396 OVERCOMING RESISTANCE TO ANTI-PD-1 WITH TUMOR AGNOSTIC NBTXR3: FROM BENCH TO BED SIDE

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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/iRECIST) 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.

Ethics Approval This study was approved by local institution's review board

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397 INTRA-TUMOR IMMUNOTHERAPY INJECTIONS UTILIZING IMAGE GUIDANCE IN INTERVENTIONAL RADIOLOGY: CLINICAL TRIAL EXPERIENCE AT A TERTIARY CARE CANCER CENTER

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Background Image guided intra-tumor administration of investigational immunotherapeutic agents represents an expanding field of interest. We present a retrospective review of the safety, feasibility & technical nuances of real-time image guidance for injection & biopsy across a spectrum of extracranial solid malignancies utilizing the discipline of Interventional Radiology.

Methods Patients who were enrolled in image guided intratumoral immunotherapy injection (ITITI) clinical trials over a 6 year period (2013–19) at a single tertiary care cancer center were included in this analysis. Malignancy, location, imaging guidance utilized for ITITI & biopsy for injected (adscopal) & non-injected (abscopal) lesions were determined and categorized. Peri-procedural adverse events were noted.

Results 262 pts (146 female, 61 yrs median) participating in 29 immunotherapeutic clinical trials (TLR & STING agonists, gene therapy, anti CD-40, viral/bacterial/metabolic oncolytics) met study criteria. Malignancies included melanoma 88, sarcoma 32, colorectal 29, breast 23, lung 17, head & neck 15, ovarian 8, neuroendocrine 7, pancreatic adenocarcinoma 6, 3 each (cholangioCA, endometrial, bladder, GI tract), 2 each (RCC, thymicCA, lymphoma, merkel cell, prostate) & others 1 each (CUP, GIST, dermatofibrosarcoma, DSRT, neuroblastoma, thyroid). All 169 & 93 patients received the intended 1371 ITITI in parietal (abdominal/chest wall, extremity, neck, pelvis) or visceral (liver, lung, peritoneum, adrenal) locations respectively; 83 patients received lymph node injections within either location. Imaging guidance was US in 68% of the cohort (US 161, CT+US 19); CT was used in 30% (81) & MRI in 1 patient. Median diameter of the ITITI lesion was 32 mm (8–230 mm). Median volume of the ITITI therapeutic material/session was 2 ml (1–6.9 ml). Lesions were accessed using a coaxial technique. ITITI delivery needles used at operator preference & tailored to lesion characteristics were either a 21G/22G Chiba, 21G Profusion (Cook Medical), 22G Morrison (AprioMed), 25G hypodermic (BD) & 18G Quadrafuse (Rex Medical). 2840 core biopsies (>18G Tru-cut core, Mission, Bard Medical) were performed in 237 patients during 690 procedures; biopsy sessions were often concurrent & of the ITITI site. 137 patients also underwent biopsy of a non-ITITI site (89 parietal location). Dimensions of the non-ITITI lesion were median 10 mm (7–113 mm); US image guidance was used in 97 patients (72%) to obtain a total of 1257, >18G Tru-core samples. 1.3% of injections resulted in SAE (NCI CTC AE >3) and 0.5% of 4097 biopsies developed major complications (SIR Criteria); both categories were manageable.

Conclusions Utilizing real time image guidance, ITITI to the administration of a myriad of investigational

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

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398 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.

Trial Registration NCT03860272

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399 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).