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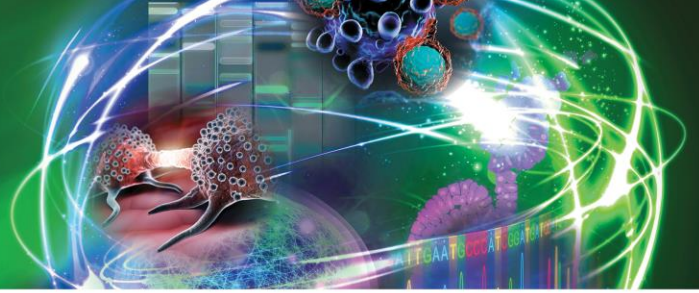

Targeting HER2 with Immune-Stimulating Antibody Conjugates (ISACs)

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Disclosure Information

David Dornan

I have the following financial relationships to disclose:

Stockholder in: Bolt Biotherapeutics, Inc.

Employee of: Bolt Biotherapeutics, Inc.

Consultant for: Teon Therapeutics, Inc.

I will discuss investigational use in my presentation: BDC-1001 in Advanced HER2-Expressing Solid Tumors

Tumor Microenvironment and Antigen Presenting Cells

TME-mediated Immunosuppression

- Various cells in the TME (Tregs, MDSCs, M2s, CAFs etc.) limit a robust anti-tumor immune response by producing immunosuppressive cytokines such as:
  - PGE2 – suppresses M1 cytokine secretion and recruits MDSCs
  - IL10 – Inhibits MHCII expression and M1 cytokine secretion
  - TGFβ – Inhibits T cell priming and infiltration

Ineffective Antigen Presenting Cells

- Antigen presenting cells in the tumor microenvironment are often tumor-supportive rather than tumor-destructive

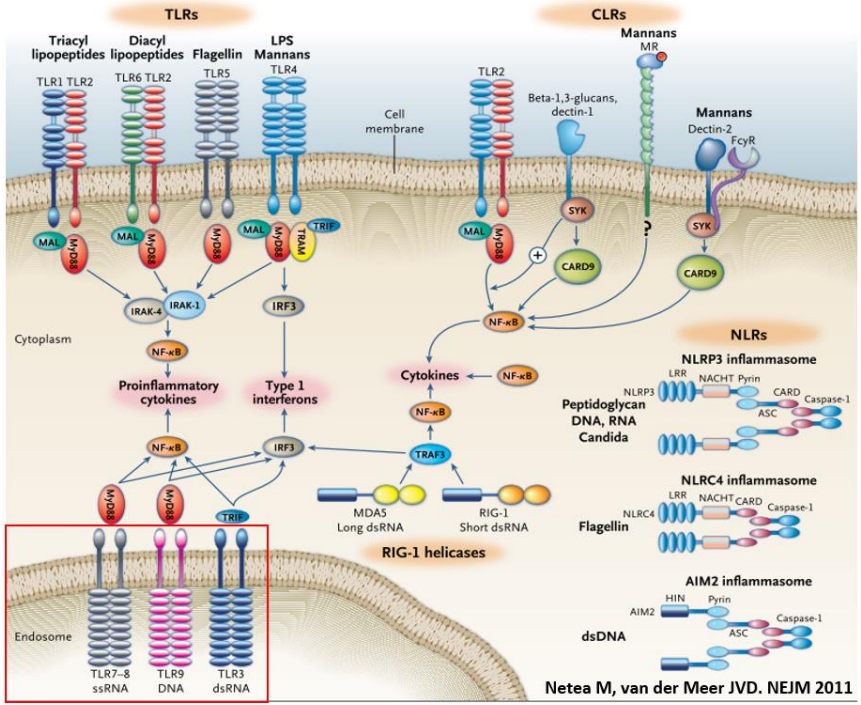
Therapeutic Hypothesis

- Reawakening immunosuppressed APCs may result in a productive and durable anti-tumor immune response

Key Experimental Observation

- Co-treatment of tumor-targeting mAbs and APC immune stimulation (CD40 + TNF) was required to eradicate tumors from mice (Carmi et al. *Nature* 2015)

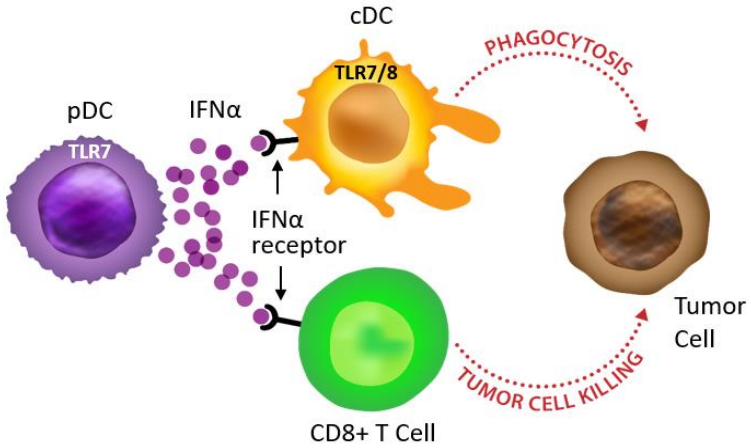
Pattern Recognition Receptors Play Key Roles in the Activation of the Innate Immune Response



- PRR agonists (e.g., TLR7/8/9, STING, and NLRP3) create an immune microenvironment poised for an anti-tumor immune response
  - Enhanced antigen presentation for T cell-mediated killing
  - Reducing function of immunosuppressive cells (Treg, M2, MDSC)
  - Activation of innate cell-mediate tumor killing (NK, M1)
- PRR agonists therapies are largely restricted to intratumoral administration due to systemic toxicity

Dual TLR7 & TLR8 Agonism Optimizes for Productive Anti-tumor Immune Response

TLR7/8 dual agonist provides an amplification of the immune response



Cell Type \ TLR	TLR7 Expression	TLR8 Expression	mTLR7 Expression
Monocyte	Yes	Yes	Yes
Macrophage	Yes	Yes	Yes
cDC	Yes	Yes	Yes
pDC	Yes	No	Yes

- TLR7 agonism activates pDCs, TLR7 and/or TLR8 agonism activate cDCs
- IFNα contributes to activation/maturation cDCs and CD8 survival
- Activated cDCs and pDCs produce cytokines and chemokines to convert “cold” to “warm” tumor microenvironment
- Dual TLR7 and TLR8 agonism provides an optimal opportunity to induce a productive anti-tumor immune response
- Potential translatability of mouse to human biology could be increased by selecting a dual TLR7/8 agonist
  - Immune cell types: mTLR7 expression = hTLR7 + hTLR8 expression

Boltbody ISAC Mechanism of Action

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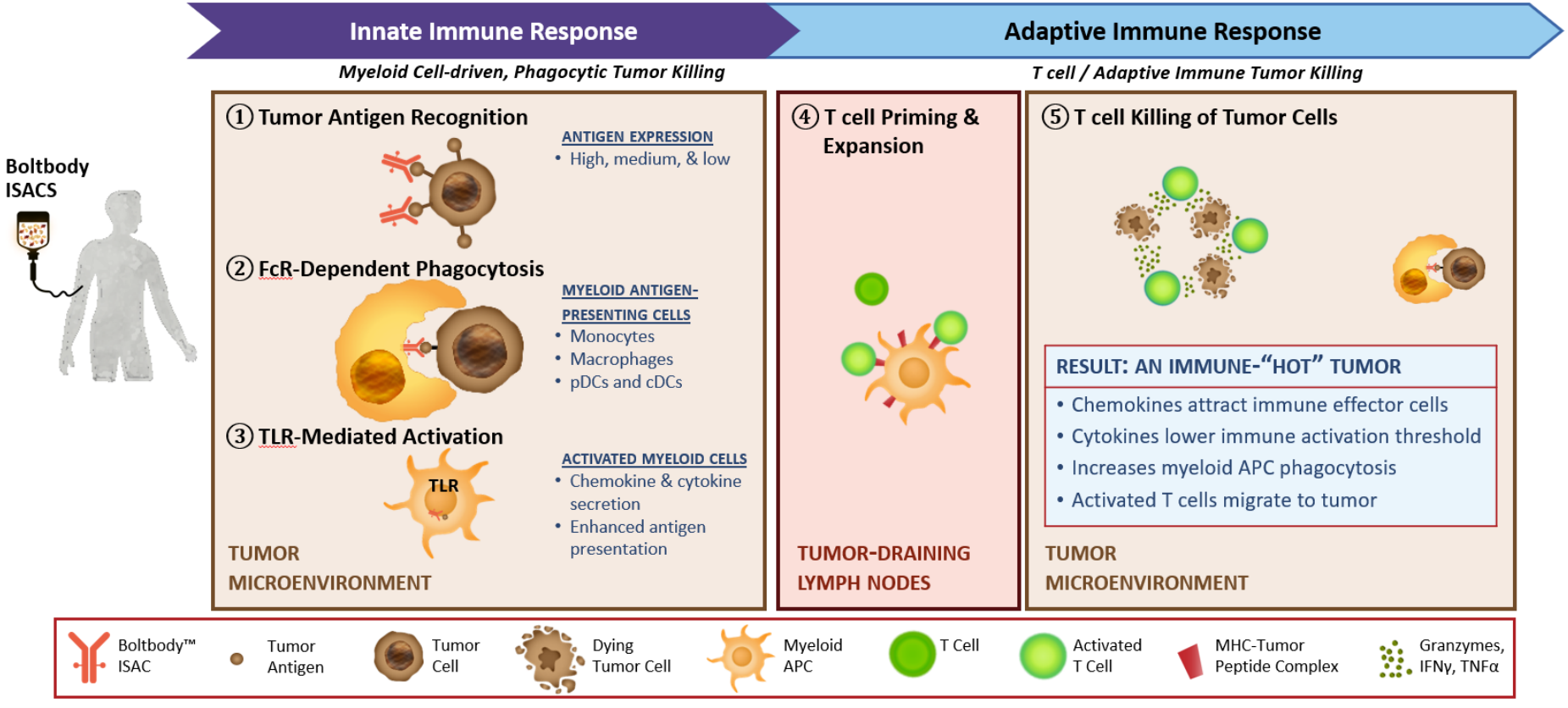
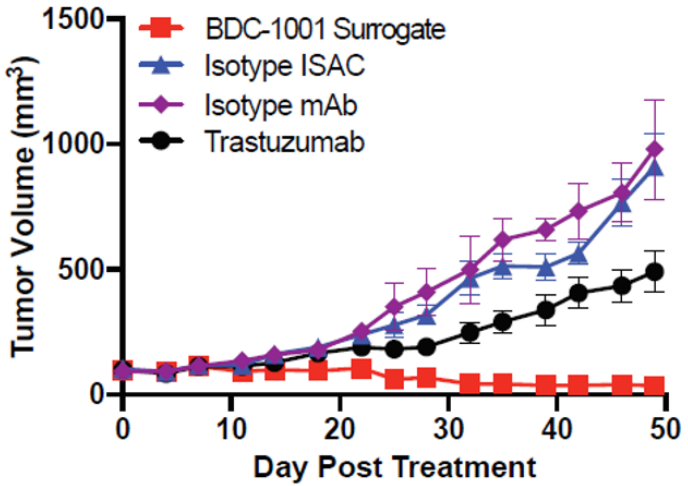


ISACs Require Tumor Antigen Recognition, FcR engagement, and TLR Agonism

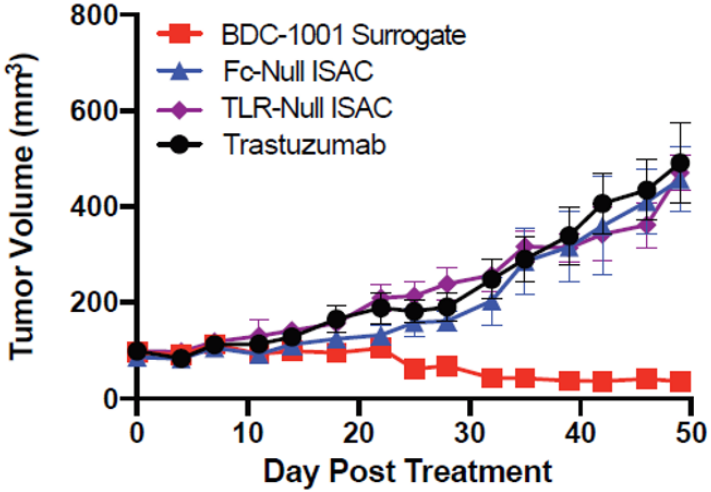
Activity dependent on
1) Tumor antigen recognition

Mice implanted with HER2-expressing HCC1954 cell line



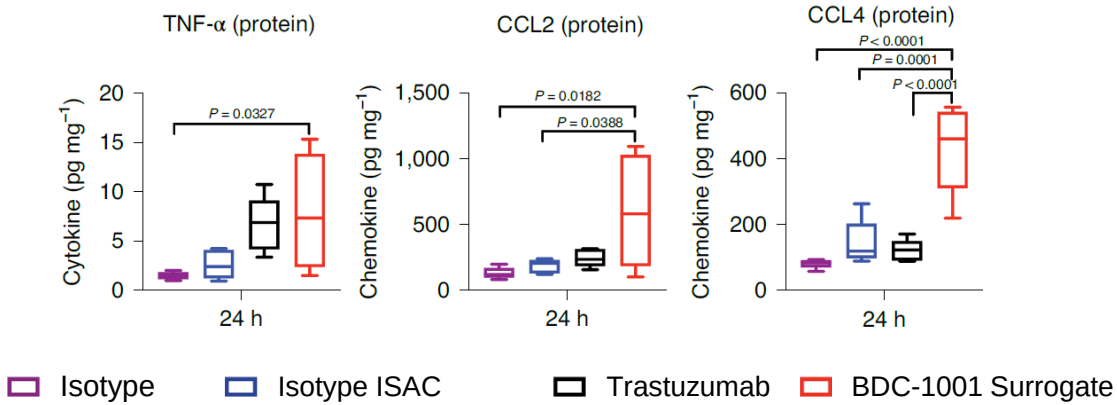
Activity dependent on both
2) FcR engagement & 3) TLR agonism

Mice implanted with HER2-expressing HCC1954 cell line

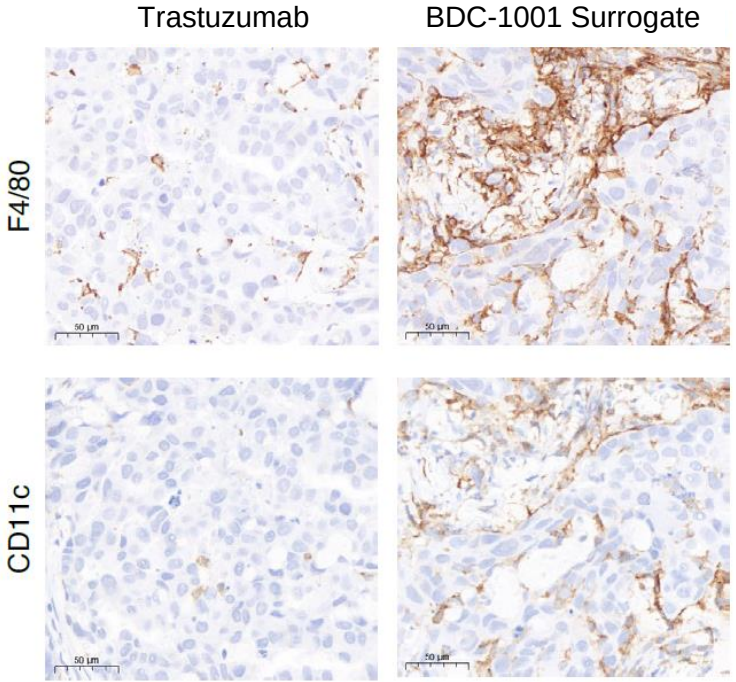


HCC1954, 5 mg/kg, q5d x 6

BDC-1001 Surrogate Enhances Secretion of Cytokines, Chemokines, and Recruitment of Myeloid Cells in the TME

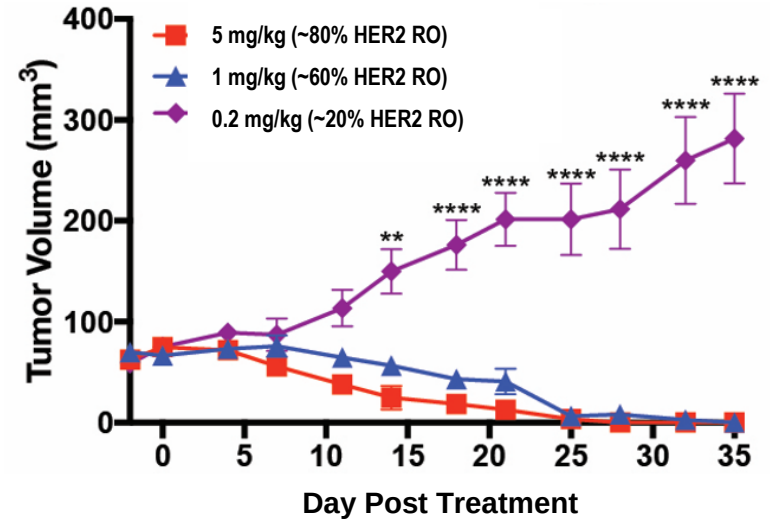


HCC1954, 5 mg/kg, 24 hours post-Tx



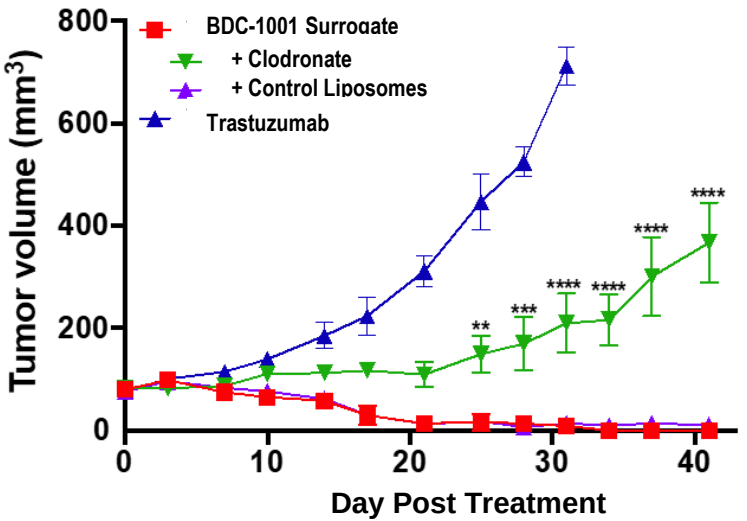
HCC1954, 9 days post-Tx

BDC-1001 Surrogate Efficacy Requirements



Requirement for ~60% HER2 RO

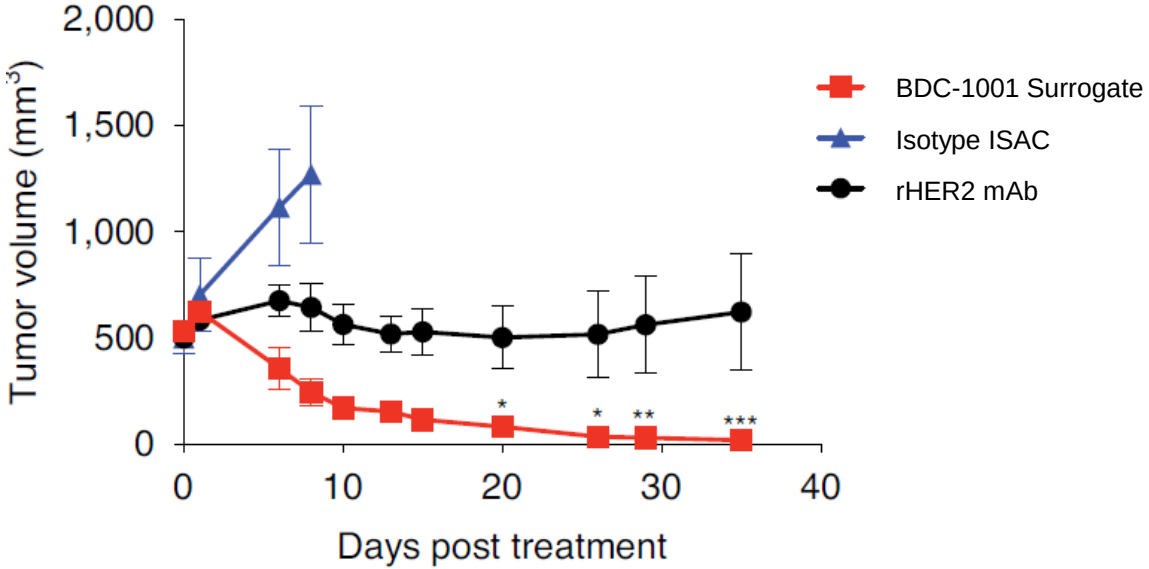
HCC1954, Tx 5 mg/kg, q5d x 6



Requirement for Phagocytes

HCC1954, Tx 5 mg/kg, q5d x 3

Tumor Elimination in Large, Immunologically Cold & Well-Established Tumors



MMC syngeneic, Tx 5 mg/kg, q5d x2

BDC-1001 Surrogate Enhances Secretion of Cytokines, Chemokines, as well as Recruitment of Myeloid and CD8 Cells in TME

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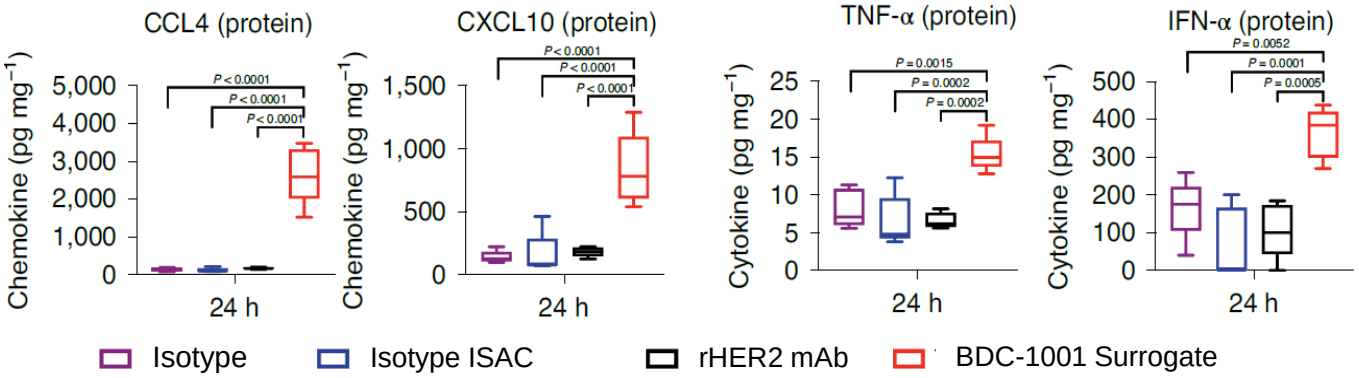
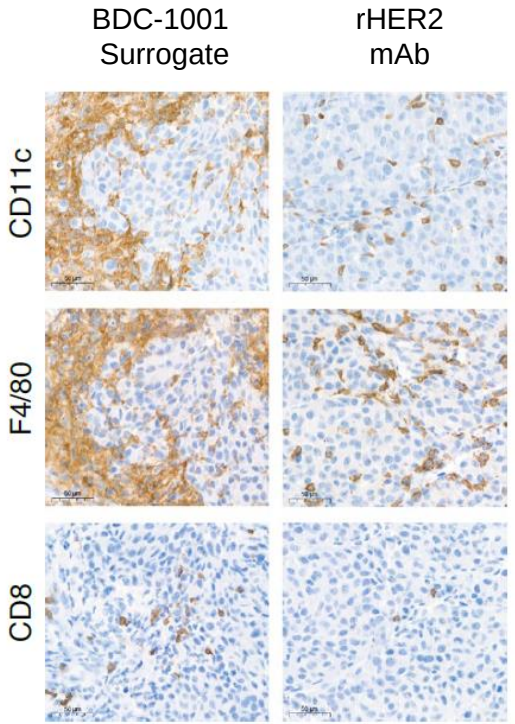


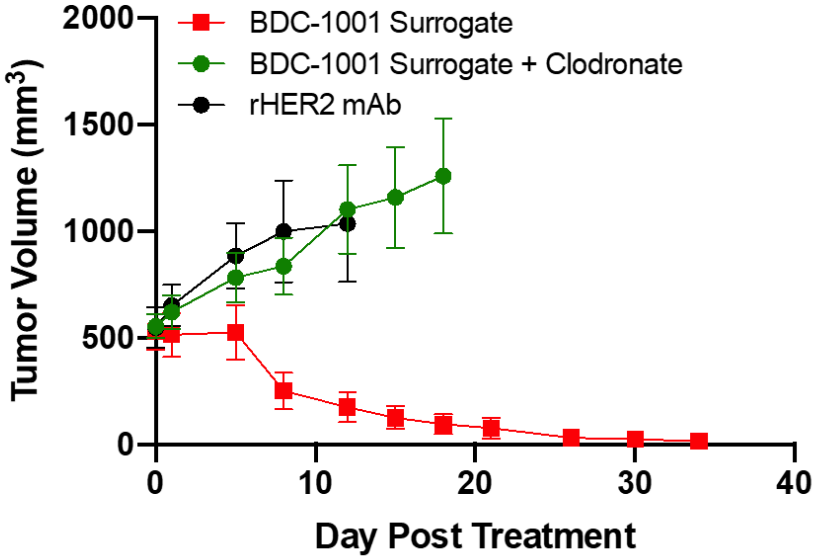
MMC syngeneic, Tx 5 mg/kg



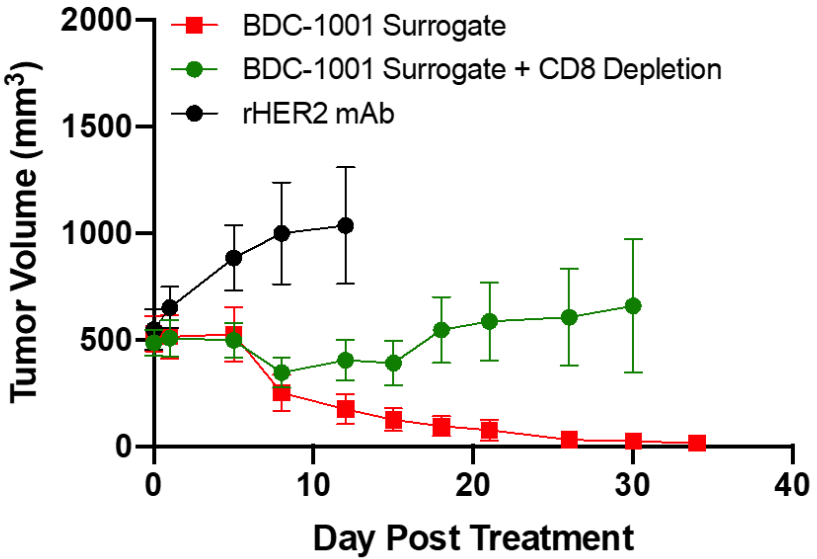
MMC syngeneic, 6 days post-Tx

Requirement for Phagocytes and CD8 T cells for Maximal ISAC Efficacy

Innate Immunity
Phagocytosis-Driven Tumor Killing

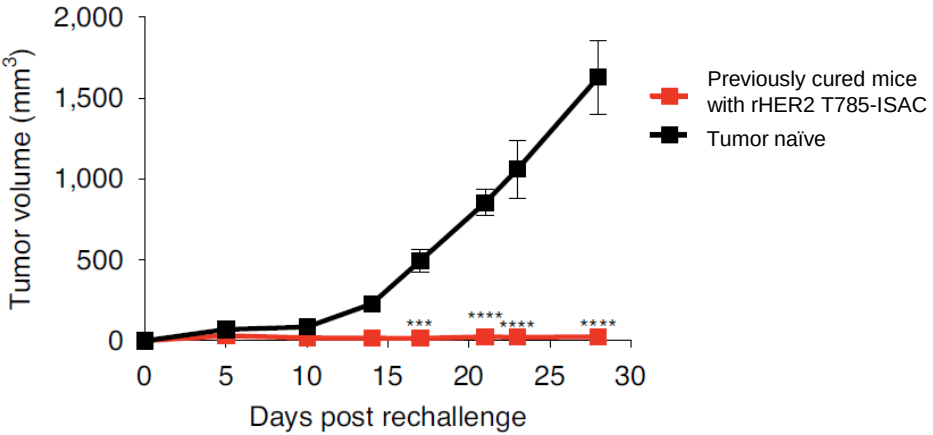


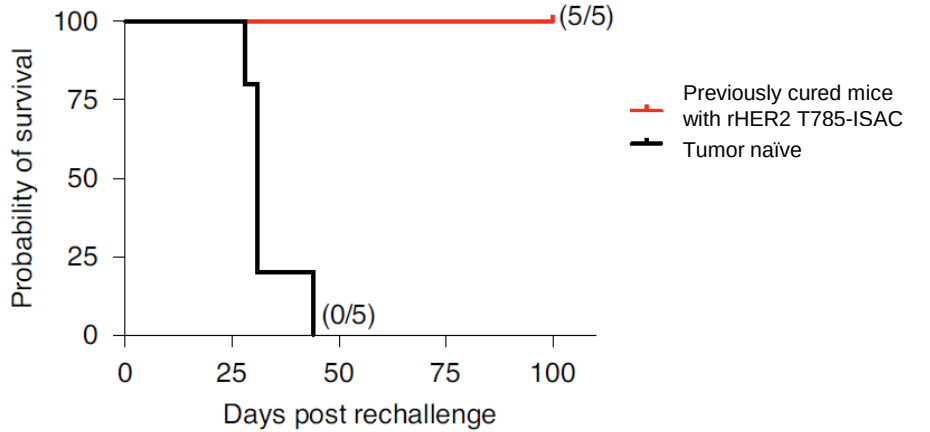
Adaptive Immunity
CD8 T Cell-Driven Tumor Killing



MMC syngeneic, Tx 5 mg/kg, q5d x 2

BDC-1001 Surrogate MMC Mice that are Cured by Tx are Resistant to Rechallenge





BDC-1001 surrogate-treated mice that experienced complete tumor regression for >90 d after their last treatment were rechallenged with the MMC tumor cell line (n=5)

BDC-1001 – Ongoing Phase 1/2 Schema in Advance HER2-Expressing Solid Tumors

ClinicalTrials.gov Identifier: NCT04278144

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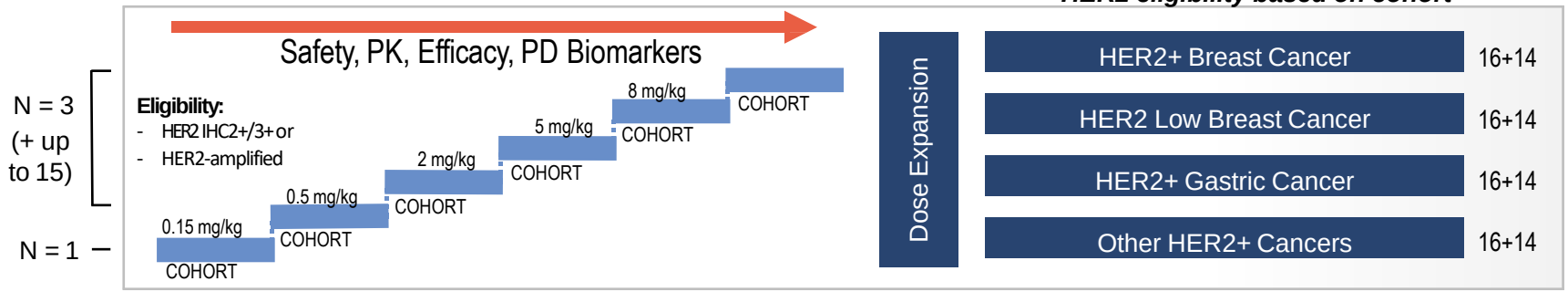
Phase 1/2 Monotherapy Trial Schema: Parts 1 and 3



HER2 eligibility based on cohort

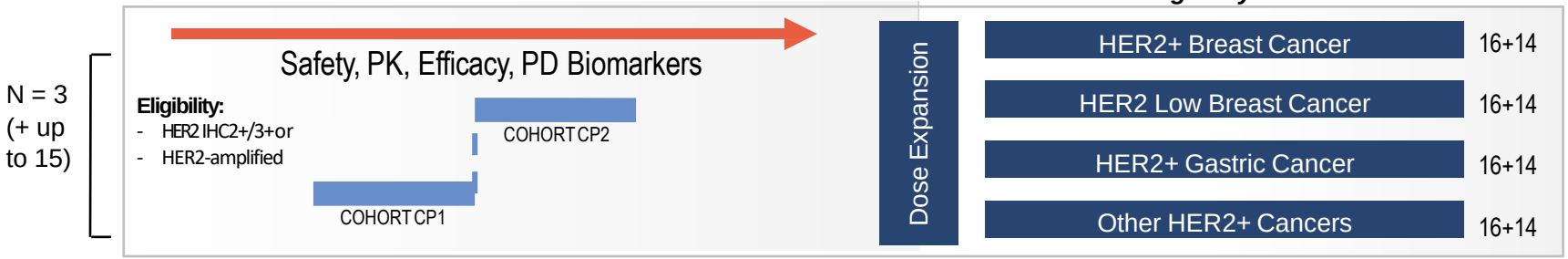
Endpoints:

- **Primary:** Safety, MTD, Dose Selection
- **Secondary:** PK, preliminary anti-tumor activity
- Expl. Biomarkers: Proof of Mechanism

Endpoints:

- **Primary:** Anti-tumor activity
- **Secondary:** Safety and tolerability of BDC-1001, PK and immunogenicity of BDC-1001
- Expl. Biomarkers: Proof of Mechanism

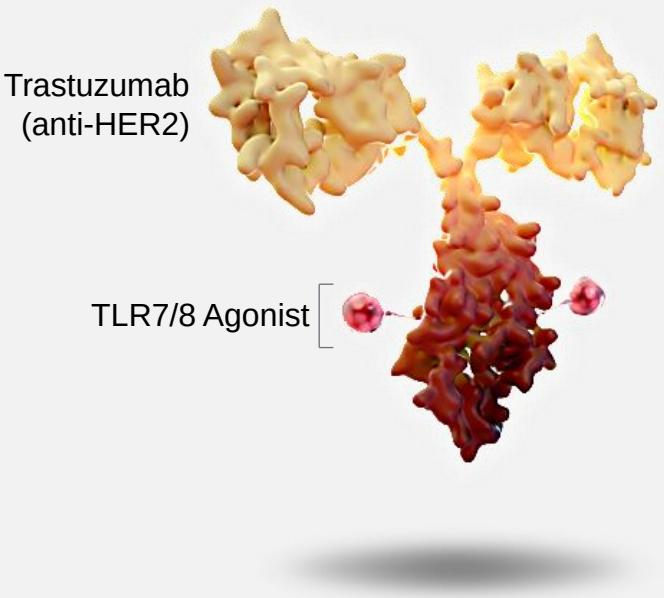
Combination Therapy with Checkpoint Inhibitor (CPI): Parts 2 and 4



HER2 eligibility based on cohort

Generating Proof of Mechanism for the ISAC Approach

BDC-1001



Trastuzumab (anti-HER2) biosimilar conjugated to proprietary TLR7/8 agonist via a non-cleavable linker

Preclinical Proof of Mechanism:

- "Three-Factor Authentication" for localized immune response and safety
- Engagement of both innate and adaptive immunity
- Elimination of established / treatment-resistant tumors

No Adverse Findings in GLP NHP Toxicology Study at Highest Dose

Status: Phase 1/2 trial dose escalation, well tolerated, PD biomarkers consistent with MOA, and signs of stable disease & tumor volume reduction

Expected Upcoming Milestones:

- Complete monotherapy dose escalation
- Initiate monotherapy Phase 2 dose expansions
- Initiate combination trial with anti-PD-1