This confirms that VISTA may play a key role as a mechanism of resistance to the currently used immunotherapies. VISTA/PSGL1 pH-selective biochemical interaction has been recently demonstrated.[5] VISTA and PSGL1 expression pattern, their correlation and their relationship to myeloid infiltrates have been evaluated in samples from patients with solid tumors. K01401-020 (W0180) is a novel anti-VISTA antibody that has the potential to activate T cells when given as a monotherapy[6], and thus to generate added activity when combined with anti-PD1/L1 antibodies in cancer patients.

Methods This phase I/Ib for W0180 consists of 2 parts: an initial dose escalation phase I followed by an expansion cohorts phase Ib. In the dose escalation phase, 2 cohorts of patients will be assessed in parallel: the first cohort will be given W0180 as a single agent and the second cohort will receive W0180 in combination with pembrolizumab. The first dose and the schedule of administration of W0180 in combination with pembrolizumab will be determined using safety and pharmacokinetic data generated in monotherapy. The phase I will allow to determine the Maximum Tolerated Dose and Schedule (MTDS), to characterize Dose-Limiting Toxicities (DLTs) and explore pharmacodynamic activity of W0180 in monotherapy and combination with pembrolizumab. The dose-toxicity relationships will support the dose escalation process and will be used to assess the MTDS and recommended doses for expansion. Following completion of the dose escalation phase, the expansion phase will enroll cohorts of patients with homogeneous tumors to validate the dose/schedule, assess preliminary activity and to explore the potential relationship with VISTA and PSGL1 expression.

Results N/A

Conclusions N/A

Trial Registration N/A

Ethics Approval The study was approved by National French Ethic committee (CPP Ile de France V) and National Spanish Ethic committee (Comité Ético de Investigación Clínica de Navarra) and was registered in the European database (EudraCT: 2019-002299-15).

Consent N/A

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http://dx.doi.org/10.1136/jitc-2020-SITC2020.0315

316 **EVICTION STUDY: PRELIMINARY RESULTS IN SOLID TUMOR PATIENTS WITH ICT01, A FIRST-IN-CLASS, GAMMA9 DELTA2 T CELL ACTIVATING ANTIBODY TARGETING BUTYROPHILIN-3A**

[1]Aurelien Marabelle*, [2]Christiane Jungels, [3]Johann De Bono, [4]Norbert Vey, [5]Martin Wermke, [6]Elena Garralda, [7]Aude de Gassart, [7]Patrick Brune, [7]Emmanuel Valentin, [8]Marina Iché, [9]Daniel Olive, [7]Paul Frohna. *[1]Gustave Roussy, Villejuif, France; [2]Institut Jules Bordet, Brussels, Belgium; [3]The Institute for Cancer Research, London, UK; [4]Institut Paoli-Calmettes, Marseille, France; [5]Medical Faculty Carl Gustav Carus, Dresden, Germany; [6]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [7]ImCheck Therapeutics, Marseille, France; [8]ILife Consulting, Paris, France; [9]Centre de recherche en Cancérologie, Marseille, France*

Background Gamma9 Delta2 (γ9δ2) T cells are an important component of the innate anti-tumor immune response whose infiltration into solid tumors has been associated with a positive prognosis, making γ9δ2 T cells an attractive target for the next generation of cancer immunotherapy. Butyrophilins (BTNs) are a family of immune checkpoint molecules that regulate γ9δ2 T cell activity, including BTN3A that is a potent endogenous activator of γ9δ2 T cells following phosphoantigen (pAg) binding to the intracellular domain of BTN3A1. This observation led to the design and development of ICT01, a humanized, monoclonal antibody that binds all 3 isoforms of BTN3A1/A2/A3 and induces pAg-independent γ9δ2 T cell activation, for the treatment of patients with solid or hematologic tumors.

Methods EVICTION (www. clinicaltrials.gov NCT04243499; EudraCT Number: 2019-003847-31) is a first-in-human, two-part, open-label, clinical study to assess the safety, tolerability and activity of intravenous doses of ICT01 as monotherapy and in combination with pembrolizumab, in patients with advanced-stage, relapsed/refractory cancer. Following Competent Authority and Ethics Committee approvals, the study is being conducted at cancer centers in France, Belgium, Spain, Germany, and the UK. Patients provide signed informed consent prior to screening. Eligible patients receive ICT01 (Range: 20 μg to 200 mg) every 3 weeks with blood samples collected at multiple timepoints for immunophenotyping and cytokine analysis (IFNγ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-13, TNFα). Tumor biopsies are collected at baseline and Day 28 and stained by immunohistochemistry for BTN3A, γ9δ2 T cells and other markers of anti-tumor immunity.

Results Cohort 1 comprising 6 patients with solid tumors (3 Colorectal, 1 Pancreatic, 1 Ovarian, 1 Melanoma) has been enrolled and treated with ICT01 doses ranging from 20 to 700 μg. No dose-limiting toxicities or related SAEs have been reported. Target occupancy on T cells at 4 hours post first dose was 10% at 70 μg (n=1), 31% at 200 μg (n=2) and 34% at 700 μg (n=2), which was reflected at 24 hours post dose by a 73%, 91% and 97% decrease from baseline in the number of circulating γ9δ2 T cells, respectively. On Day 7, γ9δ2 T cells remained decreased by 37%, 75% and 76%, respectively. There were no effects on CD4 or CD8 T cells, NK cells, or B cells. Transient increases in IFNγ, secreted by activated γ9δ2 T cells, were observed in 4/6 patients. No cytokine release syndrome was observed. Data from the paired tumor biopsies are still being generated and will be presented.

Conclusions The preliminary results demonstrate that ICT01 has the potential to safely activate the innate anti-tumor potential of γ9δ2 T cells through BTN3A.

Acknowledgements .

Trial Registration www.clinicaltrials.gov NCT04243499; EudraCT Number: 2019-003847-31

Ethics Approval This study was approved by the following Ethics Committees: COMITE DE PROTECTION DES PERSONNES, Sud-Méditerranée V (Gustave Roussy, IPC), Comité d'Ethique Institut Jules Bordet, COMITÉ DE ÉTICA DE INVESTIGACIÓN CLÍNICA CON MEDICAMENTOS del Hospital Universitari Vall d'Hebron, Ethikkommission an der TU Dresden, HRA London-Surrey Borders Research Ethics Committee.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0316

317 A PHASE 1/1B STUDY OF SBT6050, A HER2-DIRECTED MONOCLONAL ANTIBODY CONJUGATED TO A TOLL-LIKE RECEPTOR 8 AGONIST, IN SUBJECTS WITH ADVANCED HER2-EXPRESSING SOLID TUMORS

[1]Leisha Emens*, [2]Muralidhar Beeram, [3]Erika Hamilton, [4]Sarina Piha-Paul, [5]Valerie Odegard, [5]Sue Hamke, [5]Naomi Hunder, [6]Samuel Klempner. *[1]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [2]The Start Center for Cancer Care, San Antonio, TX, USA; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]MD Anderson Cancer Center, Houston, TX, USA; [5]Silverback Therapeutics, Inc., Seattle, WA, USA; [6]Massachusetts General Hospital, Boston, MA, USA*

Background New strategies are needed to improve outcomes in human epidermal growth factor receptor 2 (HER2)-expressing cancers. SBT6050 is a novel therapeutic comprising a specific small molecule toll-like receptor (TLR) 8 agonist conjugated to a HER2-directed monoclonal antibody. TLR8 is highly expressed in myeloid cells that are prevalent in human tumors, including dendritic cells (DCs) and macrophages, and modulates their pro-inflammatory activity. SBT6050 is designed to activate human myeloid cells only in the presence of moderate-to-high HER2 expression (immunohistochemistry [IHC] 2+ or 3+) and binds to the same epitope as pertuzumab. In preclinical studies, SBT6050 potently induces a broad spectrum of antitumor immune mechanisms, including proinflammatory cytokine and chemokine production, inflammasome activation, and indirect activation of T and natural killer (NK) cells. TLR8 agonism has emerged as a promising approach to overcome resistance to immune checkpoint inhibitors in tumors lacking T-cell infiltrates, as these cancers are often replete with myeloid cells. Using an SBT6050 mouse surrogate in vivo, curative single-agent efficacy was observed in multiple murine tumor models, including a model deficient in T, B, and NK cells. In preclinical toxicology studies in nonhuman primates, SBT6050 was well tolerated, supporting a first-in-human starting dose that is predicted to be pharmacologically active, with a short escalation to projected clinically active doses. Preclinical studies also support combinations with checkpoint inhibitors and with trastuzumab to further enhance antitumor activity.

Methods SBT6050-101 is an ongoing phase 1/1b, first-in-human, open-label, multicenter study. Eligible subjects are adults with histologically confirmed, HER2-expressing (IHC 2+ or 3+), locally advanced (unresectable) and/or metastatic cancer. Subjects must have measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and have previously received all therapies known to confer clinical benefit. SBT6050 is given subcutaneously every 2 weeks and treatment may continue for up to 2 years or until disease progression, unacceptable toxicity, or other reason for discontinuation. The trial objectives are to evaluate the safety and tolerability of SBT6050 and to identify the maximum tolerated dose and recommended phase 2 dose (RP2D). The study has 2 parts: Part 1, consisting of a dose escalation using a standard 3+3 design, and Part 2, consisting of 5 parallel expansion cohorts based on tumor type and HER2 expression level and treated with SBT6050 at the RP2D. Pharmacokinetics, immunogenicity, and antitumor activity will be evaluated and pharmacodynamic markers of myeloid cell activation will be assessed in peripheral blood and on-treatment tumor biopsies.

Results N/A

Conclusions N/A

Trial Registration NCT04460456

Ethics Approval The study was approved by MD Anderson Cancer Center Institutional Review Board, approval number 2020-0326 MOD001.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0317

318 OLAPARIB PLUS PEMBROLIZUMAB IN PATIENTS WITH PREVIOUSLY TREATED ADVANCED SOLID TUMORS WITH HOMOLOGOUS RECOMBINATION REPAIR MUTATION AND/OR HOMOLOGOUS RECOMBINATION REPAIR DEFICIENCY: KEYLYNK-007

[1]Timothy A Yap*, [2]Mallika Dhawan, [3]Andrew E Hendifar, [4]Michele Maio, [5]Taofeek K Owonikoko, [6]Miguel Quintela-Fandino, [7]Ronnie Shapira-Frommer, [8]Sanatan Saraf, [8]Ping Qiu, [8]Fan Jin, [8]Alexander Gozman, [9]Douglas A Levine. *[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [3]Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [4]Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy; [5]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [6]Centro Nacional de Investigaciones Oncológicas, Madrid, Spain; [7]Chaim Sheba Medical Center, Tel HaShomer, Israel; [8]Merck and Co., Inc., Kenilworth, NJ, USA; [9]Laura and Isaac Perlmutter Cancer Center, New York, NY, USA*

Background Treatment with the anti–PD-1 antibody pembrolizumab has improved clinical outcomes in multiple previously treated advanced solid tumors. The poly (ADP-ribose) polymerase (PARP) inhibitor olaparib has shown antitumor activity as monotherapy in patients with previously treated advanced ovarian, breast, pancreatic, and prostate cancers with BRCA1/BRCA2 mutations (BRCAm). Activity was also seen in patients with previously treated advanced solid tumors with other homologous recombination repair mutation (HRRm) and in those with ovarian cancer with homologous recombination repair deficiency (HRD) phenotype. PARP inhibitors have been found to increase interferon signaling and tumor infiltrating lymphocytes, enhancing tumor susceptibility to immune checkpoint blockade. Antitumor activity of PD-(L)1 plus PARP inhibition was found to be higher than expected with either agent alone in patients with recurrent ovarian cancer regardless of BRCAm or HRD status and in patients with BRCAm breast cancer. KEYLYNK-007 (NCT04123366) evaluates the antitumor activity and safety of olaparib in combination with pembrolizumab in patients with previously treated advanced solid tumors with HRRm and/or HRD.

Methods This phase 2, nonrandomized, multicenter, open-label study will enroll approximately 300 patients aged ≥18 years