The radioenhancer NBTXR3 brings anticancer efficacy to the cisplatin-based chemoradiation *in vitro* and *in vivo*

Short Title:
Combination of NBTXR3 and cisplatin

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Abstract:
NBTXR3 is a radioenhancer composed of functionalized hafnium oxide nanoparticles, designed to enhance the radiation dose deposit within the cancer cells when activated by ionizing radiations. NBTXR3 is intended for single intratumor administration and is currently evaluated in cancer clinical trials including soft tissue sarcoma, head and neck (H&N), prostate, liver and rectum.
Cisplatin (CDDP) is a cytotoxic agent considered to be a radiosensitizer and inhibits the repair of sublethal damage from irradiation. Concurrent chemoradiation using CDDP is the mainstream treatment for high risk H&N, cervix and non-small cell lung cancer patients. We hypothesized that adding NBTXR3 to radiation treatment (RT) may improve significantly anticancer effect of the chemoradiation combination
In vitro, no specific clonogenic toxicity was observed for the cells exposed only to NBTXR3. For the combined treatment CDDP was used at its IC_{50} concentrations. A marked and enhanced cell destruction (DEF) was observed with the CDDP combined treatment (added 6h or 16h prior to RT) and NBTXR3 (800µM, added 16h prior to RT) at ≥2Gy when compared to the single agent.

Treatment			Cell line (DEF*)	
CDDP	NBTXR3	Irradiation	FaDu	NCI-H460-Luc2
6h	-	2 Gy	1.0±0.06	1.2±0.06
-	16h		1.4±0.15	1.3±0.25
6h	16h		1.4±0.14	1.6±0.12
16h	-		1.0±0.12	1.9±0.32
-	16h		1.2±0.13	1.5±0.17
16h	16h		1.8±0.23	2.6±0.45
6h	-	4 Gy	1.3±0.08	2.2±0.16
-	16h		2.2±0.24	1.9±0.41
6h	16h		3.1±0.64	3.8±0.48
16h	-		1.2±0.19	2.9±0.52
-	16h		2.1±0.31	2.8±0.39
16h	16h		5.3±0.97	7.6±2.76

**For a given radiation dose, the DEF value was obtained by taking the ratio of the survival fraction in the control (radiotherapy alone) and the survival fraction of the treatment.*
In vivo, NBTXR3 enhanced the fractionated radiation treatment (5x2Gy) when injected intratumorally at 25% of tumor volume. NBTXR3 activated with ionizing radiation in combination with low dose of CDDP (1mg/kg administered 5 consecutive days, 2 hours prior to RT) delayed tumor growth when compared to single agent CDDP in combination with RT. These results strongly support the concurrent chemoradiotherapy regimen with NBTXR3

nanoparticles as an effective radioenhancer to increase the anticancer effect. A new phase I/II trial with H&N cancers patient receiving radiotherapy plus CDDP has been started evaluating the optimal dose, safety and preliminary efficacy of NBTXR3.
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