objectives include assessment of the pharmacokinetic profile, preliminary efficacy per RECIST 1.1, and immune response.

**Results** N/A

**Conclusions** N/A

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**Ethics Approval** This study was approved by:1. The Institutional Review Board (IRB) of Stanford University; eProtocol Number: 54928.2. The IRB of The University of Texas MD Anderson Cancer Center; IRB ID Number: 2020-0185_MOD001.3. Western IRB, on behalf of The Angeles Clinic and Research Institute and Henry Ford Health System IRB Office; IRB Tracking Number: 20200758.4. Bellberry Limited Human Research Ethics Committee, on behalf of Royal North Shore Hospital and Chris O'Brien Lifehouse; Application Number: 2019-10-848.

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## 417 DESIGN AND RATIONALE OF A PHASE 1 STUDY EVALUATING AMG 256, A NOVEL, TARGETED, IL-21 RECEPTOR AGONIST AND ANTI-PD-1 ANTIBODY, IN PATIENTS WITH ADVANCED SOLID TUMORS

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**Background** Checkpoint inhibitors are a promising therapy for patients with solid tumors; however, many patients require additional therapies to maximize clinical benefit or overcome resistance.[1] The type-1 cytokine interleukin-21 (IL-21) is a promising candidate for combination and has shown clinical activity in melanoma and renal cell cancer.[2] IL-21 has also shown improved efficacy when combined with anti-programmed death (PD)-1 antibodies in preclinical models.[3 4] AMG 256 is a mutated IL-21 cytokine fused to an anti-PD-1 antibody to combine IL-21 pathway stimulation with checkpoint inhibition—a strategy that is designed to prime and extend the activity of cytotoxic and memory T cells and induce anti-tumor immunity. This first-in-human (FIH) study will assess safety, tolerability, and estimated dosing of AMG 256 monotherapy in patients with advanced solid tumors.

**Methods** This is a FIH, multicenter, non-randomized, open-label, phase 1 study (NCT04362748) of AMG 256 in patients with advanced solid tumors. The planned sample size is approximately 100 patients in two parts: part 1 will evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics, and determine the maximum tolerated dose (MTD), part 2 will evaluate the MTD determined in part 1 to further characterize the safety profile and preliminary tumor response. AMG 256 will be delivered by intravenous (IV) infusion. Enrollment criteria include adults with life expectancy of > 3 months, ECOG performance status ≤ 2, histologically or cytologically confirmed metastatic or locally advanced solid tumors not amenable to curative treatment with surgery or radiation, and at least one measurable lesion ≥ 10 mm that has not undergone biopsy within 3 months of screening scan. Exclusion criteria include primary brain tumor, untreated or symptomatic brain metastases, currently receiving treatment in another investigational device or drug study, or less than 28 days since ending treatment on another investigational device or drug study, history of solid organ transplantation or major surgery within 28 days of study day 1, live vaccine therapy within 4 weeks prior to study day 1, and active infection requiring oral or IV therapy. The primary endpoints are incidence of dose-limiting toxicities and adverse events, MTD, and recommended phase 2 dose. Secondary objectives will evaluate PK parameters, preliminary antitumor activity (objective response, duration of response, progression-free survival, disease control rate, duration of stable disease, overall survival), and immunogenicity of AMG 256 via incidence of anti-AMG 256 antibodies.

**Results** N/A

**Conclusions** N/A

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**Trial Registration** NCT04362748

**Ethics Approval** The study was approved by all institutional ethics boards.

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## 418 A PHASE 1, DOSE ESCALATION AND DOSE EXPANSION STUDY OF SQZ PBMC HPV AS MONOTHERAPY AND IN COMBINATION WITH ATEZOLIZUMAB IN HLA-A*02+ PATIENTS WITH HPV16+ RECURRENT, OR METASTATIC SOLID TUMORS

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**Background** SQZ-PBMC-HPV is a therapeutic cancer vaccine created with Cell Squeeze®, a proprietary cell-engineering system. SQZ-PBMC-HPV is a novel cancer vaccine generated from peripheral blood mononuclear cells (PBMC) squeezed with HPV16 E6 and E7 antigens, resulting in delivery into the cytosol. The resulting antigen presenting cells (APCs) provide enhanced antigen presentation on MHC-I to potentially

elicit robust, antigen-specific CD8+ T cell responses. Importantly, SQZ-PBMC-HPV are neither genetically modified nor immune effector cells.Studies in MHC-I knockout mice demonstrated that activation of antigen specific CD8+ tumor infiltrating lymphocytes (TILs) was a direct effect of cytosolic antigen delivery to PBMCs. In the murine TC-1 tumor model, tumor regression correlated with an influx of HPV16-specific CD8+ TILs. In vitro studies with human volunteer PBMCs demonstrated that each subset is capable of inducing CD8+ T cell responses. The Phase 1 study includes a significant biomarker program to investigate whether pharmacodynamic effects observed in non-clinical studies correlate with potential clinical benefit. Immunogenic and pharmacodynamic endpoints include Elispot assays to measure frequency of interferon gamma secreting cells, as well as quantification and characterization of TILs and tumor microenvironment. In addition, various cytokine responses and circulating cell-free HPV16 DNA levels in plasma are measured.

**Methods** SQZ-PBMC-HPV-101 (NCT04084951) is open for enrollment to HLA A*02+ patients with HPV16+ recurrent, locally advanced or metastatic solid tumors and includes escalation cohorts for monotherapy and in combination with atezolizumab. After initial demonstration of safety, the study assesses dose effect by testing different cell dose levels, the effect of prolonged antigen priming in Cycle 1 [APC administration on Day 1 only compared to Days 1 and 2 (double priming)] and the impact of treatment duration to identify the optimal dose regimen. The cycle length is 3 weeks, and patients will receive SQZ-PBMC-HPV for up to 1 year or until available autologous drug product is exhausted. Atezolizumab will be administered for up to 1 year. Eligible patients including but not limited to anal, cervical and head and neck tumors will undergo a single leukapheresis at the study site. The manufacturing process includes a maturation step and takes less than 24 hours. The vein-to-vein time for the 1st administration is approximately one week. Patients must have a lesion that can be biopsied with acceptable clinical risk and agree to have a fresh biopsy at Screening and on study. A Study Safety Committee is in place. No formal statistical hypothesis testing will be performed.

**Results** N/A

**Conclusions** N/A

**Trial Registration** NCT04084951

**Ethics Approval** The study is registered on clinicaltrials.gov was approved by the Ethics Board of all institution listed as recruiting.

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## 419 PHARMACODYNAMIC BIOMARKERS DEMONSTRATE T-CELL ACTIVATION IN PATIENTS TREATED WITH THE ORAL PD-L1 INHIBITOR INCB086550 IN A PHASE 1 CLINICAL TRIAL

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**Background** Pharmacological blockade of the PD-1:PD-L1 interaction with monoclonal antibodies (mAbs) has shown durable clinical responses and overall survival benefit in a variety of malignancies.[1 2] Importantly, the most meaningful responses have been associated with enhancement of the anti-tumor effector functions of T cells as evidenced by increased peripheral T-cell proliferation, infiltration of T cells in tumors, together with increased expression of key interferon-γ (IFNγ) pathway genes, including CXCL9, CXCL10, and granzyme B in both biopsy and peripheral blood samples.[3 4] To date, available therapies targeting this pathway are mAbs, but the potential advantages of a small molecule, orally administered, direct antagonist of PD-1:PD-L1 binding have led to the development of INCB086550. INCB086550 is being evaluated in a phase 1 study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics in patients with solid tumors. This preliminary report describes peripheral pharmacodynamic activity.

**Methods** Peripheral blood was collected at baseline and at multiple time points posttreatment from 16 patients treated with INCB086550 QD (100, 200 mg) or BID (200, 400 mg). Pharmacodynamic assessments included binding of drug to PD-L1 and secretion of cytokines, IL-2 and IFN-γ with ex vivo restimulation. Measurement of downstream pharmacodynamic effects included evaluation of immune activation markers on peripheral blood cells by flow cytometry and measurement of a panel of interferon-related cytokines in plasma.

**Results** Following INCB086550 treatment, the ex vivo stimulation of whole blood from patients showed a dose-related reduction of up to 85% in free PD-L1 on cells after 2 hours and increases as high as 3-fold of interleukin-2 secretion after 6 hours. Increases in the proliferation of circulating T cells, as measured by Ki-67, were dose-related and as high as 2.5-fold posttreatment. Plasma concentrations of CXCL9 and CXCL10 increased following INCB086550 treatment by 1.3- and 1.4-fold, respectively. A dose-related 1.2-fold increase in the plasma concentration of soluble target (PD-L1) and a 3.4-fold increase in IFN-γ was also observed posttreatment. Other proteins related to T-cell function, including but not limited to granzyme B, granzyme H, and LAG3, also increased following drug treatment.

**Conclusions** These results indicate that oral administration of INCB086550 provides dose-related pharmacodynamic T-cell activation similar to data reported for PD-(L)1 mAbs and evidence that INCB086550 is biologically active in blocking PD-1:PD-L1 interactions, leading to T-cell proliferation and activation in patients. This trial continues to evaluate the intratumoral pharmacodynamic activity, safety, and efficacy of INCB086550.

**Ethics Approval** The study was approved by institutional review boards or independent ethics committees of participating institutions.

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