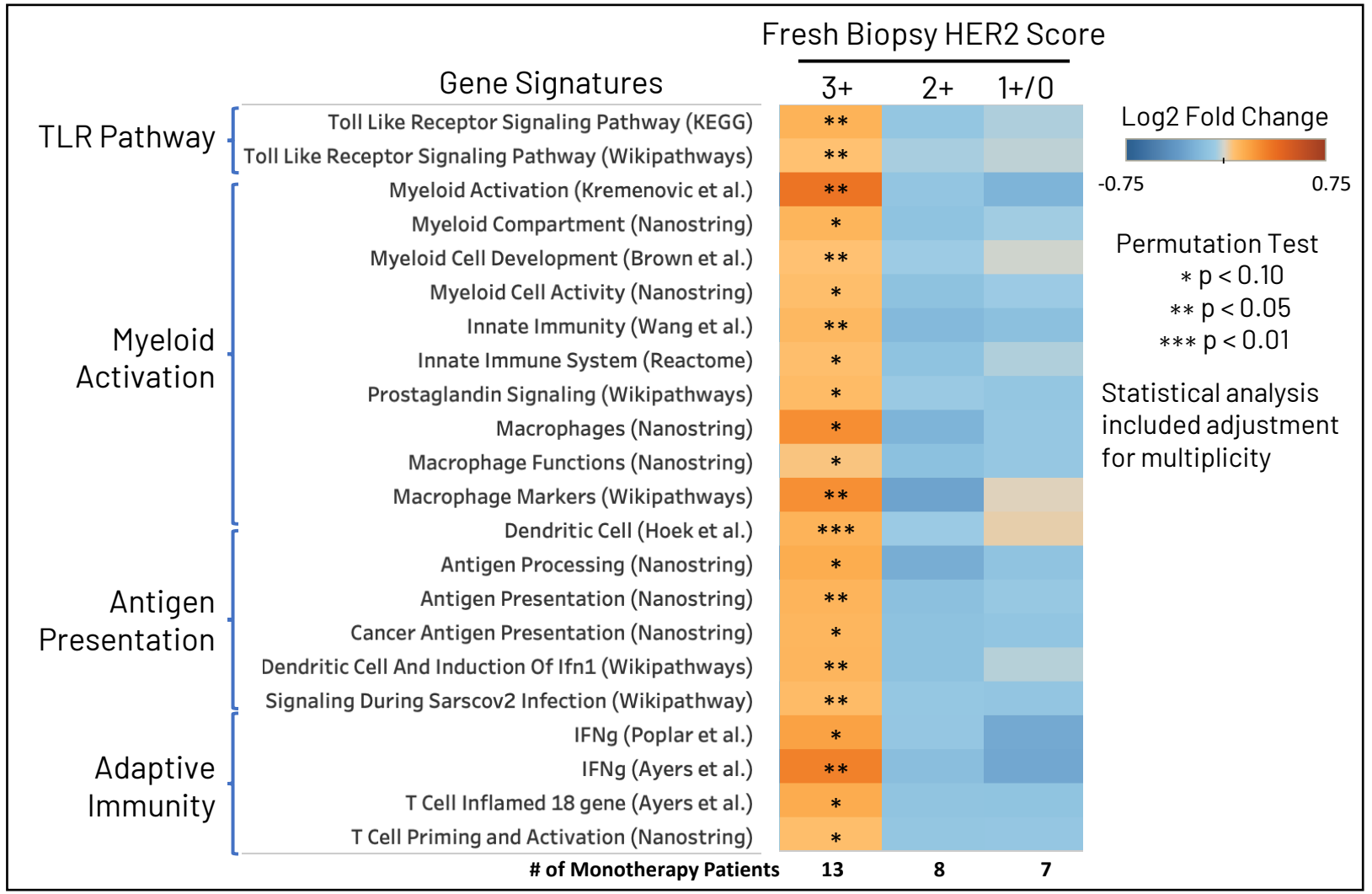
- BDC-1001 shows the potential to alter the tumor microenvironment
- These changes were statistically significant in HER2 IHC 3+ tumors only



Multiplex IHC assays were utilized to enumerate immune populations in baseline and on-treatment biopsies collected at 4 weeks after first dose
Analysis of blended monotherapy and combination data showed similar trends

BDC-1001 Monotherapy Drives Increased Immune Gene Signatures in HER2 IHC 3+ Tumors

- Transcriptomic analysis performed by RNAseq of baseline and on-treatment tumor biopsies
- Activation of TLR, innate and adaptive immunity pathways in on-treatment tumor biopsies
- Statistically significant activations in HER2 3+ tumors (n=13)



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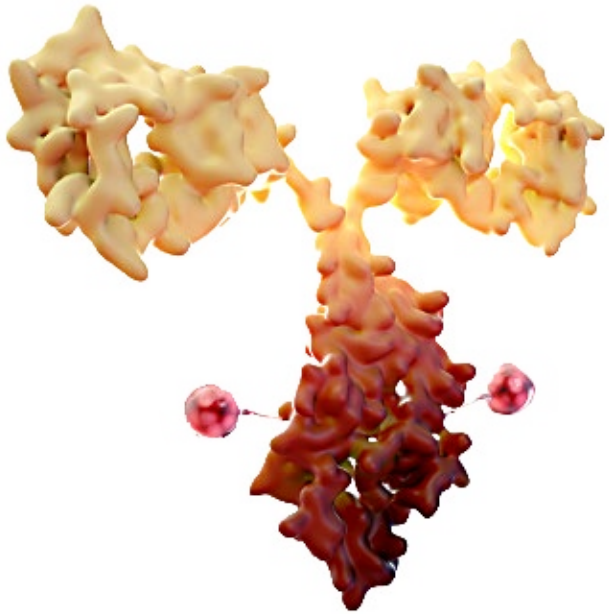

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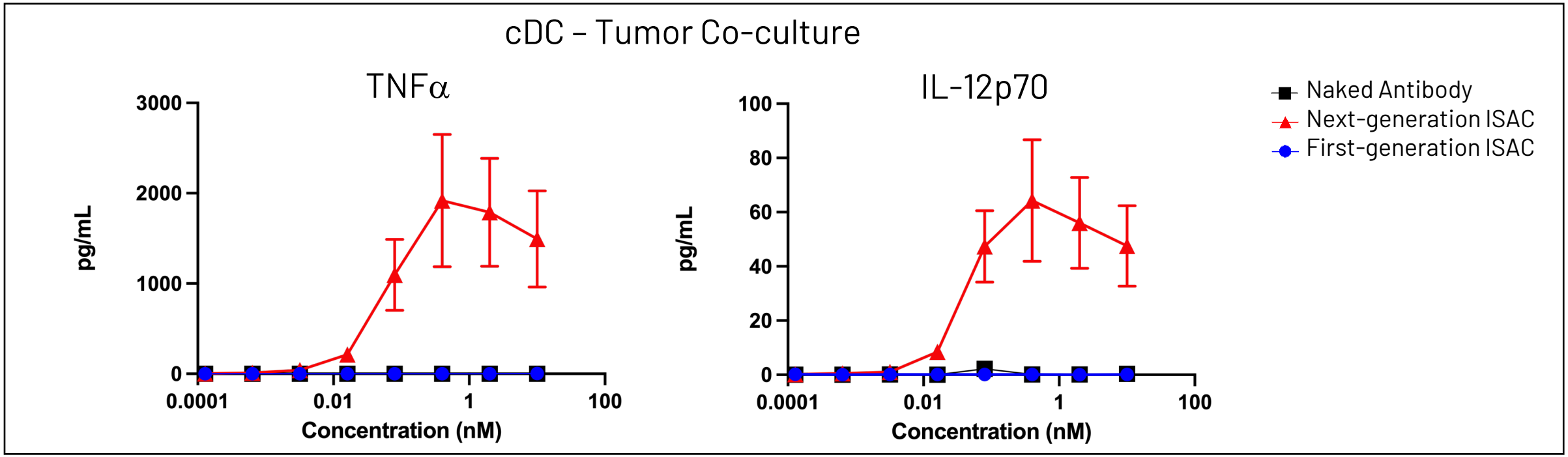
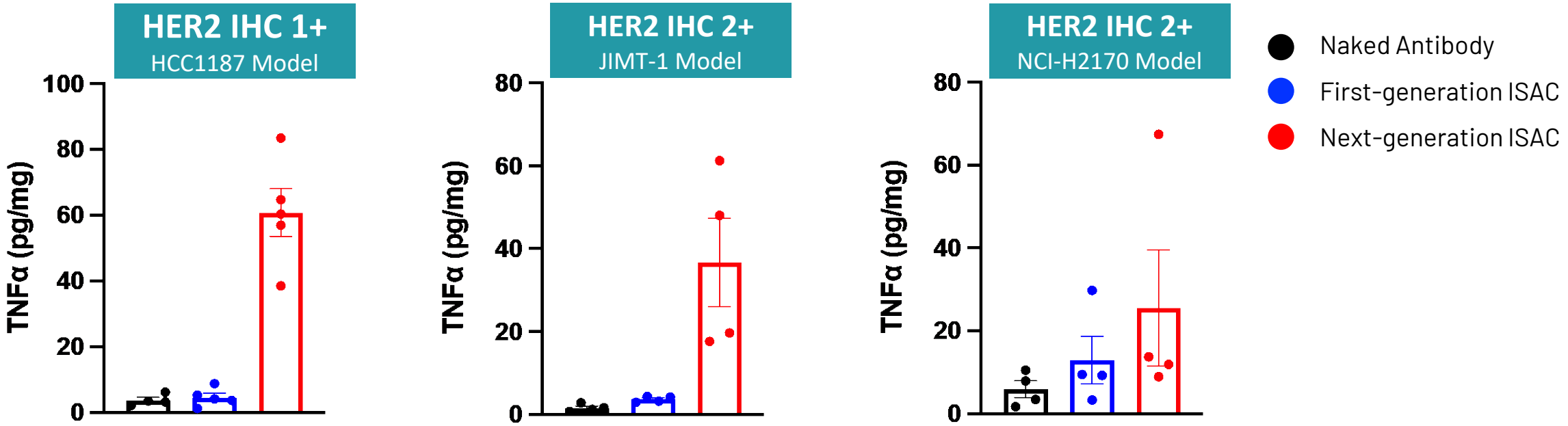
Next-Generation ISACs Show Enhanced Immune Activation *In Vitro* in Preclinical Models With Lower Antigen Levels

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



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

- 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

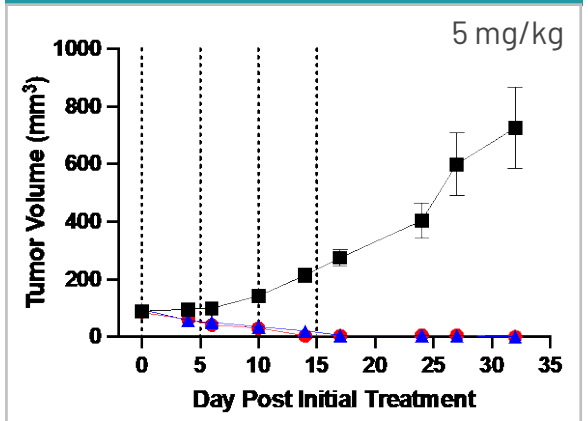


HER2-expressing tumor models were treated with test article and 20 hours post dose cytokine levels were quantified in tumor lysates

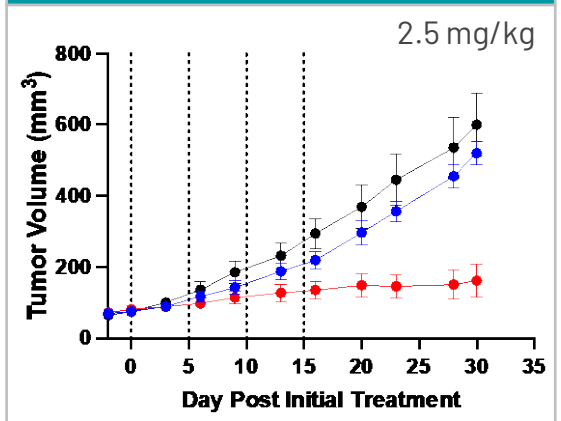
Next-Generation ISACs Outperform First-Generation ISACs and Cytotoxic ADC in Models With Lower Tumor Antigen Expression

- Multiple tumor antigens with varying expression levels were evaluated with different ISACs
- Next-generation ISACs show greater tumor growth inhibition across models compared to first-generation ISACs and cytotoxic ADC

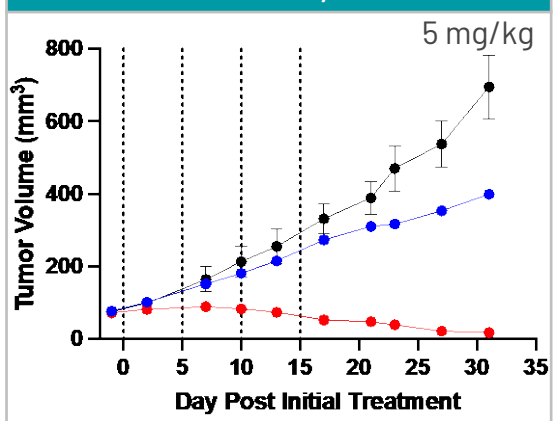
HER2
HCC1954 Model >500K Molecules/Cell



HER2
JIMT-1 Model ~25K Molecules/Cell

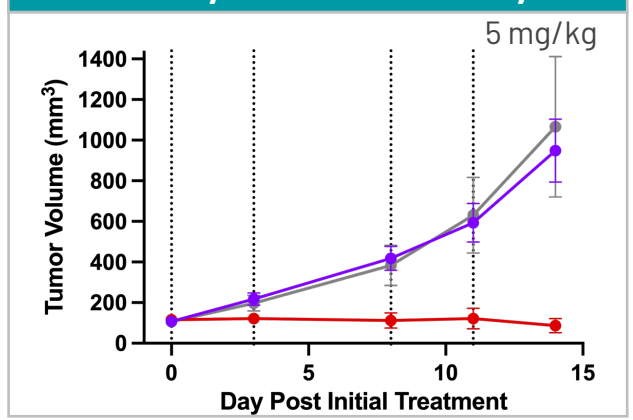


TROP2
JIMT-1 Model ~50K Molecules/Cell



Naked mAb Control First-generation ISAC Next-generation ISAC

CLAUDIN 18.2
MC38 model ~75K Molecules/Cell
Poor Cytotoxic ADC efficacy



Claudin 18.2 MMAE ADC
Claudin 18.2 ISAC Isotype mAb

Conclusions

- BDC-1001 drives immune activation, leading to anti-tumor activity
  - Stimulates the production of chemokines and cytokines, mobilizes immune cells and promote immune cell activation related to TLR signaling, innate immunity, antigen presentation, and IFN and T cell inflamed signatures
  - Pharmacodynamic changes were statistically significant in patients with HER2 IHC 3+ tumors and trended higher in patients achieving clinical benefit
- Next-generation ISACs have shown superior immunological activity and efficacy in tumors with lower antigen density in preclinical models[1]
- These enhanced next-generation ISACs outperform ADCs in preclinical studies and merit clinical advancement to assess their potential in transforming cancer treatment paradigms

[1] **SITC Abstract Number:** 1052 **Title**: Preclinical Activity of BDC-4182, a Claudin 18.2-Targeting ISAC with Enhanced Potency and an Encouraging Safety Profile

Thank You

The authors thank all participating patients and their families and all study co-investigators and research coordinators.