when it is combined with. Higher lymphocyte count is an independent factor which correlates with better response to checkpoint blockade in cancer patients. Based on the MoA of GX-I7, which induces increase of T cells in both the tumor microenvironment and peripheral blood, combining GX-I7 with pembrolizumab can potentially enhance the anti-tumor effect.

**Methods** This is an open-label, phase 1b/2 study in patients with refractory or recurrent TNBC who failed standard chemotherapy from 1st to 3rd line treatment in metastasis setting. Patients pretreated with cyclophosphamide received GX-I7 from 360 μg/kg up to 1,440 μg/kg every 12 weeks and pembrolizumab 200 mg every 3 weeks (n=21). Patients without cyclophosphamide pretreatment received GX-I7 from 720 μg/kg up to 1,440 μg/kg every 9 weeks or 12 weeks and pemrbolizumab 200 mg every 3 weeks (n=24). The objectives were dose limiting toxicities (DLTs), safety, pharmacodynamic markers including lymphocyte increase and ORR.

**Results** GX-I7 and pembrolizumab were given to 45 patients (pts) (median age 50 years [29–75], ECOG PS 1 [42.2%]). 1 DLT (skin rash, Gr 3) was reported in the 1,440 μg/kg cohort. Treatment-related AEs occurred in 97.8% of pts with Gr 1–2, 15.6% with Gr 3 and 2.2% with Gr 4. Common TEAEs were injection site reaction (75.6%), rash (40.0%), pyrexia (40.0%) which were manageable. GX-I7 treatment induced up to 7-fold increase in absolute lymphocyte counts in all dose levels ranging from 360 μg/kg to 1,440 μg/kg with or without cyclophosphamide. A total of 33 evaluable mTNBC pts showed ORR of 0/3 in 360 μg/kg, 1/9 in 720 μg/kg, 2/9 in 960 μg/kg and, 4/12 in 1,200 μg/kg. Interestingly, 4 out of 6 pts received 1,200 μg/kg of GX-I7 with cyclophosphamide achieved SD and, thus, 1,200 μg/kg of GX-I7 regimens have been selected as candidates for RP2D. The tumor assessment for 1,440 μg/kg with or without cyclophosphamide is ongoing.

**Conclusions** GX-I7 in combination with pembrolizumab with or without cyclophosphamide was safe and well tolerated in most study participants. GX-I7 significantly increased T cell numbers in combination with pembrolizumab at doses from 360 μg/kg to 1,440 μg/kg. These results suggested GX-I7 in combination with pembrolizumab show promise as a potential treatment option for patients with metastatic TNBC.

**Trial Registration** ClinicalTrials. gov Identifier: NCT03752723

**Ethics Approval** The study was approved by the Samsung Medical Center, Gachon University Gil Medical Center, National Cancer Center, Korea University Anam Hospital, Korea University Guro Hospital, Severance Hospital, Ajou University Hospital, Seoul National University Bundang Hospital, Ewha Womans University Mokdong Hospital, Asan Medical center, Catholic Medical Center and Gangnam Severance Hospital Institutional Review Board, protocol number GX-I7-CA-006 (KEYNOTE-899).

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http://dx.doi.org/10.1136/jitc-2020-SITC2020.0322

## 323 SYSTEMIC ADMINISTRATION OF LADIRATUZUMAB VEDOTIN ALONE OR IN COMBINATION WITH PEMBROLIZUMAB RESULTS IN SIGNIFICANT IMMUNE ACTIVATION IN THE TUMOR MICROENVIRONMENT IN METASTATIC BREAST CANCER PATIENTS

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**Background** Ladiratuzumab vedotin (LV) is an investigational antibody-drug conjugate (ADC) composed of a humanized anti-LIV-1 IgG1 conjugated with monomethyl auristatin E (MMAE), a microtubule-disrupting agent. LV targets LIV-1, a protein expressed by various cancers. Along with a cytotoxic effect, LV has been shown to induce immunogenic cell death (ICD) in preclinical studies. LV is currently being investigated as a monotherapy and in combination with pembrolizumab in patients with metastatic breast cancer and other solid tumors. This correlative biomarker study aims to assess the ability of LV to modulate the tumor microenvironment (TME) in breast cancer patients.

**Methods** In the SGNLVA-001 trial, metastatic breast cancer patients, predominantly of the triple negative subtype (TNBC), received LV monotherapy (2.0 or 2.5 mg/kg, every 3 weeks [q3w]). In the SGNLVA-002 trial, patients with metastatic TNBC received LV (2.0 or 2.5 mg/kg, q3w) plus pembrolizumab (200 mg, q3w). To investigate the potential effect of LV or LV plus pembrolizumab on the TME, paired pre-treatment and on-treatment tumor biopsies (Cycle [C] 1 Day [D] 5 or C1D15) were collected and analyzed by RNAseq and immunohistochemistry (IHC) staining.

**Results** Gene expression analysis of paired biopsy TNBC samples (n=59; baseline and C1D5) showed that LV monotherapy treatment significantly induces immune response-related gene expression, MHC, co-stimulatory molecules, and PD-L1. Gene set enrichment analysis (GSEA) demonstrated enrichment of macrophage and tumor inflammation signature genes, supporting the induction of ICD and enhancement of innate immune response. Paired tumor samples from subjects treated with LV plus pembrolizumab (n=16; baseline and C1D15) showed a broader range of gene expression changes on RNAseq compared to LV monotherapy. GSEA evidenced enrichment of genes associated with cytotoxic CD8 T cells, CD4 T helper cells, dendritic cells, and macrophages, further demonstrating the induction of ICD and activation of an innate immune response. Importantly, the combination had a unique adaptive immune response induction signature. IHC analysis confirmed the increased infiltration of macrophages after LV monotherapy. The combination with pembrolizumab resulted in a further increase in macrophages and a prominent influx of CD8 T cells.

**Conclusions** Systemic administration of LV monotherapy resulted in immune activation in the TME and macrophage infiltration. The combination of LV plus pembrolizumab resulted in a more potent immune activation in the TME and a prominent influx of CD8 T cells in addition to macrophages. Together these results provide a rationale for the continued clinical investigation of LV alone or in combination with pembrolizumab.

**Trial Registration** NCT01969643 and NCT03310957

**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.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0323

## 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.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0324

## 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 $O_2$ saturation of $\geq$92% on <5 l/min of $O_2$. 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 $\geq$ 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