SO-006
Hafnium oxide nanoparticles activated by SBRT: a new interventional radiation therapy approach for the treatment of unresectable liver cancers

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Introduction: The treatment of liver cancers is challenging in part due to the presence of underlying liver diseases. In patients unsuitable for surgery, interventional radiation oncology approaches, i.e. minimally invasive image-guided therapeutic procedures, offer new treatment opportunities and can achieve good local control. NBTXR3, hafnium oxide nanoparticles, administered via intratumoral injection, increases energy deposit inside tumor cells only when activated by ionizing radiation such as stereotactic body radiotherapy (SBRT) and thus increase tumor cell death compared to radiation alone. Indeed, NBTXR3 showed statistically superior efficacy over RT alone in a phase II/III trial in soft tissue sarcoma [NCT02379845] and is currently being evaluated in phase I/II trials: head and neck [NCT01946867; NCT02901483], prostate [NCT02805894] and rectal cancers [NCT02465593]. The innovative physical mode of action of NBTXR3, which does not engage liver and renal functions might thus be beneficial to patients (pts) with unresectable hepatocellular carcinoma (HCC) or liver metastasis (mets).

Methods: A phase I/II clinical trial is being conducted to evaluate NBTXR3 activated by SBRT in patients with unresectable HCC or liver mets [NCT02721056]. The Phase I part follows a 3 + 3 dose escalation design with dose levels of NBTXR3 corresponding to 10, 15, 22, 33 and 42% of baseline tumor volume. Pts are treated with a single NBTXR3 intralesional injection (ILI) followed by SBRT (45 Gy or 50Gy/3-5 fractions/5 to 15 days). Primary endpoints include determination of the recommended phase II dose(s) and early DLTs. Secondary endpoints include assessment of global safety profile, liver function evaluated by Child-Pugh score (CPS), AST to Platelet Ratio Index (APRI), and response rate (mRECIST/RECIST 1.1).

Results: Four levels of the dose escalation part are finalized (n = 17): 6 pts at 10% (2 SBRT doses tested due to organs constraints), 4 pts at 15 and 22% (due to fiducial displacement and

ILI shift) and 3 pts at 33%. ILIs were successful and SBRT was delivered as planned with no observed DLT at any dose level. One NBTXR3-related AE (G1 fatigue at 33%), 4 ILI-related AE (G2 malaise, 10%; two G3 abdominal pain, 15% and G1 bilateral pleural effusion, 22%) and one bile duct stenosis (G3) related to cancer disease and possibly to RT coupled with NBTXR3 administration were reported. There were no significant changes in CPS or APRI post-treatment. CT scan assessment demonstrated absence of NBTXR3 leakage in surrounding tissues. So far, among 7 evaluable HCC pts, best mRECIST target lesion responses were: 3 CR and 4 PR. Among 5 evaluable liver mets pts, best target lesion responses were: 2 PR, 1 SD, and 2 PD.

Conclusion: NBTXR3 was well tolerated up to the 33% dose level and demonstrated a very good safety profile. The recruitment is ongoing at 42%. In patients with unresectable liver tumors and liver dysfunction limiting treatment options, the physics-based NBTXR3 mode of action may thus constitute a valuable solution.