HAFNIUM OXIDE NANOPARTICLES ACTIVATED BY SBRT: A NEW INTERVENTIONAL RADIATION THERAPY APPROACH FOR THE TREATMENT OF UNRESECTABLE LIVER CANCERS

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BACKGROUND
Management of hepatocellular carcinomas (HCC) and liver metastases (mets) requires complementary expertise from multiple specialties, particularly for treatment beyond first-line. In addition to the complex treatment decision after recurrence or progression, physicians also face a wide range of underlying liver dysfunctions and concomitant malignancies which further limit options. Among available treatments, stereotactic body radiation therapy (SBRT) is a well-tolerated and valuable alternative for patients who are not eligible for standard treatment such as surgery, local ablation or chemosensitization [1]. Yet, like all radiation therapy (RT) techniques, the maximal energy dose able to kill tumor cells is limited by toxicity to surrounding healthy tissues. NBTXR3, composed of otherwise inert hafnium oxide nanoparticles, was designed to effectively absorb ionizing radiation to increase the RT dose deposited within the tumor cells when activated by RT, thereby increasing tumor-specific cell killing through DNA damage and enhancing immunogenic cell death [2,3]. This first-in-class radio-enhancer recently met both of its primary and key secondary endpoints in a positive Phase IIb study in locally advanced or metastatic sarcoma, and is being currently evaluated in phases III studies for head and neck (NCT01520697, NCT03356333), prostate (NCT02038085) and rectum cancers (NCT02440352). This study evaluates NBTXR3 activated by SBRT as treatment for subject with unresectable HCC or liver mets that are ineligible for standard care (SOC) or for whom SOC does not exist, such as HCC with portal vein tumor thrombosis (PVTT), and/or unresectable liver metastases.

METHODS
Study design: Phase II, prospective, open-label, single arm, randomized study of NBTXR3 administered by intravenous injection and activated by SBRT in the treatment of patients with liver cancers [NCT02048793]

Phase 1
1.3 - 3 dose esdiation design was adopted with dose levels of NBTXR3 ranging from 15, 10, 5 and 2.5% of hafnium tumor dose.

Primary Endpoint: To determine the recommended phase II Dose Level (DL) i.e. volume of NBTXR3 and the incidence of Dose Limiting Toxicity (DLT) of NBTXR3 administered by intravenous injection- activated by the NCBT3 (NCT01520697).

Key Secondary Endpoint: To evaluate the safety and tolerability of NBTXR3, and the incidence of DLT of NBTXR3 administered by intravenous injection- activated by the NCBT3 (NCT01520697).

Phase 2
Following the administration of the PFD in Phase 1, a subsequent phase IIb study was conducted in a prospective phase II trial -
- Group A: locoregional cancer
- Group B: distant hepatic metastasis

Patients included criteria:
- Age: ≥ 18 years
- NBTXR3 eligible for cancer surgery or other curative treatment at the time of the first injection
- No active infection
- No active hepatitis
- No co-morbidity

Endpoints:
- Assessment of a single administration of NBTXR3 (20 mg/kg of hafnium (Hf), as an intravenous injection) activated by SBRT at 4 fractions of 5 Gy each, 1 for the 1st and 2 for the 2nd dose level.
- The first 15 patients would be treated at the first dose level and 2 additional doses of 2 patients for the 2nd and 3rd dose levels.
- The 2nd dose level: 10 patients will receive 45 Gy or 50 Gy (or 4 fractions of 12.5 Gy each)
- Safety

PATIENTS CHARACTERISTICS

PRELIMINARY SIGNS OF EFFICACY

CONCLUSIONS

The intratumoral injection of NBTXR3 in the liver is feasible
NBTXR3 remains localized within the tumor
NBTXR3 was well tolerated up to the 33% dose level
NBTXR3 showed a very good safety profile with no early DLTs
Patient recruitment is ongoing at the 42% dose level
NBTXR3 represent a valuable option in patients with HCC not amenable to curative local treatment or with unresectable liver metastases

REFERENCES