Title: The First-In-Class Radioenhancer NBTXR3: from Cancer Cell Destruction to Antitumor Immune Response Activation

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Abstract:
For decades, radiotherapy (RT) has been a fundamental component of solid tumor treatment. Currently, at least half of cancer patients undergo radiotherapy as part of their treatment.
Significant improvements have been made in the technical aspects of RT in recent years. The development of new irradiators and imaging systems has greatly enhanced the efficacy of RT while minimizing side effects. However, the radiation-induced damages to healthy tissues traversed by X-rays before reaching the tumor mass limits the usable dose for patient treatment, making it essential to develop new approaches to unlock the full therapeutic potential of RT while preserving patient's safety.
In 2011, NBTXR3 emerged as the first-in-class radioenhancer used in clinical practice for treating patients with locally advanced soft tissue sarcoma (NCT01433068). NBTXR3 also became the first radioenhancer to receive CE mark approval (Hensify®) after successfully completing a phase II/III clinical study (Act.in.Sarc study, NCT02379845).
NBTXR3 nanoparticles, delivered to tumors in a single intratumoral injection session, consist of a functionalized core of hafnium oxide, a high atomic number element, and were specifically designed to amplify the effects of RT within cells without additional side effects on healthy tissues. Leveraging this physical mechanism, radiation-activated NBTXR3 has demonstrated superior efficacy in destroying tumor cells and controlling tumor growth in numerous preclinical models and in humans, surpassing the effects of RT alone, while maintaining a favorable safety profile.
Recent preclinical investigations have revealed that the benefits of NBTXR3 extend beyond mere radioenhancement and improved cancer cell destruction. Specifically, NBTXR3 has been reported to possess immunomodulatory properties through 1) induction of DNA damage, leading to activation of the cGAS-STING pathway, 2) promotion of immunogenic cell death, 3) enhancement of immunopeptidome presentation, 4) generation of an antitumor immune response leading to the production of an abscopal effect mediated by CD8+ cytotoxic lymphocytes. Notably, recent preclinical studies have demonstrated that the addition of NBTXR3 to RT significantly improves the efficacy of various treatment regimens (RT plus anti-PD1 and combinations with other checkpoint inhibitors) in terms of tumor growth, abscopal effect, and survival in a two-tumor mouse model of anti-PD1-resistant lung cancer. A very recent study has also shown that the immunomodulatory effects of NBTXR3 are achieved when NBTXR3 is combined with proton therapy. Moreover, all these studies (X-ray and proton) reported a robust activation of the antitumor immune response, restoration of the effectiveness of anti-PD1 therapy, and the induction of memory response in cured mice.

Biography:

Sébastien Paris obtained his Ph.D. in Cellular and Molecular Biology from the University of Rouen, France, in 2000. During this period, his work focused on understanding the mechanisms

of formation of lung metastases. After various international experiences in different research teams, he worked for several pharmaceutical and biotechnological companies for more than 15 years. Since 2014, Sébastien has been with Nanobiotix, a pioneering company at the forefront of nanomedicine for the treatment of solid tumors, where he holds the position of Director, Global Head of the Translational Science Department. Here, he and his team have had the privilege of deepening our understanding of the radioenhancer NBTXR3, particularly focusing on the profound impact of the nanoparticles on the antitumoral immune response. Throughout his career, Sébastien has been focused on cancer research.