Background Despite recent advances, resistance to immune checkpoint inhibitors (ICI), observed in over 80% of treated patients, is currently the main challenge immuno-oncology is facing. Intense efforts are being made to identify combination therapies that could improve ICI response rates. Administered intratumorally, NBTXR3 enhances the energy dose deposited by ionizing radiation within tumor cells, increasing the anti-tumor efficacy of radiation therapy (XRT) without adding toxicity to surrounding tissues. Here we present evidence that NBTXR3 activated by XRT primes the immune system, producing an anti-tumor response, including activation of the cGAS-STING pathway, that overcomes anti-PD-1 resistance both in mice models and patients.

Methods Abscopal assays were conducted in immunocompetent mice. Tumor cell lines, sensitive or resistant to anti-PD-1, were injected in both flanks of mice. Intratumoral injection of NBTXR3 (or vehicle) followed by XRT was performed in right flank (primary) tumors only. Some mice also received anti-PD-1 injections. Tumor growth was monitored, and tumor immune cell infiltrates were analyzed by immunohistochemistry (IHC). Separately, in the phase II/III randomized trial Act.in. Sarc [NCT02379845] patients with locally advanced soft tissue sarcoma (STS) received either NBTXR3+XRT or XRT alone followed by wide tumor resection. Pre- and post-treatment tumor samples from patients in both groups were analyzed by IHC and Digital Pathology for immune biomarkers. The safety and efficacy (RECIST 1.1/RECIST) of NBTXR3 plus stereotactic ablative radiotherapy (SABR) in combination with anti-PD-1 is being evaluated in three cohorts of patients with advanced cancers [NCT03589339].

Results Pre-clinical studies demonstrated that NBTXR3+XRT induces an immune response a not observed with XRT alone and enhances systemic control. IHC showed significant increase of CD8+ T-cell infiltrates in both NBTXR3+XRT treated and untreated tumors compared to XRT alone. Similarly, increased CD8+ T-cell density (pre- vs post-treatment) was observed in tumor tissues from STS patients treated with NBTXR3+XRT. Tumor samples from the NBTXR3+XRT group also displayed increased PD-1+ cell density. Furthermore, in combination with anti-PD-1, NBTXR3+XRT improved local and systemic control in mice bearing anti-PD-1 resistant lung tumors, as well as resulted in reduced number of spontaneous lung metastases. Preliminary efficacy data from the first in human trial of NBTXR3+XRT in combination with anti-PD-1 showed tumor response in patients who progressed on prior anti-PD-1.

Conclusions The clinical efficacy of NBTXR3+XRT has been demonstrated as a single agent. We now demonstrate that it potentiates anti-PD-1 treatment to overcome resistance mechanisms. These results highlight the potential of NBTXR3+XRT to positively impact the immuno-oncology field.
Abstracts

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


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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

Steven O’Day*, Anthony El Khoury†, Chethan Ramamurthy, Andrea Bullock, Yrina Shapiro, Seina, Haiyong Han, Lennik Olanjanin Nakamageri, Temigius Kaleta, Anna Wijatyk, Olivia Wijatyk, Waldo Ortuzar, Marek Arczkiewicz, Jennifer Buell, Dhani Chand, Michael Gordon, John Wayne Cancer Institute, Santa Monica, CA, USA; 2University of Southern California, Los Angeles, CA, USA; 3University of Texas at San Antonio, San Antonio, TX, USA; 4Beth Israel Deaconess Medical Center, Boston, MA, USA; 5Agenus, Inc., Lexington, MA, USA; 6Translational Genomics Research, Phoenix, AK, USA; 7Translational Genomics Research Institute, Phoenix, AZ, USA; 8Fate Therapeutics, Scottsdale, AZ, USA

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 1 study, AGEN1181 is administered intravenously 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. Neoadjuvant 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 Preliminarily, AGEN1181 demonstrated superior T cell activation than a standard IgG1 anti-CTLA-4 analogue in donors expressing either the low or high affinity FcγRIIa. 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 FcγRIIa. 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 highest dose tested. Grade 3 or greater immune-related adverse events occurred in 28.5% patients and were consistent with highest dose tested.

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.

Trial Registration NCT03860272

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

Dean Harris*, Daniel Brungs, Rahul Ludwah, Anthony Mant, Margaret McGrath, Andrea Tazikovka, Andrey Akopov, Natalia Faderova, Boris Kasparov, Nadezhda Kovalenko, Vladimir Kozlov, Fedor Moiseenko, Vasiliy Oschepkov, Piotr Koralewski, Dariusz Kowalski, Joanna Lugowska, Jaiyut Channontum, Arunee Dechaphuruk, Virote Sriruangroj, James Olivito, Philip Clingen, Christchurch Hospital, Christchurch, New Zealand; 2Southern Medical Day Care Centre, Wollongong, Australia; 3Princess Alexandra Hospital, Woolloongabba, Australia; 4Eastern Health, Box Hill, Australia; 5Greenslopes Private Hospital, Greenslopes, Australia; 6Pindara Private Hospital, Benowa, Australia; 7First St. Petersburg State Med Univ, Saint-Petersburg, Russian Federation; 8Chelyabinsk Regional Clinical Oncology Center, Chelyabinsk, Russian Federation; 9NMRC of Oncology n.a. N.N. Petrov, Saint-Petersburg, Russian Federation; 10Volgograd Regional Clinical Oncological Dispensary, Volgograd, Russian Federation; 11Novosibirsk Regional Clinical Oncological Dispensary, Novosibirsk, Russian Federation; 12St. Petersburg Clin Res and Practice Ct, Saint-Petersburg, Russian Federation; 13MultidisciplinaryClin Med Ctr, Tyumen, Russian Federation; 14SAPSpecializedCenter Ludwika Rydygier, Krakow, Poland; 15National Research Institute of Oncology, Warsaw, Poland; 16Mahanak Nakorn Chiang Mai Hospital, Chiang Mai, Thailand; 17Prince of Songkla University, Songkhla, Thailand; 18King Chulalongkorn Memorial Hospital, Bangkok, Thailand; 19Checkpoint Therapeutics, New York, NY, USA

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).