Phase I study of NBTXR3 activated by radiotherapy in patients with advanced cancers treated with an anti-PD-1 therapy.

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Background:
Despite the past decade of transformative advances in immuno-oncology, the response rate to checkpoint inhibitors (ICIs) remains low (~15%). There is significant interest in developing strategies to overcome resistance to these treatments, thus increasing response rate. Emerging evidence suggests that radiation therapy (RT) could potentially augment the antitumor response to ICIs through synergic effect. However, RT dose and ultimate efficacy are limited by toxicity related to exposure of healthy tissues. NBTXR3 is a first-in-class radioenhancer administered by direct intratumoral injection, designed at the nanoscale to increase RT dose deposition within tumor cells and RT-dependent tumor cell killing, without increasing surrounding normal tissue toxicity. Preclinical and early clinical data suggest NBTXR3 activated by RT can trigger an anti-tumor immune response, producing both local and systemic (abscopal) effects. We hypothesize that NBTXR3 activated by RT, in combination with anti-PD-1 therapy (R3/RT/PD-1), will act synergistically to maximize the local RT effect and produce a systemic response sufficient to increase the proportion of ICI responders or convert ICI non-responders to responders.

Methods:
This trial [NCT03589339] is a multicenter, open-label, phase I study to evaluate safety and tolerability of R3/RT/PD-1 in three cohorts: (1) Locoregional recurrent or recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) amenable to re-irradiation of the HN field, (2) Lung metastases, or (3) Liver metastases, both from any primary cancer eligible for anti-PD-1 treatment. Approximately two-thirds of patients in each cohort will be anti-PD-1 non-responders. NBTXR3 injected volume is based on a percentage of gross tumor volume (GTV). The primary objective is to determine the R3/RT/PD-1 recommended phase 2 dose in each cohort. Secondary objectives are to evaluate anti-tumor response (objective response rate; ORR), safety and feasibility of NBTXR3 injection, and NBTXR3 body kinetic profile. Exploratory objectives will assess biomarkers of R3/RT/PD-1 response, including PD-L1 status by IHC, as well as mRNA and cytokine immune marker profiling. To date, three patients have been treated, one in cohort 1, two in cohort 2. Clinical trial information: NCT03589339.