

Ethics Approval The study protocols for clinical trials represented in this publication were reviewed by the respective IRB/IEC at each study site and approved before trial participants were screened and enrolled.

Consent Not applicable.

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324 BDB001, A TOLL-LIKE RECEPTOR 7 AND 8 (TLR7/8) AGONIST, CAN BE SAFELY ADMINISTERED INTRAVENOUSLY AND SHOWS CLINICAL RESPONSES IN ADVANCED SOLID TUMORS

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Background TLR agonists mediate antitumor activity through dendritic cell (DC) activation. Most TLR agonists in development are administered intratumorally allowing for less than 30% of advanced solid tumor to be treated. BDB001 is an intravenously administered novel TLR7/8 agonist that activates plasmacytoid and myeloid DCs and has shown to have activity in preclinical studies. Here we report on BDB001 administration in patients with advanced solid tumors.

Methods BDB001-101 is a Phase 1, open label, dose escalation/expansion trial of BDB001 administered intravenously weekly in patients with advanced solid tumors. The primary endpoint was safety and tolerability. Secondary endpoints included efficacy, pharmacokinetics and pharmacodynamic profiling of immune activation.

Results Thirty-six subjects with 16 different tumor types were enrolled across 5 dose levels. Sixty seven percent were female, median age was 66 years (range, 38–88), median number of prior therapies was 4 (range, 0–12), and 61% of tumors had progressed on prior anti-PD-(L)1 therapy. BDB001 was well tolerated and a maximum tolerated dose was not reached. Eleven (30.5%) subjects had no treatment related adverse events (AEs) and the majority of AEs were Grade 1 or 2. Three (8.3%) subjects had Grade 3 AEs, including 2 with a cytokine release syndrome, both of whom were clinically stable and had symptoms fully resolved within 2 to 5 days. There were no Grade 4 or 5 AEs. The most common AEs included chills/rigor (19.4%), fever (19.4%), fatigue (11.1%), nausea (11.1%) and pruritus (11.1%). Of 32 subjects evaluable for efficacy, best overall response rate was: 6% durable partial response, 56% stable disease, 38% progressive disease, for a disease control rate of 62%. Durable responses were seen in renal cell carcinoma and non-small cell lung cancer. Interestingly, clinical activity favored subjects with tumors that had progressed on prior anti-PD-(L)1 therapy, compared to prior DNA-damaging chemotherapy, within 6 months of BDB001 initiation. Median time on treatment was 12.1 weeks (range, 3.1 – 68.0). Transcriptional profiling showed up-regulation of interferon inducible genes, activation of dendritic cells and macrophages. BDB001 also significantly increased serum levels of interferon gamma and interferon inducible protein-10 (IP-10).

Conclusions Intravenously administered BDB001 monotherapy was well tolerated. Clinical responses were achieved, supported by BDB001-induced immune activation. Preliminary findings suggest that BDB001 is a promising therapeutic

option for patients with tumors that progress on anti-PD-(L)1 therapy. BDB001 is also being evaluated in combination with pembrolizumab (anti-PD-1, NCT03486301) and with atezolizumab (anti-PD-L1, NCT04196530).

Trial Registration NCT03486301

Ethics Approval This study was approved by the institutional review boards at the four participating institutions. All subjects signed informed consent before enrolling in the clinical trial.

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325 IMMUNOTHERAPY WITH B CELL ACTIVATING ANTIBODY CPI-006 IN PATIENTS (PTS) WITH MILD TO MODERATE COVID-19 STIMULATES ANTI-SARS-COV-2 ANTIBODY RESPONSE, MEMORY B CELLS AND MEMORY T EFFECTOR CELLS

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Background CD73 is present on subsets of B and T cells and is involved in lymphocyte activation. CPI-006 is a humanized IgG1, Fcγ receptor deficient anti-CD73 that has agonistic properties. In vitro studies and ongoing cancer clinical trials show that CPI-006 binds to B cells leading to expression of CD69, trafficking to lymph nodes, immunoglobulin class switching, transformation to plasmablasts and generation of memory B cells.¹ Recently, a patient in the cancer trial with asymptomatic COVID-19 developed high titers of neutralizing anti-SARS-CoV-2 antibodies following administration of CPI-006. A phase 1 trial in COVID-19 was initiated to evaluate the use of CPI-006 to enhance anti-viral immune response (NCT04464395).

Methods Single intravenous dose escalation with N=5 per cohort of 0.3, 1.0, 3.0 and 5.0 mg/kg. Pt eligibility included PCR positive nasal swab for COVID-19; hospitalized with O₂ saturation of ≥92% on <5 l/min of O₂. Pts received standard care for COVID-19. Pts were monitored for safety, COVID-19 symptoms, inflammatory markers and anti-SARS-CoV-2 antibodies by ELISA. Immunophenotyping of blood by flow cytometry was performed.

Results 10 pts have been treated in the first 2 cohorts; median age 64 (range 28–76) and all had comorbidities: diabetes (4), hypertension (2), obesity (7) and/or cancer (2). Median duration of symptoms prior to CPI-006 was 8 days (range 1–21 days). No treatment-related adverse events were reported. There was no correlation between duration of symptoms and baseline anti-viral titers. Kinetics of anti-SARS-CoV-2 response to spike protein are shown for 7 pts with follow-up ≥ 7 days post CPI-006 (figure 1). One pt with lymphopenia (600/mm³) had delayed response to CPI-006; all other pts generated antibody response by Day 7 post-CPI-006 to both spike and RBD. Increasing titers of IgG and IgM antibodies were observed out to 28 days post treatment. In one pt examined, memory B cells increased from 1.81% to 4.83% of B cells 28 days after treatment with serum IgG titers to spike and to RBD of >1:50,000. 2 of 2 pts had increase in both CD4 and CD8 T effector memory cells at day 28. All pts were discharged (median 4 days) with clinical improvement.

Conclusions CPI-006 is well tolerated in COVID-19 pts. Low baseline titers of antibodies to virus were increased following CPI-006 in all treated pts. Immunomodulation with CPI-006