NBTXR3 ACTIVATED BY RADIOThERAPY GENERATES AN ANTI-TUMOR IMMUNE RESPONSE

J. Thériau1, J. Welsh2, M. Loe1, S. Carrière1, Z. Papal1, A. Ducassou3, P. Rochaux1, Z. Saggi1, I. Peyrottes1, C. Shen4, N. Fernando2, B. Perez2, T.Y. Seiwert2,5, M. C. Château1, M. P. Sunyach5, P. Agoston6, S. Paris7, D. M. Dimitriu8, H. Brisse1, C. Ulick1, A. Lemee1,9, and S. Bouchet10

1Centre François Lacassagne, Villejuif, France; 2Northside Hospital, Atlanta, GA, USA; 3Institut Curie, Paris, France; 4Memorial Sloan Kettering Cancer Center, New York, NY, USA; 5Multidisciplinary Center of Medical Oncology, Inselspital, University Hospital, Bern, Switzerland; 6Insitut Claudius Regaud, Toulouse, France; 7Centre Claudius Regaud, Toulouse, France; 8Amsterdam University Hospital, Amsterdam, The Netherlands; 9Centre Antoine Lacassagne, Toulouse, France; 10Centre François Lacassagne, Villejuif, France

PURPOSE / OBJECTIVE(s)

The number of cancer patients undergoing radiotherapy (RT) is rapidly increasing due to the progress of radiation delivery techniques (1,2). Yet, RT advancement is limited due to potential toxicity to surrounding healthy tissues, highlighting a need to develop new strategies to improve RT tumor selectivity. NBTXR3, composed of otherwise inert hafnium oxide nanoparticles, was designed to effectively augment the effect of ionizing radiation, to increase tumor cell killing through a direct physical mechanism of action. Recent data also suggest NBTXR3 may increase immunogenic cell death (3-7). This is of particular importance given most patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) demonstrate innate (primary) resistance to checkpoint inhibition (i.e., anti-PD-1/PD-1 ligand therapy) (8). Thus, we hypothesized that intra-tumoral injection of NBTXR3, followed by RT may be a powerful means to convert the local immune microenvironment from a “cold” phenotype to a “hot” phenotype, which will increase the number of patients that respond to checkpoint inhibition. NBTXR3 may therefore promote a systemic anti-tumor response to local RT treatment, the abscopal effect.

RESULTS

Figure 1

Mice were injected in both flanks with CD8+ cells murine ovarian carcinoma cells (2 independent experiments, 12-14 mice/group). An intratumoral injection of NBTXR3 (at each site) was performed in right flank tumors, followed by RT (4 Gy). Tumor growth was followed, and animals sacrificed when tumors reached 800mm3.

Figure 2

Mice were sacrificed 3 days after the last fraction of irradiation and tumors (treated and untreated) excised for IHC analyses (4 mice/group, 3 slices/tumor). CD8+, CD8+ T cell lymphocytes (CD8+) were performed in right flank tumors, followed by RT (4 Gy). Tumor growth was followed, and animals sacrificed when tumors reached 800mm3.

Figure 3

Phase I, open-label, non-randomized, single arm study evaluating safety and feasibility of single intratumoral injections of NBTXR3, followed by modified radiation therapy (MRT) in locally advanced, recurrent, or metastatic HNSCC not eligible for radical surgery or definitive RT (NCT01468774). We present the results of a randomized phase II trial (NCT01933810).

NBTXR3 in Patients with Soft Tissue Sarcoma

Phase III, randomized, two-arm study evaluating the efficacy of NBTXR3 activated by RT, compared to RT alone, in patients with soft tissue sarcoma (STS) of the extremity or trunk wall (NCT023798845) (6). In both arms, pre-treatment biopsies and post-treatment tumor resections were analyzed by IHC to evaluate CD8+ (T cells), CD8+ (cytotoxic T cells), CD68+ (macrophages) and FOXP3+ (Treg) infiltrate densities.

IHC analyses revealed that, NBTXR3 activated by RT increased the number of CD8+ and CD68+ T lymphocytes in the tumors while decreasing the number of FOXP3+ (Treg) cells in the tumors. Macrophage cell numbers remained relatively constant.

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