

Hafnium oxide nanoparticles activated by radiotherapy: potential for local treatment of a wide variety of solid tumors

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Disclosures

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Advisory activities

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Expert Testimony

- Intellectual property (Wilson Soncini)

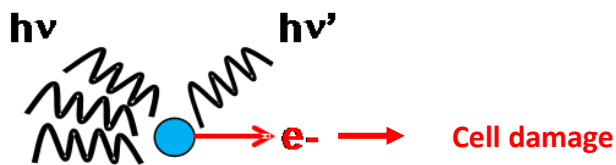
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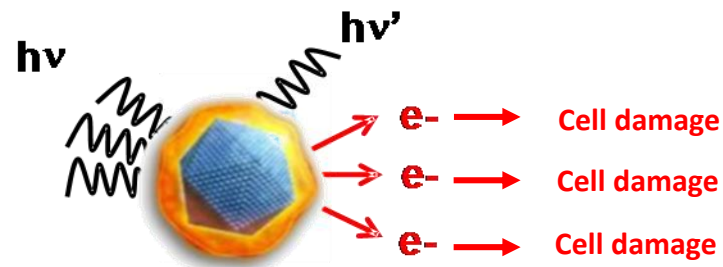
Background: NBTXR3 radiation-enhancing nanoparticles

- NBTXR3 are nanoparticles of **Hafnium oxide** that are inert unless exposed to radiation
- Injected once directly into the tumor
- **Amplifies energy deposited and has radiobiological effects**, when exposed to RT
- **Radioenhances** by generating photons and secondary electrons in the **local area** where the nanoparticles are present
- **Approved in the EU** (CE marking) for the treatment of advanced soft tissue sarcoma (STS) of the extremity and trunk wall

Radiotherapy alone



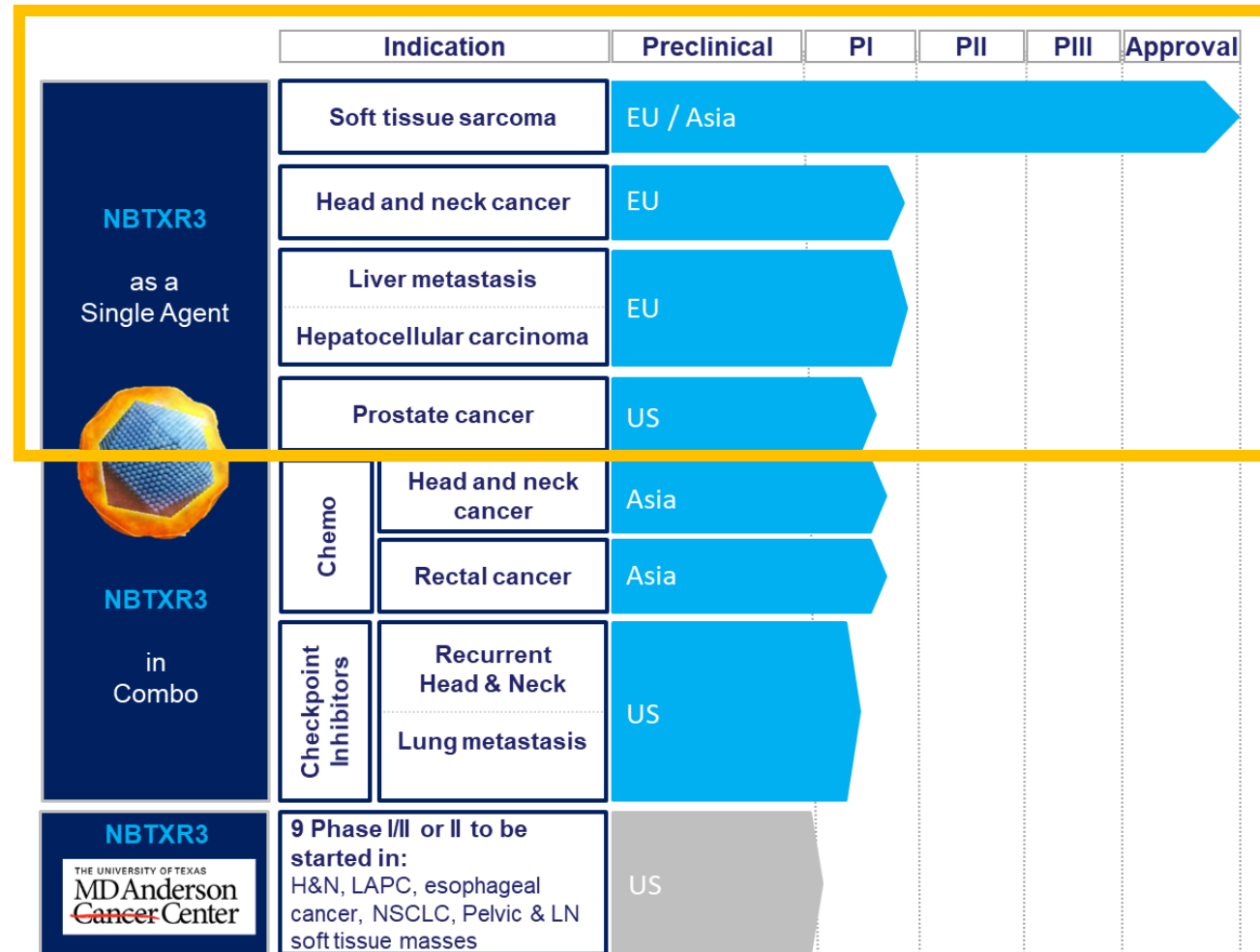
Radiotherapy with NBTXR3



9X

enhancement of
RT energy
directly to tumor

Background: ongoing and planned clinical studies



Material & Methods:

Intra-tumoral administration of NBTXR3

- A single administration before irradiation
- Intratumoral or intraorgan (prostate) injection
- Dose of NBTXR3 (at fixed concentration) determined as a % of baseline tumor volume
- Does not require RT re-planning
- RT started 1-9 days post-injection within these studies

Results: Dose levels tested by clinical trial

Tumor type	Study Name	Phase	NBTXR3 Dose*	RT type	Total dose of RT
Soft tissue sarcoma (STS)	NBTXR3-101	I	2.5-20% RP2D: 10%	EBRT	50 Gy
	NBTXR3-301	II/III	10%	EBRT or IMRT	50 Gy
H&N squamous cell carcinoma	NBTXR3-102	I - Dose escalation	5-22% RP2D: 22%	IMRT	70 Gy
Liver cancers: hepatocellular carcinoma or liver metastases	NBTXR3-103	I/II - Dose escalation	10-42%	SBRT	45 Gy
Prostate	NBTXR3-104	I/II - Dose escalation	5-22%	EBRT	79.2 Gy
				Brachy + EBRT	15 + 45 Gy

EBRT, External beam radiotherapy; IMRT, Intensity-modulated radiation therapy; SBRT, stereotactic body radiation therapy

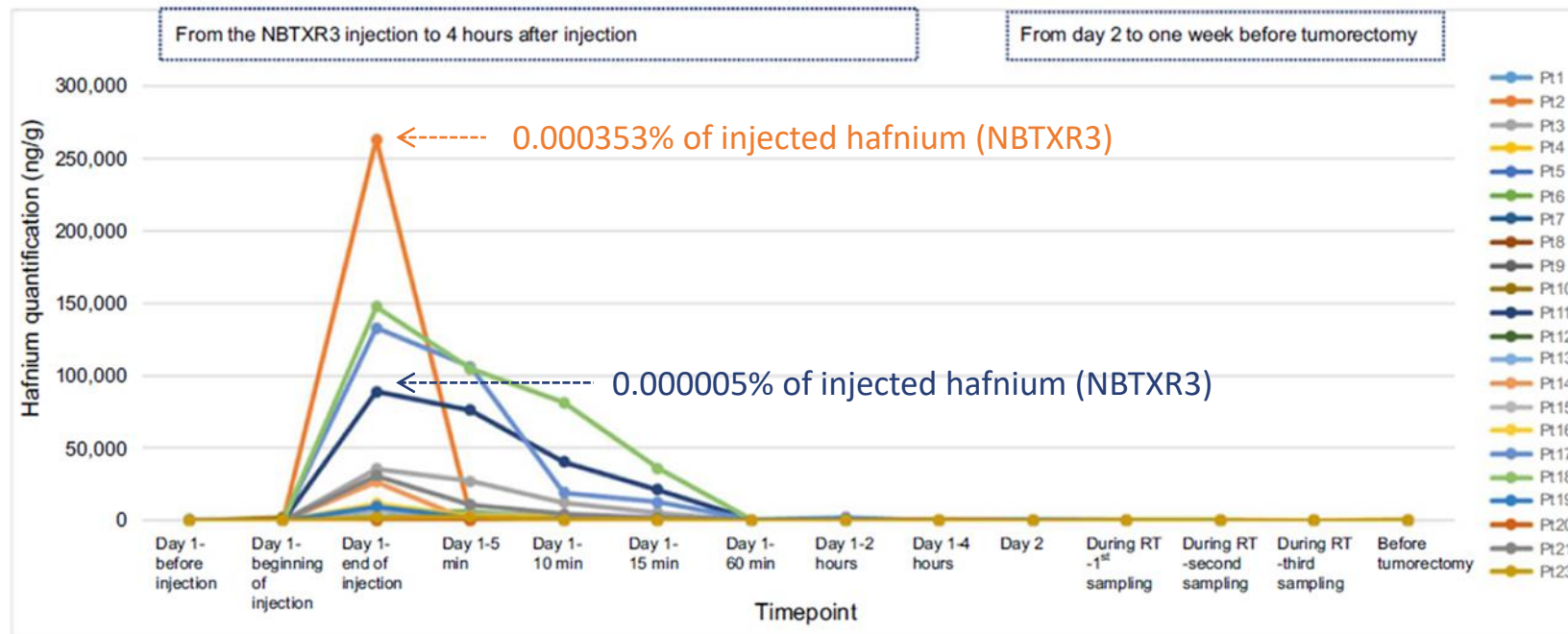
* Dose corresponds to a percentage of tumor volume at baseline

Results: Range of tumor size treated with NBTXR3 activated by RT as single agent

Tumor type	Study Name	Phase	Number of patients	Tumor/Organ volume range (mL)	NBTXR3 injected volume range (mL)
Soft tissue sarcoma (STS)	NBTXR3-101	I	22	55 - 3682 mL	1.4 – 192 mL
	NBTXR3-301	II/III	89 (NBTXR3 arm)	16 - 6326 mL	2 – 450 mL
H&N squamous cell carcinoma	NBTXR3-102	I - Dose escalation	19	1.1 - 123.8 mL	0.24 - 23.6 mL
Liver cancers	NBTXR3-103	I/II -Dose escalation	17	3.3 - 66.7 mL	0.3 – 11 mL
Prostate	NBTXR3-104	I/II - Dose escalation	5	14.7 - 69.8 mL	0.74 - 3.5 mL

Results: NBTXR3 body kinetics: STS Phase I study results

Whole blood hafnium concentration



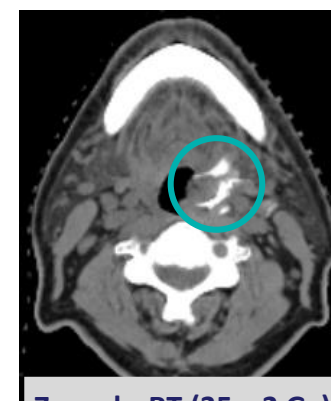
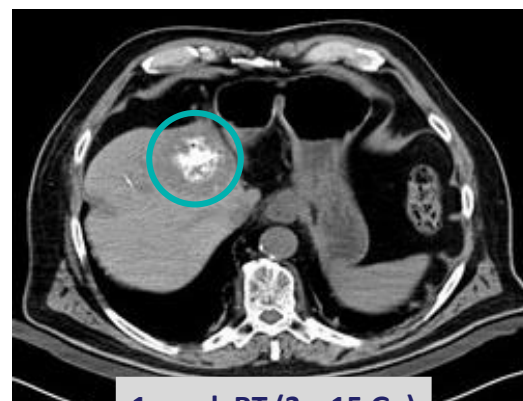
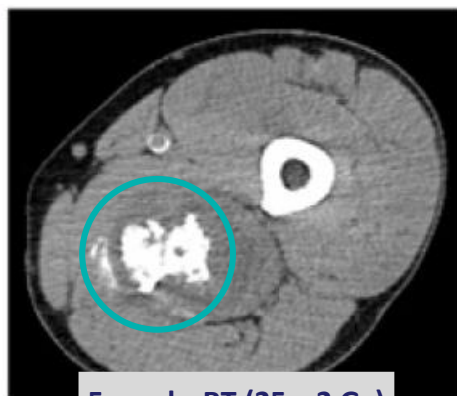
Results: NBTXR3 remains in place during RT

STS

Liver

H&N

24h post NBTXR3 injection



Post-RT



Week 10 post injection

Week 15 post injection

Week 7 post injection

No leakage into surrounding healthy tissues

Results - Safety : NBTXR3-Related Adverse Events

	N Pts	AE (n)		SAE (n)	DLT (n)
		Grade 1-2	Grade 3		
Phase I/II Studies – All AE					
NBTXR3-101 STS	22	11*	2	4	2
<i>Injection site pain</i>		3	1	0	1
<i>Pyrexia</i>		2	0	1	-
<i>Abdominal pain</i>		1	0	1	-
<i>Injection-site reaction</i>		1	0	1	-
<i>Post-operative wound complication</i>		0	1	1	1
NBTXR3-102 H&N	19	1	0	0	0
<i>Asthenia</i>		1	0	0	0
NBTXR3-103 Liver cancers	17	1	1	1	0
<i>Bile duct stenosis</i>		0	1	1	0
NBTXR3-104 Prostate	5	7	0	0	0

*Other 4 Grade 1-2 AE were: edema peripheral, paraesthesia, hypotension, headache

	N Pts	AE (n)		SAE (n)
		Grade 1-2	Grade 3-4	
Phase III-NBTXR3-301 (NBTXR3 arm)				
All AE	89	49	14	12
All SAE				
<i>Injection site pain</i>				1
<i>Anaphylactic shock</i>				1
<i>Cytokine Release Syndrome</i>				1
<i>Hypersensitivity</i>				1
<i>Femur fracture</i>				0
<i>Postoperative wound complication</i>				1
<i>Post-procedural complication</i>				1
<i>Post-procedural infection</i>				1
<i>Osteonecrosis</i>				0
<i>Apnea</i>				1
<i>Panniculitis</i>				1
<i>Hypotension</i>				3

Note: as of July 7th, 2019; AE adverse event; SAE serious adverse event

Results - Safety : AEs Related to the injection

	N Pts	AE (n)		SAE (n)
		Grade 1-2	Grade 3	
Phase I/II – All AE				
NBTXR3-101 STS	22	20*	4	2
<i>Injection site pain</i>		14	1	1
<i>Presyncope</i>		0	2	0
<i>Hypoaesthesia</i>		0	1	1
NBTXR3-102 H&N	19	4	0	0
<i>Asthenia</i>		1	0	0
<i>Injection site haemorrhage</i>		1	0	0
<i>Oral pain</i>		1	0	0
<i>Tumor haemorrhage</i>		1	0	0
NBTXR3-103 Liver cancers	17	2	2	0
<i>Malaise</i>		1	0	0
<i>Abdominal pain</i>		0	2	0
<i>Bilateral pleural effusion</i>		1	0	0

* The other 6 Grade 1-2 AE were: nausea, paraesthesia, injection site bruising, oedema peripheral, pain in extremity and pruritus

	N Pts	AE (n)		SAE (n)
		Grade 1-2	Grade 3-4	
Phase III -NBTXR3-301 STS (NBTXR3 arm)				
All AE	89	53	13	9
All Grade 3-4 and SAE				
<i>Injection site pain</i>			4	2
<i>Tumor pain</i>			2	0
<i>Hypotension</i>			4	2
<i>Presyncope</i>			1	1
<i>Injection site extravasation</i>			0	1
<i>Cytokine release syndrome</i>			0	1
<i>Apnea</i>			1	1
<i>Pulmonary embolism*</i>			1	1

* Undue duration of procedure because of hospital difficulties in a patient with hypercoagulation and systemic inflammatory syndrome

**The most frequent AE related to the injection procedure was injection site pain
(50% of reported AE in Phase I Studies)**

Note: as of July 7th, 2019. In Study 104 AE related to the injection were not recorded as injection in the prostate gland is a standard procedure. AE adverse event; SAE serious adverse event.

Results - Efficacy : Responses in H&N and STS

H&N Phase I NBTXR3-102

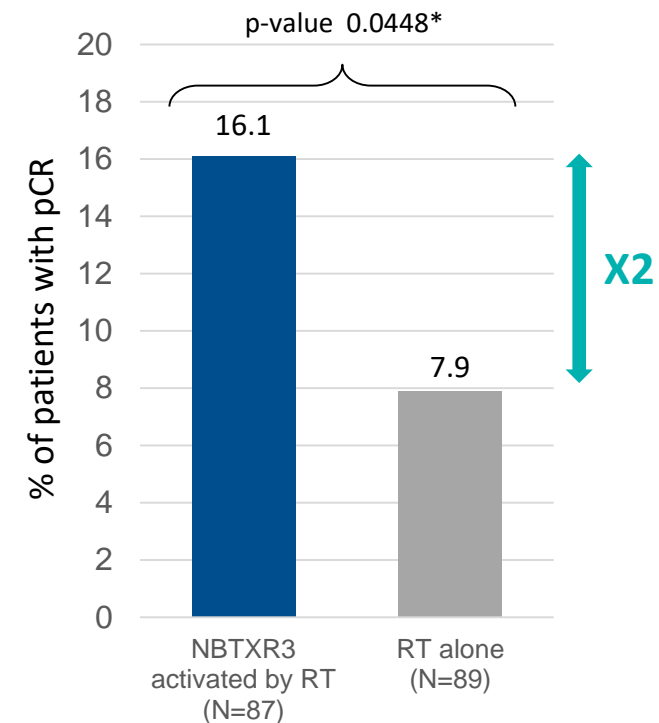
Dose level	Evaluable Pts N	Primary Lesion Best Response RECIST 1.1		
		CR n, (%)	PR n, (%)	SD n, (%)
Level 1- 5%	3	0 (0.0)	2 (66.7)	1 (33.3)
Level 2 -10%	3	2* (66.7)	0 (0.0)	1 (33.3)
Level 3 -15%	5	4 (80.0)	0 (0.0)	1 (20.0)
Level 4 -22%	5	3* (60.0)	0 (0.0)	2 (40.0)
All	16	9 (56.3)	2 (12.5)	5 (31.2)

*One unconfirmed CR

Note: 3 Patients at level 4 (22%) are not evaluated as they did not receive the intended dose of NBTXR3 and/or schedule of radiation therapy

STS Phase II/III - NBTXR3-301

Pathological complete response rate



*Statistically significant at an adjusted α of 0.04575
Bonvalot S. et al, Lancet Oncol. 2019

Liver cancer results will be presented by
Dr Enrique CHAJON on Sep 18, 2:45 p.m. - 4:00 p.m.

Summary

- **Intratumoral injection** of NBTXR3 is **feasible** and **safe** :
179 patients injected and who received RT across all studies as of July 2019
- NBTXR3 **remained localized within the tumor** throughout RT treatment
- **Recommended Phase 2 Dose** (% of baseline tumor volume)
 - **STS : 10%**
 - **HNSCC: 22%**
 - Liver cancers : highest dose level (42%) is currently being evaluated
 - Prostate cancer: recruitment at level 5% is ongoing for cohort B, level 10% for cohort A
- **Proof of concept** and efficacy demonstrated in STS and encouraging preliminary signs of efficacy in H&N cancers and liver cancers
- NBTXR3 may represent a valuable option for patients with solid tumors eligible for radiation therapy

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STS – NBTXR3-101 & 301

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H&N cancers – NBTXR3-102

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Liver cancers – NBTXR3-103

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Prostate – NBTXR3-104

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