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 cytoplasmic 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. Immuneogenic 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.

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0418

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

1Sarina Pha-Paul*, 2Tara Mitchell, 3Solmaz Sahiehjazi, 4Janice Mehner, 5Thomas Karasic, 6Kevin O’Hayer, 7Ryan Geschwindt, 8Susan Spitz, 9Hao Liu, 10Johanna Bendell. 1M. D. Anderson Cancer Center, Houston, TX, USA; 2Abramson Cancer Center of the University, Philadelphia, PA, USA; 3Moffitt Cancer Center, Tampa, FL, USA; 4Perlmutter Cancer Center of NYU Langone, New York, NY, USA; 5University of Pennsylvania, Philadelphia, PA, USA; 6Incyte Corporation, Wilmington, DE, USA; 7Sarah Cannon Research Institute, Nashville, TN, USA

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.

REFERENCES

http://dx.doi.org/10.1136/jitc-2020-SITC2020.0419