

CHANGING THE RADIATION AND IMMUNE-ONCOLOGY PARADIGM WITH THE RADIOENHANCER NBTXR3: OVERCOMING RESISTANCE TO ANTI-PD-1 BLOCKADE FROM THE BENCH TO THE CLINIC

¹Ari Rosenberg*, ²Jessica Frakes, ³Jiixin Niu, ⁴Jared Weiss, ²Jimmy Caudell, ⁵Patricia Said, ⁵Pavel Tyan, ⁵Sebastien Paris, ⁶Tanguy Seiwert, ⁴Colette Shen, ⁵Sergio Szyldergemajn, ⁵Omar Vivar, ⁵Leonard Farber. ¹University of Chicago, Chicago, IL, USA; ²Moffitt Cancer Center, Tampa, FL, USA; ³Banner MD Anderson Cancer Center, Gilbert, AZ, USA; ⁴University of North Carolina, Chapel Hill, NC, USA; ⁵Nanobiotix, Paris, France; ⁶Johns Hopkins Medicine, Baltimore, MD, USA

Background Numerous recent studies have assessed the future direction of radiation oncology. Now more than ever there is a need to examine the changing landscape of novel agents and approaches that improve radiation efficacy as well as amplify the immune response with certain therapies. Immune checkpoint inhibitors (ICIs) have led to improved treatment outcomes in a variety of cancers, however many patients exhibit resistance. Overcoming this resistance is a major challenge in immuno-oncology. Radiation therapy (RT) has emerged as a promising combination with ICIs since it may act in some settings to produce an immunomodulatory effect. NBTXR3, a radioenhancer, is injected one time intratumorally and activated by RT. NBTXR3 increases RT energy deposition inside tumor cells, subsequent tumor cell death, and tumor antigen release and thus in combination with ICI may overcome resistance.

Methods Pre-Clinical: Abscopal assays were conducted in immunocompetent mice. Anti-PD-1 sensitive or resistant lung tumor cell lines were injected in both flanks. Intratumoral injection of NBTXR3 (or vehicle) followed by RT 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 analyzed by immunohistochemistry (IHC).

Clinical A multicenter phase I trial [NCT03589339] is evaluating NBTXR3/RT/anti-PD-1 in 3 cohorts of patients with advanced solid tumors eligible for anti-PD-1: 1) Locoregional recurrent or recurrent and metastatic HNSCC, 2) Lung metastases, or 3) Liver metastases. NBTXR3 was administered by intratumoral injection. Stereotactic body RT (SBRT) was delivered at tumor-site selective doses per standard practice.

Results Pre-clinical studies demonstrated that NBTXR3/RT induces an immune response not observed with RT alone and enhances systemic control. IHC showed significant increase of CD8+ T-cell infiltrates in both NBTXR3/RT treated, and untreated tumors. Furthermore, NBTXR3/RT/anti-PD-1 improved local and systemic control in mice bearing anti-PD-1 resistant lung tumors, produced long-term memory, and reduced spontaneous lung metastases.

NBTXR3 intratumoral injection was feasible and safe. Preliminary signs of efficacy were observed in patients treated with NBTXR3/RT/anti-PD-1 including in patients refractory to anti-PD-1. Responses in distal, non-irradiated lesions were also observed in patients with resistance to anti-PD-1.

Conclusions With demonstrated radioenhancement as well as immune system priming, NBTXR3 positions itself to be a paradigm shift catalyst in the treatment of cancers in a variety of clinical settings- definitive, palliative, and metastatic. These data support further development of NBTXR3 in combination with anti-PD-1 as well as other ICIs.

Trial Registration NCT03589339

<http://dx.doi.org/10.1136/jitc-2022-SITC2022.0682>