A Phase I/II clinical study of NBTXR3 activated by SABR in combination with PD-1 inhibition in patients with advanced HNSCC or NSCLC

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Hafnium oxide nanoparticles (NBTXR3) activated by radiotherapy (RT) increase radiation dose deposit within cancer cells compared to RT alone. There are currently 7 clinical trials underway to evaluate NBTRX3 activated by RT, including a phase I/II study in elderly frail patients with locally advanced head and neck squamous cell carcinoma (HNSCC) [NCT01946867]. To date, no dose limiting toxicities (DLTs) have been observed. Studies in animals showed that NBTXR3 + RT can induce an immunogenic cell death-mediated abscopal effect which was not observed with RT alone. Furthermore, the immune cell infiltration profiles pre-treatment (biopsy) vs post-treatment (tumor resection) in patients with locally advanced Soft Tissue Sarcoma were modified in patients who received NBTXR3 + RT, compared to RT alone, as measured by immunohistochemistry. These results have led us to investigate the safety and systemic effect of NBTXR3 activated by stereotactic ablative radiotherapy (SABR) in combination with anti-PD-1 antibody in patients with more advanced disease: locoregionally recurrent or metastatic (to lung or liver) HNSCC, as well as in metastatic non-small cell lung cancer (NSCLC) and liver metastasis patients [NCT03589339].

Recent clinical studies have demonstrated the efficacy of anti-PD-1 in recurrent/metastatic HNSCC and metastatic NSCLC patients. However, only a subset of these patients benefits from this treatment, while most patients with recurrent/metastatic HNSCC and metastatic NSCLC demonstrate innate (primary) resistance to checkpoint inhibition and do not respond to initial therapy. There is thus an important unmet medical need of a curative treatment for this checkpoint inhibition-resistant population. We hypothesize that intra-tumoral/intralesional injection of NBXTR3 in the primary tumor or in one of the liver or lung metastases, followed by SABR may be a powerful mechanism to convert the local immune microenvironment to a “hot” phenotype and thus help to overcome resistance to immune checkpoint inhibition.

We have therefore designed an open label phase I/II, non-randomized clinical study of NBTXR3 activated by SABR in combination with PD-1 blockade in patients with recurrent or metastatic HNSCC, metastatic NSCLC , or liver metastasis*. The phase I primary objective is to determine the maximum tolerated dose(s), the early DLTs and the recommended dose(s) of NBTXR3. The Phase II primary objectives are Complete Response Rate of target lesion/s by

RECIST v1.1 for the locoregional recurrent group, Objective Response Rate by RECIST v1.1 for the metastatic group, and safety and tolerability of SABR activated NBTXR3 in combination with anti-PD-1 at the recommended dose(s) in both groups.

The mode of action of first-in-class NBTXR3 has already been demonstrated in a phase II/III randomized trial in locally advanced soft tissue sarcoma patients. NBTXR3 activated by RT met both primary and main secondary endpoints and demonstrated a significant superiority in terms of clinical benefits compared to RT alone [NCT02379845]. The combination of NBTXR3 activated by SABR and PD-1 inhibition may therefore be able to improve patient response in advanced HNSCC and NSCLC.

*****Metastatic patients must have received an approved anti-PD1 with SD for at least for 12 weeks or with confirmed PD at 12 weeks.

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