

immunotherapeutic agents with concomitant biopsy procedures to date are associated with a high technical success rate & favorable safety profile.

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Trial Registration N/A

Ethics Approval The study was approved by Institution's Ethics Board, approval number 2020-0536: A retrospective study to determine the safety, feasibility and technical challenges of real-time image guidance for intra-tumor injection and biopsy across multiple solid tumors.

Consent 2020-0536 Waiver of Informed Consent

REFERENCE

- Sheth RA, Murthy R, Hong DS, *et al.* Assessment of image-guided intratumoral delivery of immunotherapeutics in patients with cancer. *JAMA Netw Open* 2020;3(7):e207911. doi:10.1001/jamanetworkopen.2020.7911

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AGEN1181, AN FC ENGINEERED ANTI-CTLA-4 ANTIBODY, DEMONSTRATES CLINICAL ACTIVITY, ALONE OR IN COMBINATION WITH BALSTILIMAB (ANTI-PD-1), AND BROADENS THE THERAPEUTIC POTENTIAL OF CTLA-4 THERAPY

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Background Immune checkpoint therapies targeting CTLA-4, alone, or in combination with anti-PD-1 have shown durable responses in cancer patients. However, responses are limited to a small subset of patients in the most common immunogenic cancers. Here we describe, a novel anti-CTLA-4 antibody, AGEN1181, with enhanced FcγR-dependent functionality that harnesses a novel mechanism of action to promote superior T cell activation and anti-cancer immunity. Concordant with preclinical findings, we report preliminary safety, pharmacodynamic and efficacy data from a phase 1 study of AGEN1181 (NCT03860272), alone or in combination with balstilimab (anti-PD-1 antibody) in a range of immunogenic and non-immunogenic tumors.

Methods The functional activity of AGEN1181 or AGEN1181-like mouse surrogate were assessed in primary cell-based assays or in PD-1 refractory syngeneic tumor-bearing mouse models (B16F10 or KPC pancreatic tumor). Efficacy was evaluated as monotherapy, or in combination with anti-PD-1, focal radiation or chemotherapy. In an ongoing phase I study, AGEN1181 is administered intravenously once every 3- or 6-weeks as monotherapy (0.1–4 mg/kg), or every 6-weeks (1–4 mg/kg) in combination with balstilimab (3 mg/kg) dosed every 2 weeks. Dose-limiting toxicities were evaluated in the first 28 days of treatment. Neoantigen burden was assessed from pre-treatment tumor biopsy, as available, by next-generation sequencing. Fcγ receptor genotyping was assessed by real-time PCR. Immunophenotyping of peripheral blood mononuclear cells collected pre- and post-treatment were analyzed by flow cytometry.

Results Preclinically, AGEN1181 demonstrated superior T cell activation than a standard IgG1 anti-CTLA-4 analogue in donors expressing either the low or high affinity FcγRIIIA. In poorly immunogenic tumor-bearing mouse models, AGEN1181-like surrogate demonstrated robust tumor control in combination with anti-PD-1 and focal radiation or chemotherapy. As of August 25th, 2020, we observed a clinical benefit rate of 63–53% at 6 and 12 weeks respectively among evaluable treated patients. We observed two durable responses in patients with endometrial cancer that were BRCA-, microsatellite stable and PD-L1 negative. These patients progressed on prior PD-1 therapy or chemoradiation respectively. Notably, responders expressed either the low or high affinity FcγRIIIA. AGEN1181 showed potent dose-dependent increases in peripheral CD4+Ki67+, CD4+ICOS+ and CD4+HLA-DR+ T-cells. Treatment was well tolerated through the highest dose tested. Grade 3 or greater immune-related adverse events occurred in 28.5% patients and were consistent with CTLA-4 therapies.

Conclusions AGEN1181 is designed to expand the benefit of anti-CTLA-4 therapy to a broader patient population. AGEN1181, alone or in combination with balstilimab, demonstrates clinical activity in heavily pretreated patients.

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COSIBELIMAB, AN ANTI-PD-L1 ANTIBODY: PRELIMINARY SAFETY AND EFFICACY RESULTS FROM A GLOBAL, MULTICOHORT PHASE 1 CLINICAL TRIAL

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Background Cosibelimab is a high affinity, fully-human IgG1 monoclonal antibody that directly binds to programmed death ligand-1 (PD-L1) and blocks its interaction with the programmed death receptor-1 (PD-1) and B7.1 receptors to restore an anti-tumor immune response. Cosibelimab has the additional benefit of a functional Fc domain capable of inducing antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity against tumor cells. Study CK-301-101 is a global, multicenter, multicohort trial that is enrolling patients (pts) with select advanced cancers, including pivotal cohorts of pts with metastatic and locally advanced cutaneous squamous cell carcinoma (cSCC) and a cohort of pts with previously untreated advanced non-small cell lung cancer (NSCLC).

Methods Eligible pts were aged ≥ 18 years with an Eastern Cooperative Oncology Group performance status of 0–1. The cSCC cohorts enrolled pts with histologically confirmed metastatic or locally advanced cSCC not amenable to local therapy. The NSCLC cohort enrolled previously untreated NSCLC pts with advanced disease and a PD-L1 tumor proportion score of at least 50%. Pts received a fixed dose of 800 mg cosibelimab administered intravenously every two weeks. Anti-tumor activity was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and were conducted every 8 weeks for the initial 32 weeks on study, and every 12 weeks thereafter.

Results As of August 2020, 114 pts (73M/41F, median age 66 years) with diverse tumor types have been enrolled and treated with cosibelimab. Among these pts, 103 (90%) experienced ≥ 1 treatment-emergent adverse event (AE), 42 (37%) experienced a grade ≥ 3 AE, and 6 (5%) experienced a grade ≥ 3 drug-related AE. The most common AEs were fatigue (25%), anemia (21%), rash (18%) and nausea (16%) and the most common drug-related AEs were fatigue (15%) and rash (14%). In 42 cSCC pts evaluable for response, ORR based on investigator assessment of tumor response was 55% (95% confidence interval [CI]: 39, 70), including 5 (12%) complete responses, with 20/23 (87%) responses ongoing and 10 responses ≥ 6 months in duration as of data cutoff. In 25 NSCLC pts evaluable for response, ORR based on investigator assessment was 44% (95% CI: 24, 65), with 5/11 (45%) responses ongoing and 10 responses ≥ 6 months in duration.

Conclusions Cosibelimab has a predictable and manageable safety profile and demonstrated robust clinical activity in cSCC and NSCLC pts, including durable complete and partial responses. Updated results will be presented.

Trial Registration NCT03212404

Ethics Approval The study was approved by an appropriate ethics committee for each participating institution. Informed consent was obtained for all subjects.

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.

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COUPLED CARTM TECHNOLOGY FOR TREATING THYROID CANCER

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Background Chimeric antigen receptor modified T cells (CAR T) have demonstrated remarkable clinical efficacy in the treatment of B cell malignancies and multiple myeloma. Significant challenges restrict their application across solid tumors due to multiple obstacles, including the lack of robust in vivo CAR-T cell expansion and persistence, the immunosuppressive tumor microenvironment, and tumor escape due to heterogeneous tumor cell composition with a potential loss of the targeted tumor antigen. To address these difficulties, we generated CAR T cells using a novel CoupledCAR[®] technology. Specifically, we engineered CoupledCAR T cells with lentiviral vectors encoding an anti-thyroid stimulating hormone receptor (TSHR) CAR molecule. Immunohistochemistry (IHC) results

showed that TSHR was highly expressed in thyroid cancer cells making it an ideal tumor-specific target antigen. In vitro co-culture experiments showed that TSHR CAR T cells specifically recognized and subsequently killed TSHR-positive tumor cells. Animal model experiments showed that TSHR CAR T cells inhibited the proliferation of TSHR-positive tumor cells.

Methods We designed a 'CoupledCAR' lentivirus vector containing a single-chain variable fragment (scFv) targeting human TSHR. The lentivirus was produced by transfecting HEK-293T cells with 'CoupledCAR' lentiviral vectors and viral packaging plasmids. Patient's CD3 T cells were cultured in X-VIVO medium containing 125U/mL interleukin-2 (IL-2), and transduced with 'CoupledCAR' lentivirus at certain MOI. Transduction efficiency and was evaluated at 7 to 9 days after 'CoupledCAR' lentivirus transduction, and quality controls for fungi, bacteria, mycoplasma, chlamydia, and endotoxin were performed. After infusion, serial peripheral blood samples were collected, and the expansion and the cytokine release of CART cells were detected by FACS and QPCR. The evaluation of response level for patients were performed at month 1, month 3, and month 6 by PET/CT.

Results To evaluate the clinical safety and efficacy of anti-TSHR CoupledCAR T cells on refractory or relapsed thyroid cancer, we treated refractory/relapsed post-thyroidectomy thyroid cancer patients according to an IRB approved protocol. We treated two patients using anti-TSHR CoupledCAR T cells and observed the rapid expansion of CAR T cells and enhanced the killing of tumor cells. One patient's best response was complete remission, and the other was near complete remission. **Patient Profile:** Patient 1 Male, 64Y, Papillary Thyroid Carcinoma. In May 2017, Thyroid cancer was diagnosed, bilateral total thyroidectomy, and right cervical lymph node functional dissection were performed in Jun 2018, followed by iodine 131 isotope therapy. In December 2018, bilateral multiple cervical lymph nodes were enlarged, especially on the right side. In February 2019, right neck lymphadenectomy was performed. Patient 2 Female, 60Y, Thyroid Carcinoma. In Aug 2013, a 'double lobectomy of the thyroid gland' was performed. From Oct 2013 to Jan 2014, she received iodine 131 isotope therapy. In Sep 2014, she was diagnosed with iodine - resistant thyroid cancer. From Sep to Jan 2016, 5 cycles of chemotherapy were performed. In Jun 2016, she enrolled in the Anlotinib experimental group. In Mar 2019, multiple metastases in both lungs and multiple enlarged lymph nodes in the mediastinum were observed. **Observations and Results:** Patient 1: One month after infusion (M1), the patient was evaluated as PR: lymph node metastasis became undetectable and the size of the thoracic paratracheal tumor nodules decreased significantly. Three months after infusion (M3), the patient was evaluated as CR, and the tumor tissue was substantially smaller than M1. Patient 2: M1, the patient was evaluated as PR (Partial Response): the tumor volume in the right lower lobe of the lung was reduced by approximately 67.51% (decreased from 65*55 mm to 42*39 mm). Three months after infusion (M3), compared with that before, the tumor volume was reduced by approximately 73.54% and SUV max value decreased from 14.9 to 2.8, therefore, the patient was evaluated as nCR (near complete remission).

Conclusions We show that TSHR is a good target for treating thyroid cancer, and our anti-TSHR CoupledCAR T cells are safe and effective for treating thyroid cancer. Recruitment is ongoing to evaluate the safety and efficacy of our CoupledCAR T cells. Further, since our CoupledCAR[®] technology is a