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Title (maximum 100 characters)

Phase I/II trial of hafnium oxide nanoparticles activated by SBRT in the treatment of liver cancers

E. Chajon[1], M. Pracht[2], T. De Baere[3], T. V. F. Nguyen[3], J. P. Bronowicki[4], V. Vendrely[5], A. S. Baumann[6], V. V. Croisé-Laurent[4], E. Rio[7], Y. Rolland[1], S. Le Sourd[1], P. Gustin[3], C. Perret[7], F. Mornex[8], D. Peiffert[9], P. Merle[8], and E. Deutsch[3]

[1]Centre Eugène Marquis - Département de Radiothérapie, Rennes, France, [2]Centre Eugene Marquis, Rennes, France, [3]Gustave Roussy, Villejuif, France, [4]CHU de Nancy, Nancy, France, [5]University Hospital of Bordeaux, Bordeaux, France, [6]Institut de Cancérologie de Lorraine, Nancy, France, [7]Institut de Cancérologie de l'Ouest, Nantes, France, [8]Centre Hospitalier Lyon Sud, Pierre Bénite, France, [9]Institut de Cancérologie de Lorraine, Vandoeuvre-Les-Nancy, France

Purpose/Objective

Patients with hepatocellular carcinoma (HCC) and liver metastasis (mets) present with a wide range of underlying liver dysfunctions and concomitant malignancies. Stereotactic body radiation therapy (SBRT) is well-tolerated and a valuable alternative for patients who are not eligible for invasive procedures. Yet, like all radiation therapy (RT) techniques, the energy dose deposit to tumor cells is limited by the surrounding healthy tissues. NBTXR3, composed of hafnium oxide nanoparticles, was designed to effectively absorb ionizing radiation and augment the dose deposit within the tumor cells only when activated by RT, thereby increasing tumor-specific physical killing through DNA damage/cell destruction and enhancing the immunogenic tumor cell death.

Material/methods

Patients suffering from primary HCC (with/without portal vein tumor thrombosis) or liver mets were included and treated with a single intralesional injection (IL) of NBTXR3 followed by SBRT (45 Gy/3 fractions/5 to 7 days).

The phase I part of the study was designed as a 3 + 3 escalation dose with tested dose levels at 10%, 15%, 22% and 33% of baseline tumor volume. Primary endpoints include the determination of the recommended dose and incidence of early dose limiting toxicities (DLTs). Secondary endpoints include assessment of global safety profile, characterization of the body kinetic profile, liver function evaluated by Child-Pugh score (CPS), AST to Platelet Ratio Index (APRI), and response rate (mRECIST/RECIST v1.1).

Results

The enrollment is complete in the first 3 dose levels: 10% (6 pts), 15% (4 pts) and 22% (4 pts) and is ongoing at the last IL dose level at 33% with no early DLTs, no AE related to NBTXR3, and no serious AE related to RT or the injection. So far, four AEs related to the IL were observed (Malaise, grade 2; two Abdominal pain, grade 3 and Bilateral pleural effusion, grade 1) at dose level 10%, 15% and 22% respectively. NBTXR3 remained localized within the tumor, validating the relevance of the single IL. No relevant change in CPS or APRI was observed over time which is consistent with the low toxicity observed.

In 7 HCC pts evaluable for response, the mRECIST assessment by MRI on target lesions resulted in the following best observed response: 3 complete responses, 3 partial responses and 1 stable disease. In

5 evaluable liver mets pts, the RECIST v1.1 assessment by MRI on target lesions resulted in the following best observed response: 1 partial response, 3 stable disease and 1 local progressive disease.

Conclusion

NBTXR3 was well tolerated and showed a promising safety profile. Recruitment at the highest dose level of 33% is ongoing for the IL part and, once completed, will be followed by the expansion phase.

NBTXR3 is also being evaluated in 6 other clinical trials, including a phase II/III trial in soft tissue sarcoma [NCT02379845] and phase I/II trials in prostate [NCT02805894], head and neck [NCT01946867] and rectum cancers [NCT02465593].