The combination of a trastuzumab ISAC and pertuzumab augments anti-tumor efficacy in multiple HER2+ tumor models relative to trastuzumab plus pertuzumab

Immune-Stimulating Antibody Conjugates
- Immunostimulating antibody conjugates (ISACs) are comprised of immune stimulants conjugated to tumor-targeting antibodies.
- Trastuzumab-T785 ISAC, referred to as BDC-1001.S, is a murine surrogate of trastuzumab-HER2 targeting ISAC currently under evaluation in multiple Phase 2 studies. Trastuzumab-T785 is a toxoids of trastuzumab conjugated to a TLR7/8 agonist with a non-degradable linker.
- Combination of trastuzumab, pertuzumab, and chemotherapy is the current standard of care for patients with HER2+ breast cancers.
- Multiple mechanisms of action govern the activity of these two antibodies:  
  - Direct binding to HER2 inhibits HER2 dimerization with HER3/EGFR
  - Activation of the complement cascade induces ADCC
  - Pertuzumab inhibits HER2 dimerization with HER3/EGFR
  - Inhibits survival signals
- Multiple mechanisms of action govern the activity of the combination of pertuzumab and BDC-1001.S:  
  - Addition of pertuzumab to BDC-1001.S and combination of both with chemotherapy could enhance anti-tumor efficacy by increasing Fc clustering and promoting phagocytosis.

**METHODS**

**Experimental Design: Efficacy of BDC-1001.S and Pertuzumab Combination**
- Test Articles with Dose Levels
  - BDC-1001.S
  - Pertuzumab

**RESULTS**

**Combination of BDC-1001.S and Pertuzumab Enhances In Vivo Anti-Tumor Efficacy**
- BDC-1001.S + Pertuzumab
- Trastuzumab + Pertuzumab

**Phagocytes Mediate Enhanced Efficacy in BDC-1001.S + Pertuzumab Combination**
- BDC-1001.S + Pertuzumab
- Trastuzumab + Pertuzumab

**Pertuzumab Fc-Effector Function is Required for Enhanced Anti-Tumor Activity in Combination with BDC-1001.S**

**BDC-1001.S and Pertuzumab Combination Enhances Cytokine Secretion in Tumor**
- Innate Immune Activation

**BDC-1001.S and Pertuzumab Combination Enhances Chemokine Secretion in Tumor**
- Myeloid Recruitment

**CONCLUSIONS**
- Combination of BDC-1001.S and pertuzumab significantly enhances anti-tumor efficacy in multiple HER2+ expressing tumor models.
- Addition of pertuzumab provides an additional source of “eat me” signals that likely enhances antibody-dependent cellular phagocytosis.
- Anti-tumor efficacy was dependent on antibody-dependent cellular phagocytosis or depletion of phagocytes or the use of a pertuzumab variant lacking Fc effector function reduced efficacy.
- This combination is being assessed in a multi-national, randomized Phase 2 clinical trial with BDC-1001 and pertuzumab in patients with HER2+ breast cancer (NCT039554143) who have received prior treatment with Enbrelte.