Phase II biomarker study of BND-22 in combination with cemiplimab in patients with cholangiocarcinoma

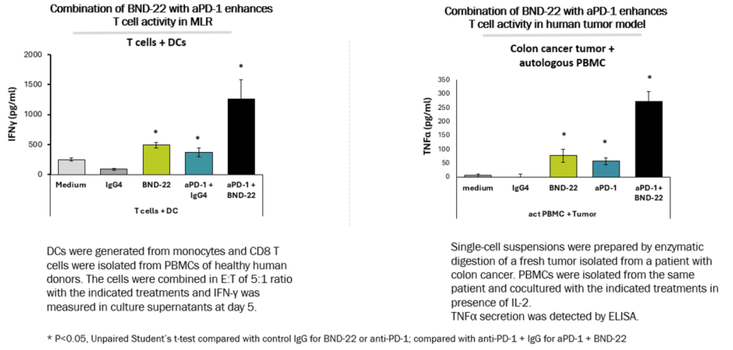
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Abstract # 515

BACKGROUND

- The immune checkpoint landscape continues to expand beyond PD-1/PD-L1
- Inhibitory receptors such as immunoglobulin-like transcript-2 (ILT2) are emerging as promising therapeutic targets
- ITL2 is expressed on immune cells, including monocytes, dendritic cells, NK cells, and a subset of T-cells (1)
- ILT2 exerts its immunosuppressive effects primarily through binding MHC class-I molecules, with high affinity for HLA-G, which is frequently overexpressed in solid tumors (2, 3)
- Engagement of the HLA-G/ITL2 axis suppresses a broad spectrum of immune functions, including cytotoxicity, cytokine production, antigen presentation, phagocytosis and proliferation (2, 4)
- ILT2 expression has been increased following anti-PD-1 therapy (4), identifying it as a potential mediator of resistance to checkpoint blockade and a compelling target for combination immunotherapy strategies
- BND-22 is a first-in-class humanized IgG4 mAb that selectively targets ILT2 on NK/T cells, and macrophages, disrupting its interaction with HLA-G (4)
- Preclinical studies (Fig 1) (4) and a phase I trial (5, 6) demonstrated that BND-22 as a monotherapy and in combination with a PD-1 inhibitor (NCT04717375) enhanced anti-tumor activity, with evidence of dose-dependent immune activation



DCs were generated from monocytes and CD8 T cells were isolated from PBMCs of healthy human donors. The cells were combined in E:T of 5:1 ratio with the indicated treatments and IFN-γ was measured in culture supernatants at day 5.

Single-cell suspensions were prepared by enzymatic digestion of a fresh tumor isolated from a patient with colon cancer. PBMCs were isolated from the same patient and cocultured with the indicated treatments in presence of IL-2.
TNFα secretion was detected by ELISA.

* P<0.05, Unpaired Student's t-test compared with control IgG for BND-22 or anti-PD-1; compared with anti-PD-1 + IgG for aPD-1 + BND-22

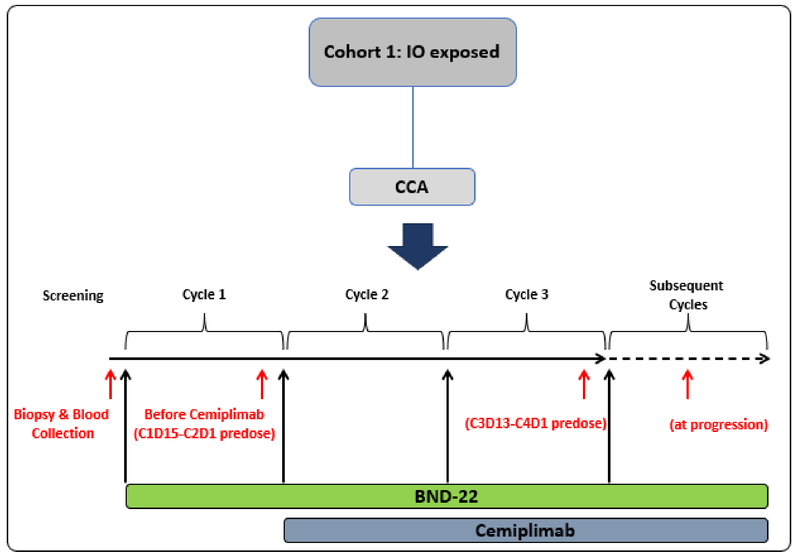
Fig. 1. BND-22 enhances anti-tumor functions of anti-PD-1 antibodies in a primary human T cell-based mixed lymphocyte reaction (MLR) assay

- In the Phase I/II dose-escalation and expansion study (5, 6), BND-22 was evaluated as a monotherapy (0.1–20 mg/kg) and in combination with pembrolizumab (1–20 mg/kg) or cetuximab (1–20 mg/kg)
- Across these evaluated cohorts, the antibody demonstrated a highly favorable safety and tolerability profile, yielding no dose-limiting toxicities (DLTs)
- Established a recommended dose of 10 mg/kg
- Antitumor activity was particularly notable in historically refractory populations, including patients with MSS CRC and cholangiocarcinoma, some of whom presented with liver metastases or prior resistance to cetuximab
- This clinical benefit was supported by pharmacodynamic data showing dose-dependent activation of circulating ILT2-expressing T cells, NK cells, and monocytes
- Building on these findings, we initiated a phase II biomarker study (NCT06651593) of BND-22 in combination with cemiplimab

METHODS

- The patient population in Cohort 1 will comprise patients with Cholangiocarcinoma who have had prior IO therapy.
- Initially 10 patients will be enrolled
- Based on emerging data, there is a potential for expansion to 10 additional patients
- The dose of BND-22 is 10 mg/kg IV on Day 1 every 3 weeks (Q3W), based on the dose escalation trial (NCT04717375). The dose of cemiplimab is the FDA-approved dose of 350 mg IV on Day 1 Q3W, starting at C2D1. Each cycle=21 days.
- The combination will be administered for a max of 24 months in the absence of progression or until progression, unacceptable toxicity, death, withdrawal of consent, or discontinuation.
- Biopsy tissues and peripheral blood samples for biomarker analyses will be collected at baseline, on treatment, and at progression (for patients with CR, PR, or SD≥6 months).

Study Design



Study Objectives

- **Primary objectives**:
  - Identify biomarkers related to mechanism of action and predictors of response, resistance, and survival
  - Evaluate the association between the biomarkers and outcomes.
- **Secondary objectives**:
  - Evaluate efficacy, safety, and tolerability of this combination
  - Identify imaging characteristics predictive of response and toxicity
  - Evaluate TCR beta variable polymorphism and its relationship with immune-related adverse events.

Enrollment is ongoing

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