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Review of clinical applications of radiation-enhancing nanoparticles

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ABSTRACT

Purpose: Clinical evidence of the radiation-enhancing effects of nanoparticles has emerged.
Materials and methods: We searched the literature in English and French on PubMed up to October 2019. The search term was “nanoparticle” AND “radiotherapy”, yielding 1270 results.
Results: The two main NP used in clinical trials were hafnium oxide and gadolinium involving a total of 229 patients. Hafnium oxide NP were used in three phase 1/2 trials on sarcoma, head and neck squamous cell carcinoma or liver cancer and one phase 2/3 trial. There are six ongoing phase 1/2 clinical trials to evaluate the combination of gadolinium-based NP and RT for the treatment of brain metastases and cervical cancer.
Conclusion: So far, intratumoral hafnium oxide nanoparticles were safe and improved efficacy in locally advanced sarcoma.

1. Introduction

Approximately three million patients in Europe are undergoing cancer treatment. Treatment options include systemic (chemotherapy, targeted therapies, immunotherapy) as well as local therapies. Radiotherapy is a cornerstone of local tumor control and is used in more than half of cases. Some tumors are not resectable, and local treatment is performed with RT alone. Technical advances in radiotherapy have allowed treated patients to live longer and with fewer side effects. However, despite recent technological innovations, more than half of these patients will have a local or distant recurrence, as some tumors are resistant to conventional radiotherapy treatments. For these patients, the challenge is to further optimize the efficacy/tolerability ratio of radiotherapy. To this end, a new class of drug without systemic effects and a new generation of radio-enhancing treatments, based on nanoparticles, has recently been developed in order to optimize the therapeutic index. A nanoparticle is defined as an element whose three dimensions are on a nanometric scale, i.e. a particle having a nominal diameter of less than approximately 100 nm. On this scale, the laws of physics for a given compound are not the same as on a macroscopic scale: New, additional, and specific properties appear (described in the next section).

Proof of concept of nanoparticles activated by radiotherapy has been established for several years. Most of the data are from preclinical studies [1]. More recently, clinical evidence for combining nanoparticles with radiotherapy has begun to emerge for certain tumors, holding great promise as an addition to the therapeutic arsenal in oncology. No published paper reports the clinical applications of nanoparticles in combination with radiotherapy. In this context, the purpose of this manuscript was to review the clinical evidence of the radiation-enhancing effect of nanoparticles and the state of current clinical research.

2. Materiel and methods

We conducted a systematic review of the English and French literature, published up to March 2020, using search terms including “radiotherapy” AND “nanoparticles”. The search yielded 1270 results, among which only clinical studies were selected.

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Articles concerning nanoparticles used as chemotherapy vectors were excluded from the analysis and only nanoparticles with a direct radio-enhancing effect were retained (Fig. 1). Ultimately, two nanoparticles stood out for their use in clinical trials in combination with radiotherapy: Hafnium oxide known as NBTXR3 and gadolinium-based nanoparticles or AguiX. These nanoparticles have been selected among other nanoparticles as radioenhancers because of the absence of degradation and redox activities, its capacity to amplify the energy deposit within tumors when radiotherapy is on, its intratumoral persistence during radiotherapy, and its very good safety when radiotherapy is off.

This review also discusses open clinical studies registered on clinicaltrial.gov concerning radiation-enhancing nanoparticles. The results presented below are organized by tumor location to give an overview of the potential clinical applications.

3. Radio-enhancement by NP

The goal of radiotherapy is to improve local control by optimizing the destruction of tumor tissue while preserving surrounding healthy tissues. Two main strategies are used to achieve this result:

- Improve delivery of the treatmentby increasing precision and dose deposition using recent high-precision radiotherapy techniques such as conformational intensity-modulated radiotherapy and stereotactic radiotherapy.
- Radio-enhance the destruction of cancer cellsby using radiosensitizing or radio-enhancing agents.

In addition to the radio-sensitizing chemical agents acting on hypoxia and presence of oxygen in tumors, a new generation of so-called radio-enhancer molecules has emerged in recent years along with the development of nanoparticles.

Two types of nanoparticles can be distinguished:

- NP as vectors for chemotherapy, which deliver chemotherapy drugs into the tumor. Examples include paclitaxel (nab-paclitaxel) and camptothecin (CRLX101).
- NP with a direct radio-enhancing effect, the metal-based NP.

Nanoparticles that have shown evidence of clinical efficacy are those composed of elements with a high atomic number (Z), able to absorb high energy photons, which locally amplifies energy deposition directly within the cancer cells (described in the next section).

3.1. Physical mechanism of NP radio-enhancement

When a beam of ionizing radiation penetrates into a tissue, part of the radiation is absorbed, part is deviated from its trajectory (phenomenon of diffusion) and a third part is delivered without interaction. The phenomenon of diffusion explains why zones situated outside the radiation beam can nonetheless receive a part of the radiation dose.

3.1.1. Interactions of radiation with tissue

Incident photons transfer their energy to the molecules in the medium they cross, *via* different fundamental mechanisms of interaction. This leads to ionization or excitation of atoms, then to emission of lower energy secondary photons when the molecules relax to a stable state. These secondary photons can in turn lead to ionization or excitation of electrons.

3.1.2. Interactions of radiation with tissues in the presence of nanoparticles

The mode of action of nanoparticles is analogous to that of ionizing radiation and can be described as follows:

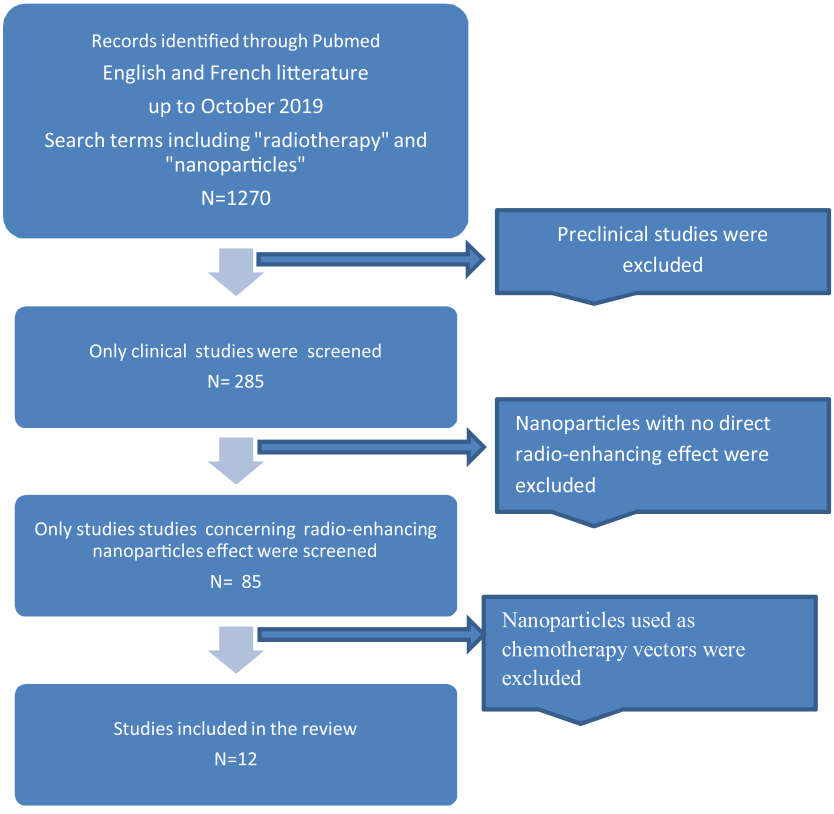

Fig. 1. Flow diagram for selection of studies.

When nanoparticles are not activated, they have no effect because they are inert. When activated by X-rays, the X-rays are absorbed by the metal-based NP.

As the probability of an element absorbing a photon is proportional to its atomic number (Z), the core of the nanoparticle will generate the same types of effects as those of water, but of a much higher order of magnitude;

- The ejected electron crosses the cellular medium and loses its energy by interacting several times with water molecules (present in all tissues), creating free radicals (the major source of the sought-after cellular damage);
- The atom returns to its initial state by removing an electron from a water molecule in the ambient medium.

Thus, X-ray irradiation can be applied several times on the same nanoparticles, because these particles return to their initial state after interacting with X photons (on-off effect).

3.2. Biological mechanisms of NP radio-enhancement

Parallel to this physical interaction characterized by the secondary diffusion of energy on the surface of the metallic particles, which leads to an increase in DNA damage, some studies suggest that biological pathways are also involved. The free radicals generated by the electrons ejected from the metal-based NP and from water are highly reactive and tend to break the covalent bonds of molecules they encounter. In fact, an increase in cell death mechanisms such as apoptosis, necrosis and autophagy has been demonstrated when irradiated cells enter into contact with NP [2]. Nanoparticles with a physical mode of action were able to enhance pathway activity of cancer cells via increased DNA damage, compared to RT alone [3]. In this way, non-specific damage occurs in the cells surrounding the nanoparticles or along the path followed by the electrons during their many interactions with the surrounding medium. The resulting cell destruction is caused by the usual effect of free radicals, as with radiotherapy, but it is enhanced thanks to the X-ray-activated nanoparticles, whose mode of action is analogous to that of ionizing radiation on biological systems. Therefore, in addition to the physical properties of NP, these biological effects largely contribute to the radio-potentiation of tumor tissue. To conclude, RT-activated nanoparticles could play an important role in the enhancement of the antitumor immune response [3].

3.3. Routes of administration

Two routes of administration are used in the clinic: Direct intratumoral injection or intravenous. Studies have suggested that intratumoral injection can increase the concentration of agents at the target site, while decreasing their localization to healthy tissues. This route of administration can be used for accessible tumors and has the advantage of delivering the exact quantity of NPs for the tumor volume. Hafnium oxide nanoparticles are intended for intratumoral injection and have been classified in the EU as a medical device. Gadolinium based nanoparticles are smaller intravenous drugs. After their intravenous administration, nanoparticles can circulate in blood vessels and extravasate in tumoral tissue due to Enhanced Permeability and Retention (EPR) effect without extravasation in healthy tissues, before their elimination by the kidneys.

4. Clinical use of NP according to tumor type

Table 1 present a summary of clinical applications of radiation enhancing nanoparticles according tumor locations.

4.1. Soft tissue sarcoma (STS)

The first clinical study on the combination of NP and RT was conducted in France between 2011 and 2014 (NCT01433068) [4]. The results of this phase 1 study were reported for the first time by Bonvalot et al. at the 2014 ASCO congress. The study endpoints included determining the recommended dose, the safety profile, and the feasibility of combining an intratumoral injection of hafnium oxide nanoparticles (NBTXR3) with external beam radiotherapy (50 Gy) for preoperative treatment of adults with locally advanced soft tissue sarcoma. A single intratumoral injection of NP corresponding to 10 % of the baseline tumor volume was technically feasible with manageable toxicity. The NP injections were well tolerated and the NP were stable and remained within the tumor volume with no leakage in the surrounding tissue (CT scan post injection) or intravenously (PK) after injection. Encouraging signs of antitumor activity were observed in different sarcoma subtypes.

Based on these results, a randomized, multicenter, international phase 2/3 trial was conducted between 2015 and 2017 comparing preoperative RT alone versus an investigational arm involving intratumoral NBTXR3 injection prior to RT. The study results were initially presented at ASTRO in October 2018 and recently published by Bonvalot et al. [5]. One hundred eighty patients with STS of the extremity or trunk wall, and requiring preoperative RT were enrolled and randomized in a 1:1 ratio. RT was administered as 25 fractions of 2 Gy in three-dimensional mode or by intensity-modulated radiotherapy. A total of 176 patients (89 in the NP group and 87 in the RT alone group) subsequently underwent surgery after completion of RT. The primary endpoint was the proportion of pathological complete response with central blind review, defined as the presence of < 5 % residual malignant viable cells. The pathological complete response rate was 16.1 % in the NP group versus 7.9 % in the RT alone group ($p = 0.04$), i.e. rate increased by twofold in the presence of nanoparticles. 77 % of patients in the NP group versus 64 % with RT alone achieved R0 resection margins ($p = 0.04$). The overall safety profile of NBTXR3 activated by RT was similar to that of patients receiving RT alone, with transient, reversible and manageable immune reactions

Table 1
Summary of clinical applications of radiation enhancing nanoparticles according tumor locations.

Radiation-enhancing nanoparticles	Clinical applications according tumor locations
hafnium oxide nanoparticles	Soft tissue sarcoma of the extremity and trunk wall Head and neck squamous cell carcinoma in patients not eligible for chemotherapy locally advanced cervical cancer Unfavorable intermediate risk or high risk prostate adenocarcinoma Hepatocellular carcinoma and liver metastasis Locally advanced or unresectable rectal cancer Recurrent head and neck squamous cell carcinoma, lung or liver metastases in association with PD-1 inhibitors
gadolinium-based nanoparticles	Brain metastases Locally advanced cervical cancer

observed in patients from both arms. This is the first phase 2/3 trial comparing the efficacy of NP radio-enhancement in combination with RT. The data from Act.In.Sarc form the basis of the first European market approval (CE marking) for NBTXR3 in advanced Soft Tissue Sarcoma of the extremity or trunk wall, under the name Hensify®.

4.2. HNSCC (Head and neck squamous cell carcinoma)

Head and neck cancers are the second tumor location studied with the combination of hafnium oxide NP and RT.

RT in combination with systemic therapies is currently the standard care for locally advanced head and neck cancer. This combination confers a significant improvement in local control but at the cost of higher toxicity and no survival benefit in the oldest patients [6–10]. The benefit of NP in this indication would be to increase the destruction of cancer cells while preserving adjoining tissues and local functional status in patients over age 65 who are not eligible to receive concomitant systemic therapy.

The preliminary data of the phase 1 study (NCT01946867) were reported for the first time at ASCO 2017 by Le Tourneau et al. [11], and the final results were presented by Calugaru et al. at ASTRO 2018 [12]. This was a phase 1/2, single arm, open-label, non-randomized study evaluating safety and feasibility of a single intratumoral injection of NBTXR3 followed by IMRT. The study was conducted in elderly patients with locally advanced squamous cell carcinoma of the oral cavity and oropharynx, not eligible for cisplatin or to cetuximab. The primary endpoint included determination of the recommended dose (RD) and the incidence of early DLT. Secondary endpoints were the objective response rate, progression-free survival, local progression-free survival and NBTXR3 pharmacokinetics. The NBTXR3 recommended dose was determined by a 3 + 3 escalation dose with four dose levels at 5 %, 10 %, 15 % and 22 % of the baseline tumor volume. Patients received a single intratumoral injection of NP on day 1, followed by IMRT starting 24 h later (day 2), 70 Gy in 35 fractions of 2 Gy. The study followed 17 patients with a mean age of 79 years, 12 men and 5 women. Six patients had a tumor of the oral cavity and 11 of the oropharynx and 9 patients were HPV+ (8 oropharynx). No early DLT or serious adverse events related to hafnium oxide NP or injection procedure were observed at the tested dose. The authors verified the persistence of NBTXR3 within the tumor and absence of leakage. Target response was assessed by RECIST 1.1: 8 patients had a complete response (6 at doses > 10 %) and 4 patients had a partial response. Recruitment is complete at the maximum dose level at 22 %. The escalating doses were well tolerated and the overall safety profile is positive, even at the highest dose level (22 %) with no early DLT or SAE related to NBTXR3 or to the injection procedure. The current preliminary efficacy findings are encouraging with complete responses and durable disease control over time. Since January 2019 a consolidation study has been started with the aim of recruiting 44 patients treated with RT and an intratumoral injection at the highest dose level (22 %). These results open promising perspectives for a population that is poorly represented in clinical trials. Based on these results, a phase III clinical trial is planned.

NBTXR3 has also been evaluated in combination with concurrent chemotherapy in patients with head and neck cancer. This phase 1–2, single arm, open-label, non-randomized study in Taiwan will evaluate safety and feasibility of a single intratumoral injection of NBTXR3 followed by radiochemotherapy [NCT02901483]. The objectives of this study are similar to those above. Its originality lies in the fact that eligible patients will receive standard radiochemotherapy with cisplatin 40 mg/m^2 weekly for inoperable T3 or T4 squamous cell carcinoma of the oral cavity or who refuse surgery. Recruitment is ongoing and the preliminary results are pending.

4.3. Pelvis

Radiochemotherapy followed by uterovaginal brachytherapy is the standard treatment for locally advanced cervical cancer [13]. A phase 1 study *(NCT03308604)* begun in 2017 aims to evaluate the safety and tolerability of gadolinium nanoparticles AGuIX in combination with radiochemotherapy and brachytherapy for locally advanced cervical cancer. All patients will receive external beam RT to the pelvis over 5 weeks with an integrated boost in case of macroscopic lymph node metastases. Patients will also receive concurrent weekly intravenous cisplatin chemotherapy for 5 cycles followed by uterovaginal brachytherapy within 14 days following external beam RT. AGuIX nanoparticles will be administered by IV at escalating doses (3 dose levels: 20, 30 then 50 mg/kg) on the first day of RT, then 10 days later. A third injection will be given at the time of brachytherapy.

For locally advanced prostate cancer, external beam radiotherapy plus hormone therapy is the standard treatment. Hafnium oxide NP is being investigated in a phase 1/2 study *(NCT02805894)* in the USA in patients with unfavorable intermediate risk or high-risk prostate adenocarcinoma. This is an open-label, non-randomized trial in two parallel groups and in two consecutive steps with a dose escalation and a subsequent expansion of the final dose. The NP is administered by intra-prostate injection 10 days before RT (the injected dose is not known). Group A will receive exclusive external beam IMRT to the prostate and proximal seminal vesicles at a dose of 45 Gy in 25 fractions of 1.8 Gy, followed by an additional dose of 34.2 Gy in 10 fractions to the prostate and proximal seminal vesicles. Group B will receive high dose rate brachytherapy 15 Gy as a single fraction to the prostate followed by an additional dose to the prostate and proximal seminal vesicles delivered as 45 Gy in 25 fractions of 1.8 Gy using IMRT. Both groups will receive androgen deprivation therapy. Recruitment is ongoing and the preliminary results are not yet known.

4.4. Gastro-intestinal (GI)

Controlling liver cancer in case of hepatic impairment is a challenge despite advances in RT. The use of stereotactic RT has increased the rate of local control of liver metastases and HCC. Nevertheless, in case of hepatic dysfunction or immediate proximity to radiosensitive organs (intestine, duodenum), it is difficult to deliver sufficient doses. It is in this context that NBTXR3 could be beneficial when used in combination with SBRT. In a phase 1/2 open-label, prospective study conducted in several French centers (NCT02721056), patients were given NP by a single intralesional injection or by super selective transcatheter arterial injection one day prior to SBRT at a dose of 45 Gy in 3 fractions delivered every other day. This was a two-phase study with dose escalation at 10 %, 15 %, 22 %, and 33 % of the baseline tumor volume. A first dose escalation phase determined the recommended dose of NBTXR3 and provided data on the toxicity profile, tolerability and clinical activity. A second expansion phase in the cohort using the recommended dose of NBTXR3 is scheduled to evaluate efficacy. The results of this trial were reported at ASTRO 2019 by Chajon et al. [14]. 17 patients have been treated up to a dose level of 33 %. No significant side effects or dose limiting toxicity occurred. Hepatic biological tolerability was good. The only adverse event reported in one patient was grade 1 fatigue at the 33 % dose level. No leakage of NP was detected on the CT scans. In the efficacy analysis, a radiological response was observed in 9 out of 12 evaluable patients and progressive disease in 2 patients. A higher dose level of 42 % is currently under study.

In locally advanced rectal cancer, preoperative chemotherapy plus external beam RT improves local control [15]. A trial is under

way in Taiwan to study RT plus NBTXR3 chemotherapy for treatment of locally advanced T3 or 4 unresectable rectal cancer *(NCT02465593)*. This is a phase 1/2, prospective, open-label trial with a first 3 + 3 dose escalation phase to identify the recommended NP dose for intratumoral injection, followed by an expansion phase at the recommended NP dose to evaluate for efficacy. Eligible patients will receive an NP intratumoral injection the day before IMRT, delivered as 50 Gy in 25 fractions, to gross tumor volume and involved lymph nodes combined with prophylactic pelvic lymph node irradiation at 45 Gy in 25 fractions. This treatment will be given concurrently with oral capecitabine chemotherapy and 5-FU according to the standard protocol. Total mesorectal excision surgery will take place 8 weeks after completion of radiochemotherapy. Recruitment for this study is ongoing and the preliminary results are pending.

4.5. Brain metastases

RT is commonly used in the treatment of brain metastases, either as adjuvant therapy to increase local control after surgical resection, or as an exclusive treatment [16]. Stereotactic RT helps to increase local control rates but applies only to patients with few metastases measuring $\leq$5 and small in size without extracerebral evolutive disease [17].

Gadolinium nanoparticles, or AGuIX, are the only nanoparticles to be tested for this indication in combination with brain RT. NANO-RAD (NCT02820454) is a phase 1 trial in patients with brain metastases that are not eligible for surgical resection or SBRT [18]. This study aims to determine the maximum tolerable dose and the toxicity profile of AGuIX NP in combination with whole brain RT in three-dimensional mode (30 Gy in 10 fractions). The particularity of this NP is that it must be injected intravenously, in contrast to the intratumoral injections described above. Dose escalation was studied using the modified toxicity probability interval with 3 dose levels: 20, 30 and 50 mg/kg. Another advantage besides their radio-enhancing properties could be their theranostic capacity as shown in preclinical studies with the possibility of acting as an MRI contrast agent [19]. The results of this study are not yet known but are expected shortly. Meanwhile, a phase I trial (NCT04094077) and a phase 2 multicenter trial (NCT03818386) were opened in January 2019.

5. Immunotherapy, radiotherapy and nanoparticles

Historically, RT exerts its local antitumor effect by inducing DNA damage in tumor cells. RT can also induce a systemic anti-tumor immune response by activating the immune system, leading to immunogenic cell death with release of neoantigens and pro-inflammatory molecules. This so-called abscopal effect is responsible for the tumor response, not only at the irradiated site but also in tumor tissue at a distance from the irradiated site. However, this phenomenon is rare and RT alone is not sufficient to overcome the immunosuppression induced by the tumor and its microenvironment. This is why the combination of RT and immunotherapy is being widely studied and the results seem very promising. More recently, the combination of NP and RT seems to show a potentiation of immune reactions.

The initial findings were presented at ASTRO 2019 by Thariat et al. [20]. Animal studies have shown that NBTXR3 + RT can prime an immune response which is not observed with RT alone, with an increase in CD8 + T cell infiltrates. In the same way, tumor tissue was analyzed from patients with soft tissue sarcoma enrolled in the *Act.in.Sarc* trial cited above. Pre-treatment (biopsies) and post-treatment samples (tumor resection specimens) were analyzed and compared between the two arms. There was a larger increase in CD8 + T cells and CD8 and PD1 biomarkers in patients treated with NP + RT versus RT alone. Other preclinical studies have shown that hafnium oxide increased IFN-β secretion in irradiated cells [21]. The data suggest that NBTXR3 could increase the efficacy of radiation and improve tumor immunogenicity. These NP could therefore convert the local tumor microenvironment to a more sensitive phenotype that would be more responsive to immunotherapy.

In light of this, a phase 1 trial (NCT03589339) in the USA is investigating NBTXR3 in combination with an anti-PD1 checkpoint inhibitor and SBRT in patients with locally recurrent or metastatic HNSCC, metastatic NSCLC and in patients with liver metastases. Recruitment for this study is ongoing and the preliminary results are pending.

6. Conclusion

Two radio-enhancer nanoparticles are currently under investigation in clinical trials: hafnium oxide NP and gadolinium NP. When activated by RT, they increase dose deposition within tumor tissue compared to RT alone. Recently, clinical evidence of the benefits of adding NP to RT has emerged. Eleven clinical trials investigating hafnium oxide or gadolinium NP in combination with RT have been started and concern different tumor locations: STS, head and neck, liver, lung, prostate, cervical cancer, brain, and rectal cancer for primary or secondary tumors (Fig. 2). For the moment, 4 studies have been published, all of which relate to hafnium oxide NP in combination with RT. So far, 229 patients have been treated with NP and RT for soft tissue sarcoma, head and neck cancers or liver cancer. No dose limiting toxicity has been observed. To date, the first and only published phase 2/3 trial on NP radio-enhancement concerns hafnium oxide NP. The NP is administered by intratumoral injection before RT is administered preoperatively for treatment of soft tissue sarcoma of the extremity or trunk wall. A significant radio-enhancing effect was achieved in the presence of the NP, doubling the pathological complete response rate compared to RT alone, and comparable toxicity profiles between the two groups.

Based on the data currently available in the literature, no significant acute toxicity of NP + RT has been demonstrated and there is evidence of superior efficacy of RT in the presence of NP. The anti-tumor immune response also seems to be augmented by addition of hafnium oxide NP to RT treatment, opening new avenues of research for combinations of NP/immunotherapy/radiotherapy.

Declaration of Competing Interest

NS, EC, CV: None

SB: honorarium, travel grant, meeting grant, unrestricted grant for the phase 1/2 and phase 3 trials NBTXR3 in sarcoma

CLT: Participation in advisory boards from Nanobiotix

JT: personal fees from Nanobiotix

VC: personal fees from Nanobiotix

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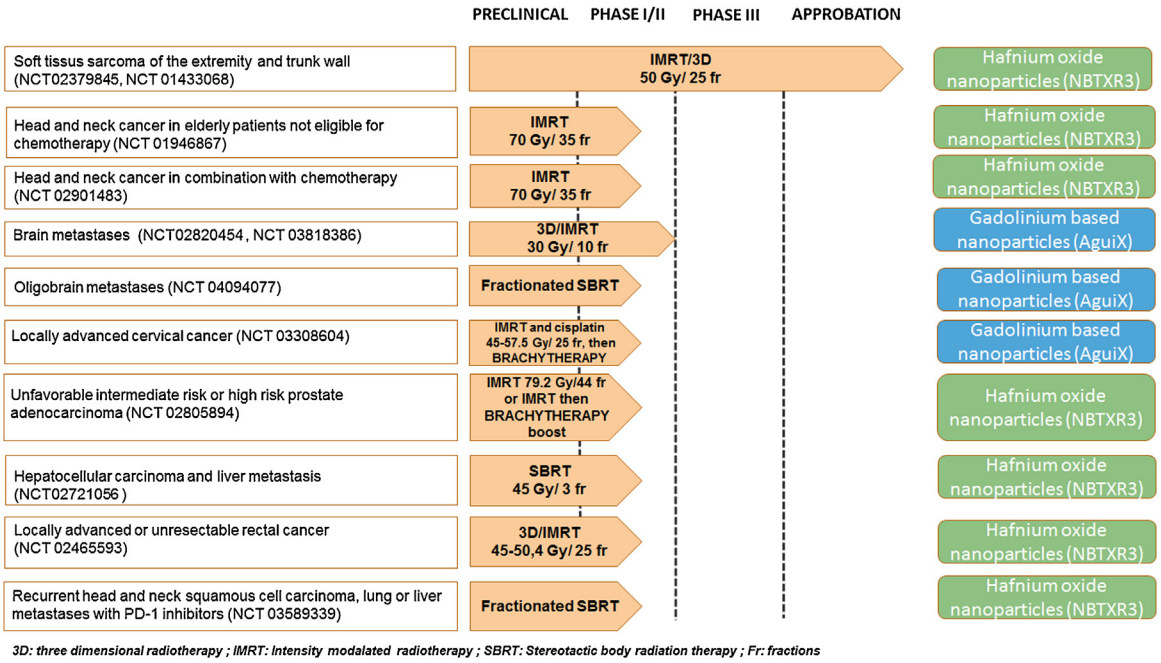

Fig. 2. List of completed and ongoing clinical trials evaluating nanoparticles activated by radiotherapy.

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