TITLE
Hafnium oxide nanoparticles activated by radiotherapy triggers an abscopal effect dependent on CD8 T cells.

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Background
Hafnium oxide nanoparticles (HfO2-NP) increase radiation dose deposit within the cancer cells when activated by radiotherapy. Recent results of a phase II/III in locally advanced Soft Tissue Sarcoma patients demonstrated clinical benefits of intratumorally injected HfO2-NP activated by radiotherapy compared to radiotherapy alone, validating their first-in-class mode of action. In addition, animal studies have reported that HfO2-NP+RT can induce an abscopal effect, where RT alone cannot. Here, using a mouse abscopal assay, we measured T cells infiltrates in treated and untreated tumors after HfO2-NP intratumor injection and activation with RT, and their role in the abscopal effect.

Materials and methods
CT26 (murine colorectal cancer cells) were subcutaneously injected in both flanks of BALB/c mice. Once the right-side tumors reached a mean volume of 115±30 mm3, they were intratumorally injected with HfO2-NP (or vehicle) and irradiated with 3x4Gy. Tumors from both flanks were removed 3 days after the last fraction of RT and CD8+ cell infiltrates were determined by immunohistochemistry (IHC) and digital pathology analyses.
To investigate the role of CD8+ T cells in the antitumor immune response and abscopal effect, the experiment was conducted after CD8+ T cells depletion prior treatment with HfO2-NP+RT or RT alone.

Results
IHC analyses showed an important increase of CD8+ T cells infiltrates in both flanks of mice treated with HfO2-NP+RT, while this was not observed in animals treated with RT alone.
This abscopal effect of HfO2-NP+RT treatment was completely abolished upon CD8+ T cells depletion. In addition, growth control of right-side tumors by HfO2-NP + RT was less efficient than with HfO2-NP+RT once CD8+ T cells were depleted.

Conclusions
These data indicate that the immunogenic conversion of the tumor microenvironment triggered by HfO2-NP+RT generates the abscopal effect by activation of CD8+ T cells. HfO2-NP+RT may potentiate a pro-inflammatory microenvironment appropriate for enabling an anti-tumor immune response. It may act as effective in-situ cancer vaccine and be combined with immunotherapeutic agents across oncology.