Hafnium oxide nanoparticles: an emergent promising treatment for solid tumors

L. Levy[1], C. Le Tourneau[2], P. Sargos[3], Le Pechoux[4], G. Kantor[3], T. De Baere[4], A. Le Cesne[4], V. Moreno[5], E. Calvo[5], S. Bonvalot[2]

[1]Nanobiotix, Paris, France; [2]Institut Curie, Paris, France; [3]Institut Bergonié, Bordeaux, France; [4]Institut Gustave Roussy, Villejuif, France; [5]START Madrid, Spain

To improve tumor response, radiotherapy (RT) has been combined with chemical agents, radiosensitizers and monoclonal antibodies. However, the complexity of these associations in terms of pharmacology, local control, clinical outcome benefits or patient quality of life underlines the need for the development of new therapeutic approaches.
A new class of material with high electron density, hafnium oxide, was designed at the nanoscale in the form of crystalline 50nm-particles (HfO2-NP) to efficiently absorb ionizing radiation and increase the radiation dose deposited - "hot spots" of energy deposit - from within the tumor cells to more focus and efficient cell killing. Additionally, this physical cell killing that could be applicable across solid tumor also triggers immunogenic cell death that could lead to immune response reinforcing local effect but also opening a potential systemic activity.

Preclinical studies have demonstrated increase of cancer cells death *in vitro* and marked antitumor efficacy *in vivo* in presence of these nanoparticles (HfO_2-NP) exposed to RT, when compared to RT alone. Hafnium oxide nanoparticles efficacy was assessed in cancer epithelial and mesenchymal tumor models and on patient-derived tumor xenografts in nude mice, showing superior anti-tumor effects, over radiation therapy alone in terms of complete response and overall survival. Additionally, *in vivo* cancer epithelial models in immunocompetent mouse have showed that HfO2-NP + RT triggers immunogenic conversion of the tumor microenvironment and generate an abscopal effect while this effect is not observed with RT alone.

HfO2-NP (NBTXR3), administered as a single intratumoral injection and activated by radiotherapy, is currently evaluated in clinical trials including soft tissue sarcoma (STS) [NCT02379845], head and neck [NCT01946867], prostate [NCT02805894], liver [NCT02721056; NCT02721056] and rectum cancers [NCT02465593]. Patients treated in phases I have had a good tolerance to the product and received radiotherapy as planned, confirming a very good local safety profile.
Besides, consistently with non-clinical studies, preliminary results of the phase II / III in patients with STS, beyond the expected cytotoxic effect induced by NBTXR3 + RT, suggest a release of tumor neoantigens during cancer cell death and stimulation of local immunological effects. This immunogenic cell death might convert “cold” tumor into “hot” tumor. Further analyses are ongoing to reinforce these findings.

So far, 131 patients have been treated with NBTXR3 + RT. These first-in-class nanoparticles have showed marked antitumor efficacy in non-clinical studies, and promising results in terms of benefit-risk ratio assessment in patients with locally advanced soft tissue sarcomas and head and neck squamous cell carcinoma. Moreover, the immunogenic cell death and improvement of the immune response demonstrated in preclinical studies and under investigation in clinical trials, lead to new perspectives to use this product as a local and systemic treatment or to be combined with immunotherapeutic agents.