

Nanoparticules Therapies and Radiotherapy in STS

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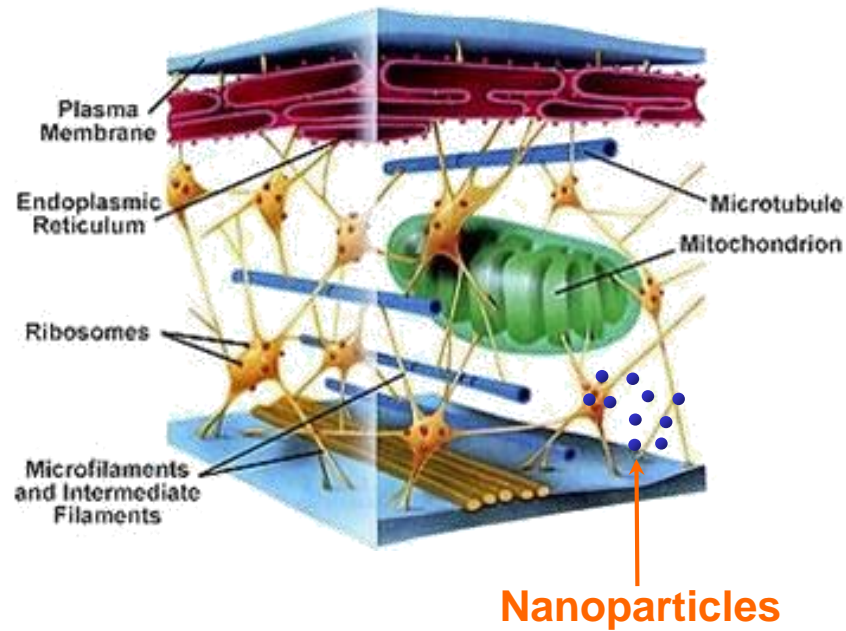
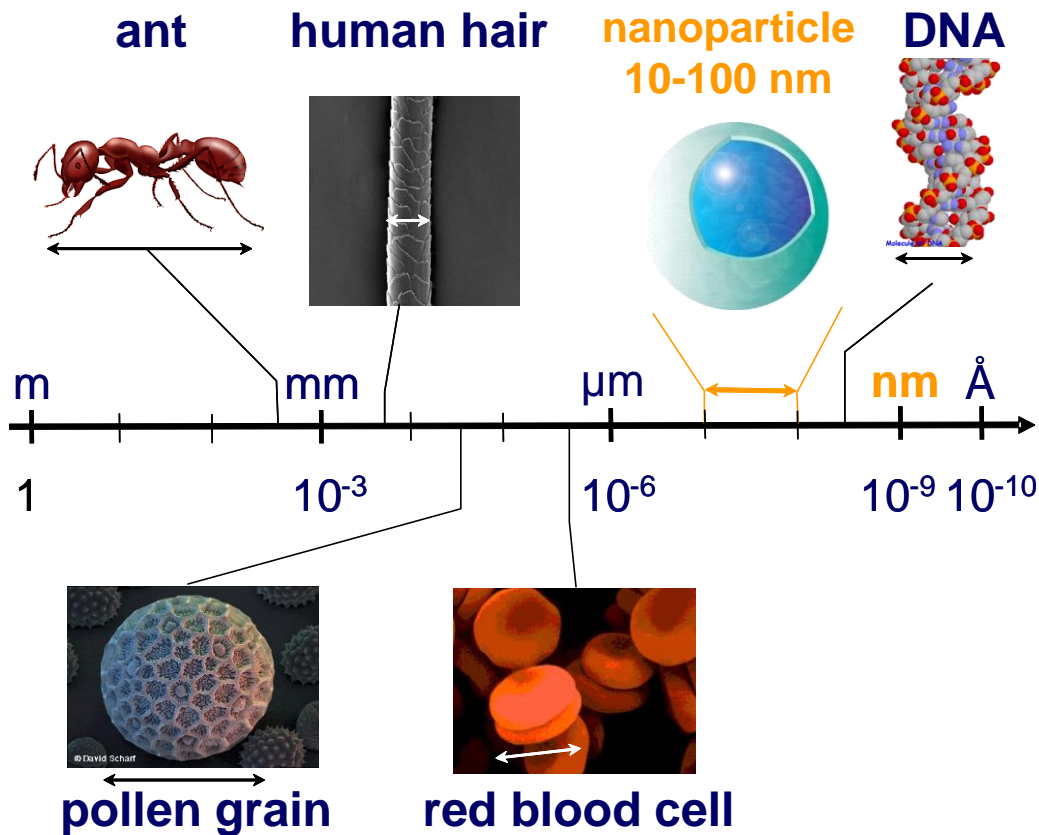
Department of Surgery



Conflict Of Interest

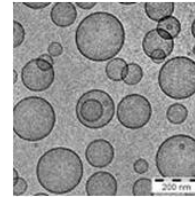
- PI phase 1 and phase 3 in STS
- Nanobiotix: honorarium, consultant

The importance of being small



Some commercial applications of nanoparticles.

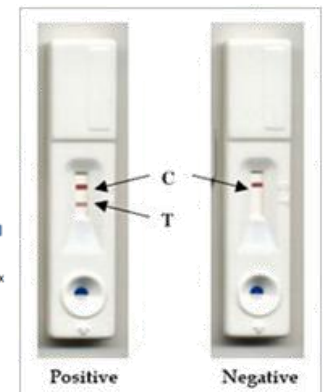
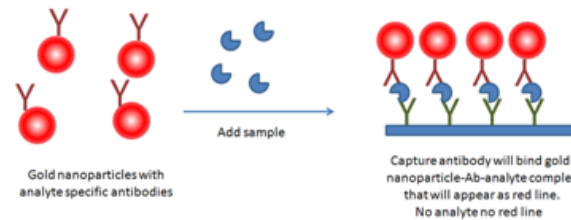
Organic-based Nanomaterials: Drug Delivery Systems



Iron oxide : imaging agent/MRI



Immunoassays : Pregnancy test



Nanoparticles for drug delivery system

Table 5

Confirmed and likely nanomedicine applications and products identified that utilize active targeting

Application(s)/Product(s)	Company	Status	Condition	Nanocomponent	Targeting Mechanism
Ontak [^{45,46}]	Seragen, Inc.	Approved (1999)	T-Cell Lymphoma	Protein NP	IL-2 Protein
MBP-Y003, MBP-Y004, MBP-Y005 [⁴⁷]	Mebiopharm Co., Ltd	Preclinical	Lymphoma	Liposome	Transferrin
MBP-426 [⁴⁷⁻⁴⁹]	Mebiopharm Co., Ltd	Phase I/II	Solid Tumors	Liposome	Transferrin
CALAA-01 [^{19,50}]	Calando Pharmaceuticals	Phase I	Solid Tumors	NP	Transferrin
SGT-53 [^{19,51}]	SynerGene Therapeutics, Inc.	Phase I	Solid Tumors	Liposome	Transferrin
MCC-465 [^{48,52}]	Mitsubishi Tanabe Pharma Corp	Phase I	Stomach Cancer	Liposome	GAH Antibody
Actinium-225-HuM195 [⁵³]	National Cancer Institute	Phase I	Leukemia	NP	HuM195 Antibody
AS15 [⁵⁴]	GlaxoSmithKline Biologicals	Phase I/II	Metastatic Breast Cancer	Liposome	dHER2 Antibody
PK2 [^{48,55}]	Pharmacia & Upjohn Inc.	Phase I	Liver Cancer	Polymeric NP	Galactose
Rexin-G, Reximmune-C [^{56,57}]	Epeius Biotechnologies	Phase I/II	Solid Tumors	NP	von Willebrand factor (Collagen-Binding)
Aurimune (CYT-6091) [^{19,58}] Auritol (CYT-21001) [⁵⁹]	CytImmune Sciences, Inc.	Phase II Preclinical	Solid Tumors	Colloid Gold	TNF- α
SapC-DOPS [^{60,61}]	Bexion Pharmaceuticals, Inc.	Preclinical	Solid Tumors	Liposome	Sapoin C
Targeted Emulsions [^{62,63}]	Kereos, Inc.	Preclinical	<i>In Vivo</i> Imaging	Emulsion	"Ligands"
Opaxio [^{42,64}]	Cell Therapeutics, Inc.	Phase III	Solid Tumors	Polymeric NP	Enzyme-Activated
ThermoDox [⁴³]	Celsion Corporation	Phase II/III	Solid Tumors	Liposome	Thermosensitive
DM-CHOC-PEN [^{44,65}]	DEKK-TEC, Inc.	Phase I	Brain Neoplasms	Emulsion	Penetrate Blood- Brain-Barrier

Radioenhancer nanoparticles

Tested

HfO₂ crystalline NPs

- Radio-enhancer
- Inert material
- Local administration
- Single injection

- e⁻ density slightly lower than gold

Phase III

Gold NPs

- Radio-enhancer
- e⁻ density slightly higher than HfO₂

- Metallic material, Intrinsic activity Red/Ox (Safety)
- Systemic injection / exposure
- Leakage from tumor over time?
- Multiple injections?

Preclinical model

Not tested

other High Z Nanomaterial

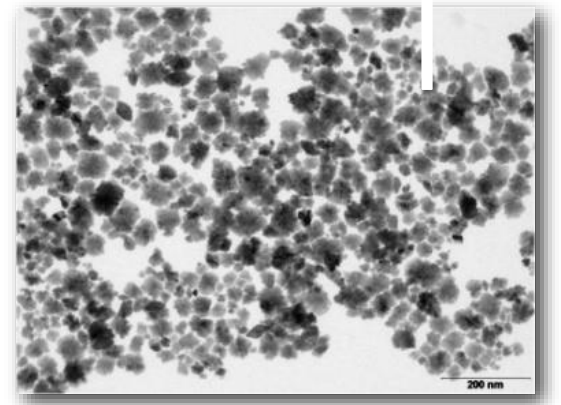
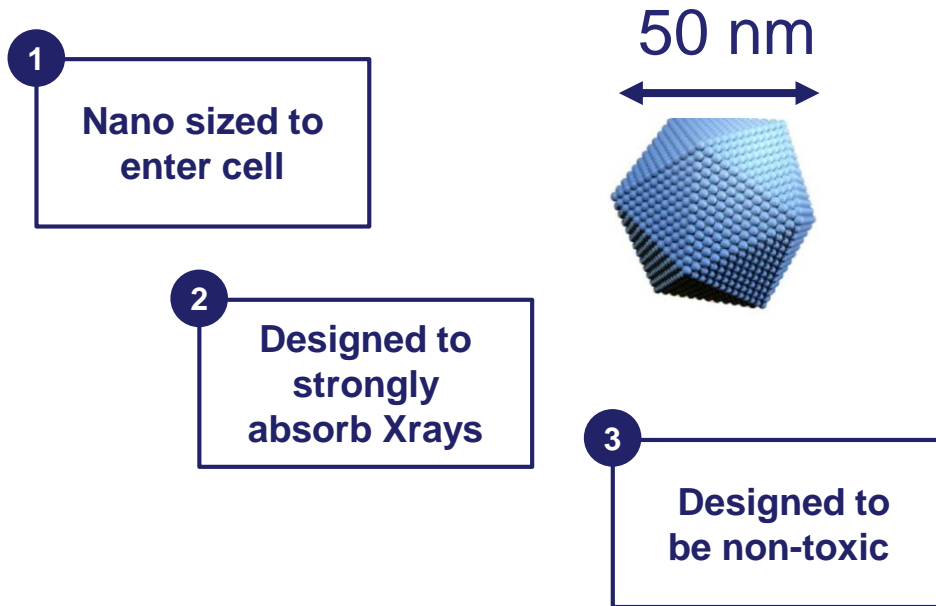
- Radio-enhancer

TOX

NA

Selection of the right nanoparticle should be done in regard to benefit risk ratio

NanoXray Technology / key features

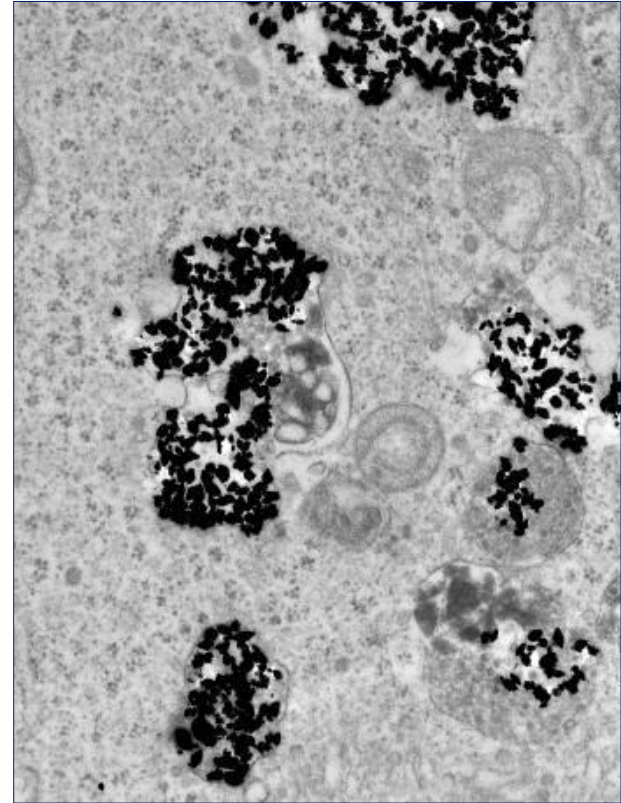
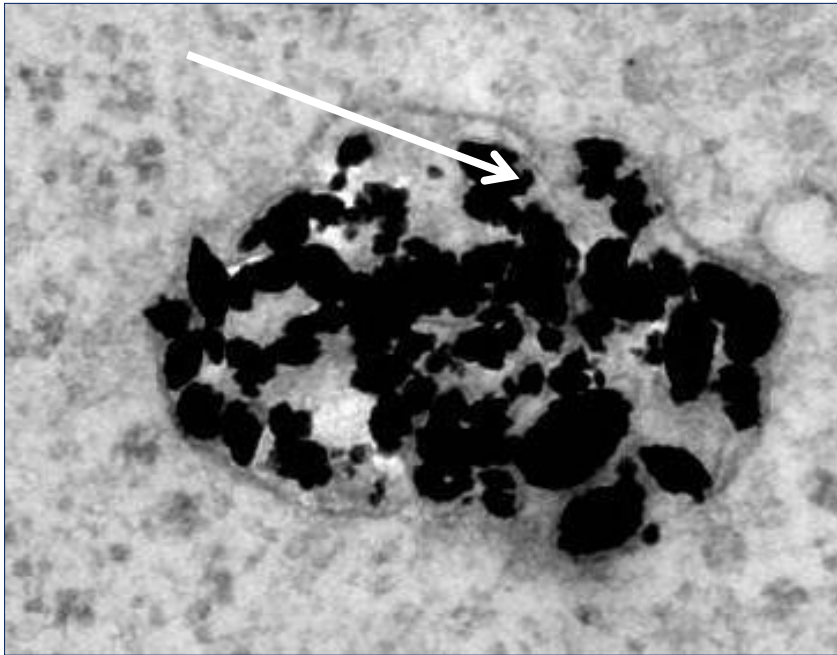


HfO₂ nanoparticles; electron microscopy picture

50 nanometer HfO₂ particles were chosen because they have the best ratio for X-ray absorption and non-toxicity*

***NanoXray is a radioenhancer with a physical mode of action
6 patent families protect concept and products until 2029 minimum***

Localized accumulation inside HCT116 cell by TEM

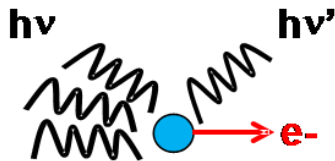


NBTXR3 penetrate cells via non specific endocytosis type mechanism

NanoXray/NBTXR3 has a purely physical mode of action

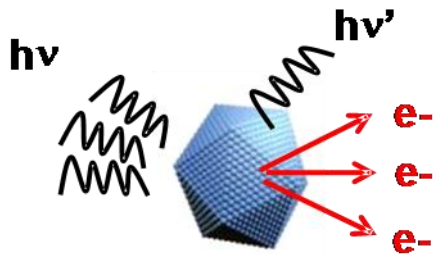
Same as RTx but amplified

Radiotherapy alone



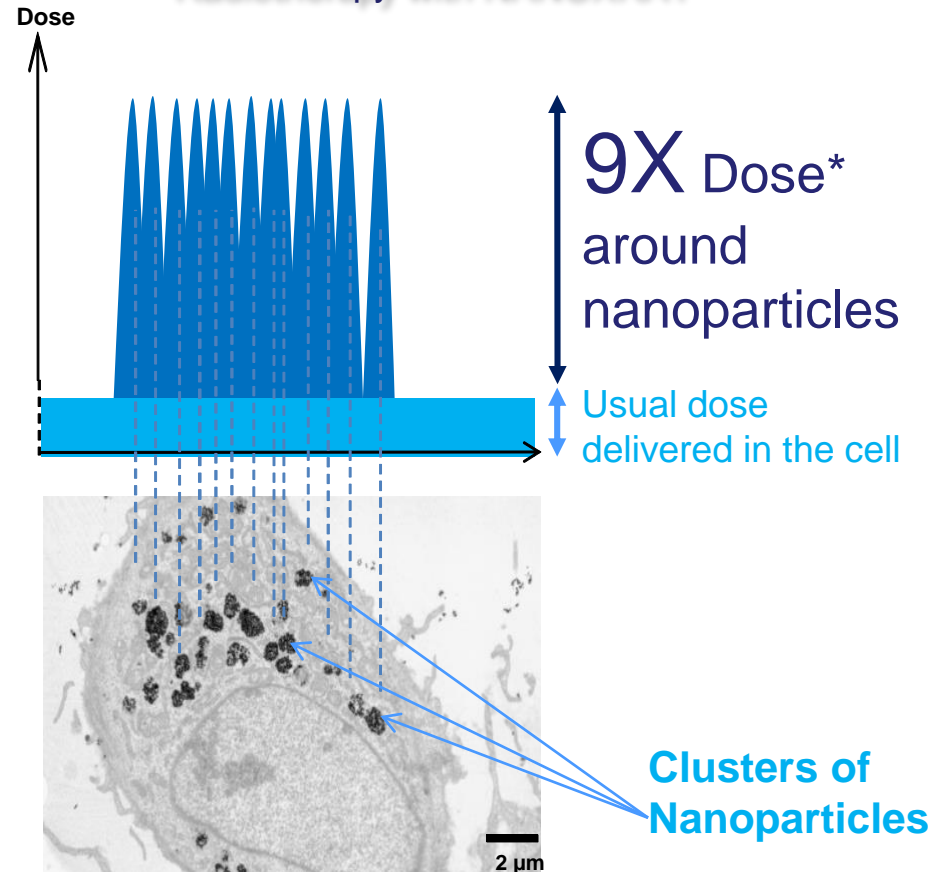
Interaction of Xray with water generates electrons

Radiotherapy with NanoXray



Interaction with Hafnium is higher and generates much more electrons

Radiotherapy with NANOXRAY



NanoXray is a true radioenhancer with a physical mode of action
Increasing the dose absorbed by 9x and delivering more damage regardless of cell

Antitumor efficacy in animal models

Overview of proof of performance

In vivo (xenografted model, intratumoral injection)

RTx alone



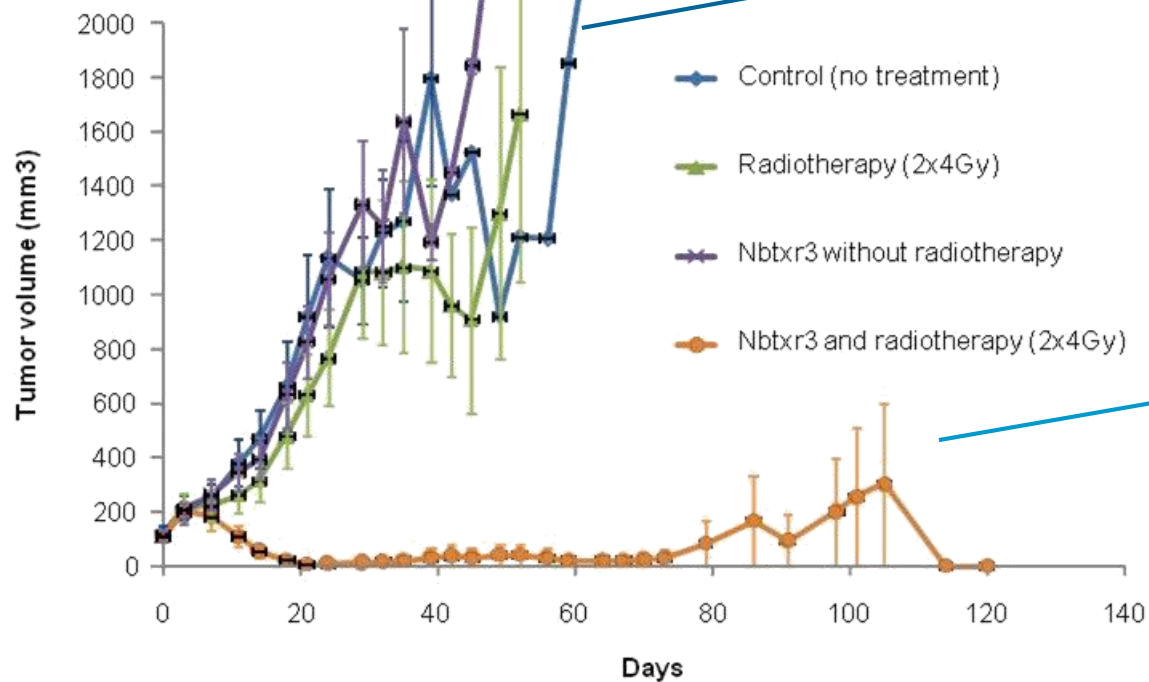
RTx + NBTXR3



Human Cancer Model (16 studies)	200 KV Xrays	¹⁹² Ir	⁶⁰ Co
HT1080, Fibrosarcoma cell line	OS / TC	OS / TC	OS / TC
A673, Ewing sarcoma cell line	-		OS / TC
LPS80T3, Liposarcoma patient's fragment	OS / TC		
HCT116, Colon cancer cell line		OS / TC	
NCI H460, Lung adenocarcinoma cell line	OS / TC		
FADU, Hypopharyngeal carcinoma cell line	OS / TC		
CAL33, Tongue squamous carcinoma cell line	OS / TC		

Complete response and prolongation of survival

Antitumor activity of NBTXR3 activated by high energy (Cobalt-60) in Ewing Sarcoma family (A673 model)



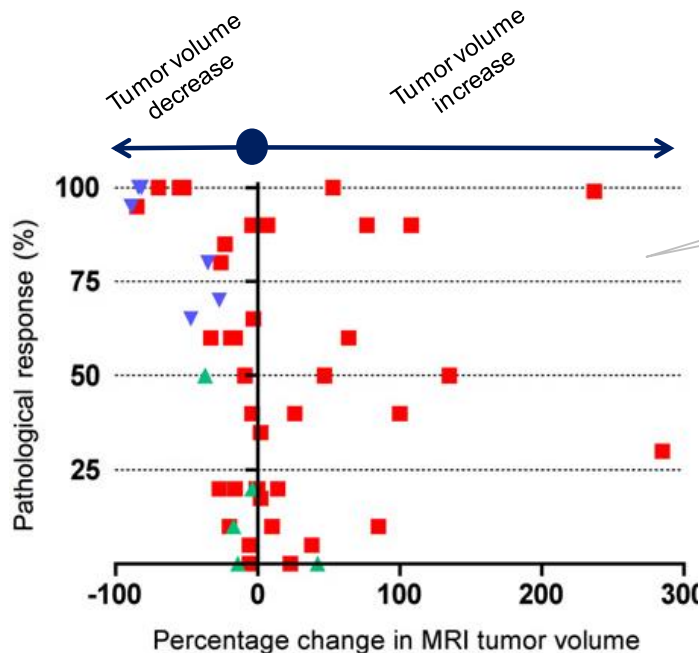
Radiotherapy alone



Radiotherapy +NBTXR3

RT in locally advanced soft tissue sarcoma

Radiotherapy is a standard of care in high risk limbs sarcomas



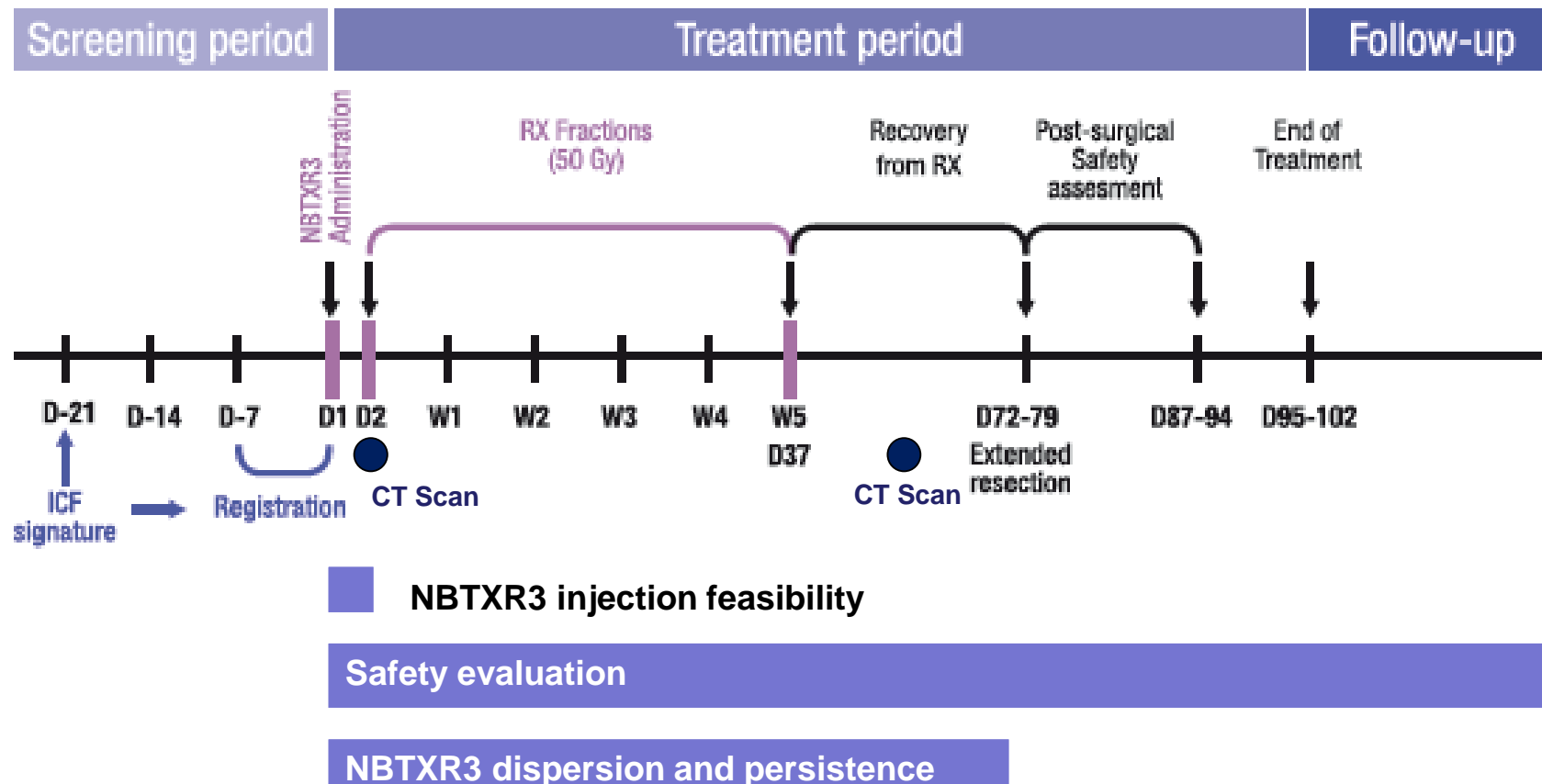
* **Reference:** D. Roberge et al.
Radiotherapy and Oncology 97 (2010)
404–407

*D. Roberge et. al. Radiotherapy and
Oncology 97 (2010) 404–7*

Average tumor shrinkage (RR)	+15%
Average pR	50%

Current radiation treatment has less than 8% Pathological Complete Response, without significant tumor shrinking

Phase 1/2 Soft Tissue Sarcoma trial flowchart



Main objectives: feasibility and safety for escalate of volume of NBTXR3 at fixed concentration (53.3 g/L)

Safety & feasibility of the injection procedure

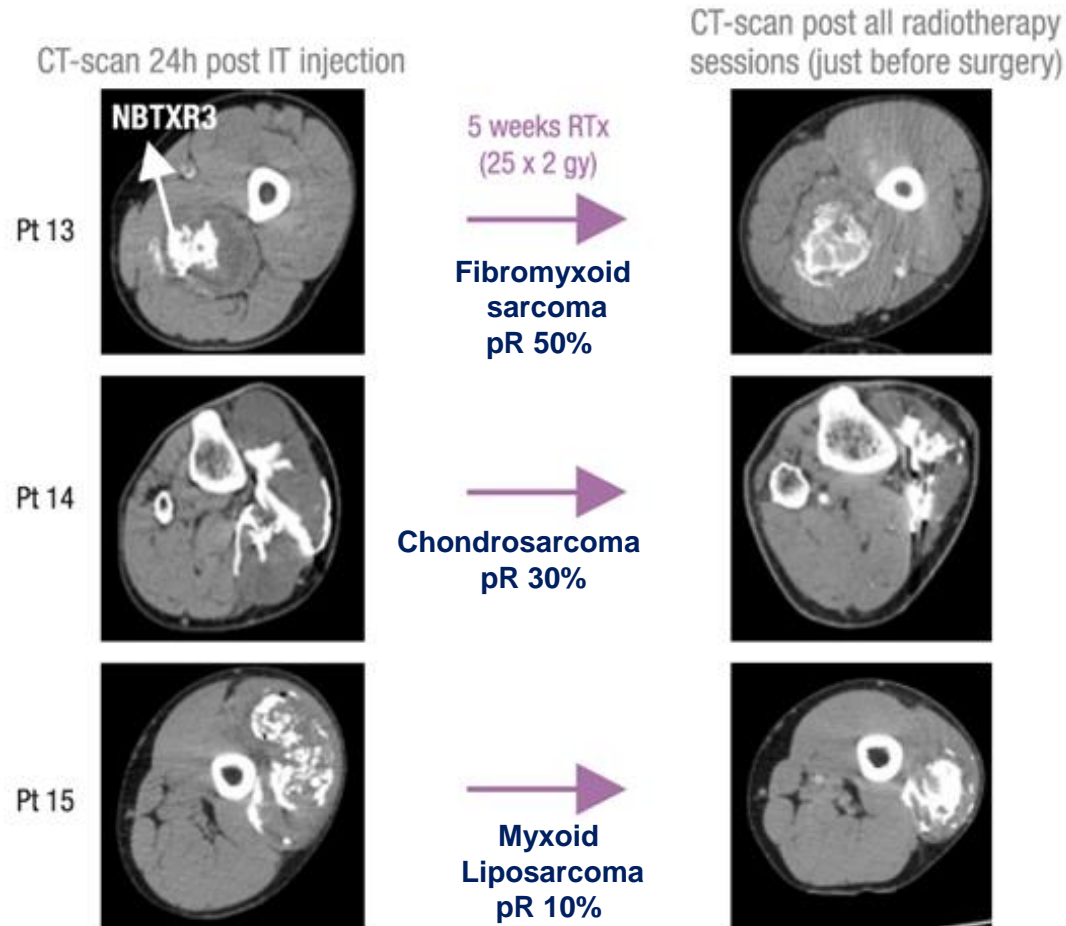
Table 2. NBTXR3 (53.3 g/L) intratumoral injection characteristics; values shown are median (range)

	Dose level (% of tumor volume)			
	1 (2.5%) <i>n</i> = 6	2 (5%) <i>n</i> = 6	3 (10%) <i>n</i> = 8	4 (20%) <i>n</i> = 2
Tumor volume, mL	185 (55–1,814)	567 (85–3,682)	305 (130–1,001)	725 (490–960)
Volume of NBTXR3 injected, mL	5 (1–45)	27 (4–184)	30 (13–101)	138 (84–192)
Number of punctures	4 (2–10)	6 (2–11)	8 (5–33)	13 (12–13)
Duration of injection procedure, min	5 (2–15)	6 (2–16)	11 (6–55)	34 (19–48)



2 grd 3 pain

Dispersion and persistency of NBTXR3 in the tumor



Persistence of NBTXR3 during all sessions of RTx: optimal bioavailability over time

leakage

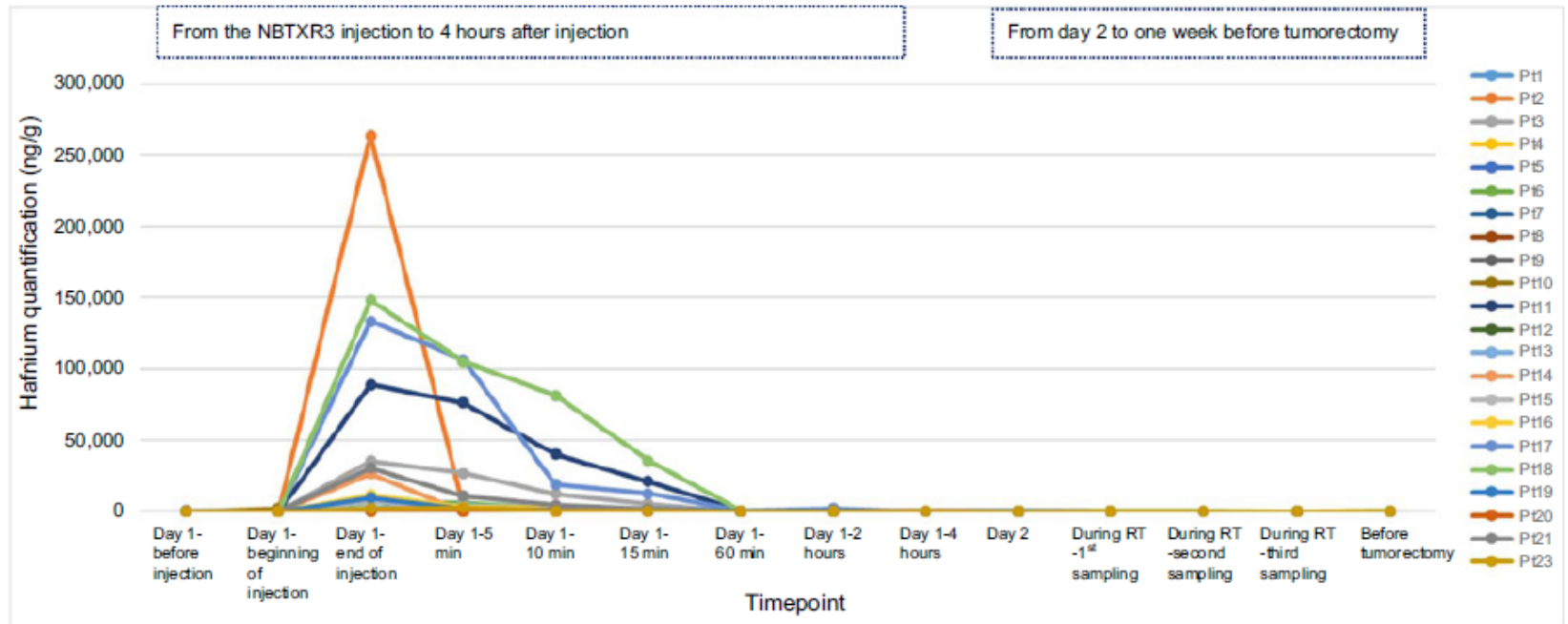
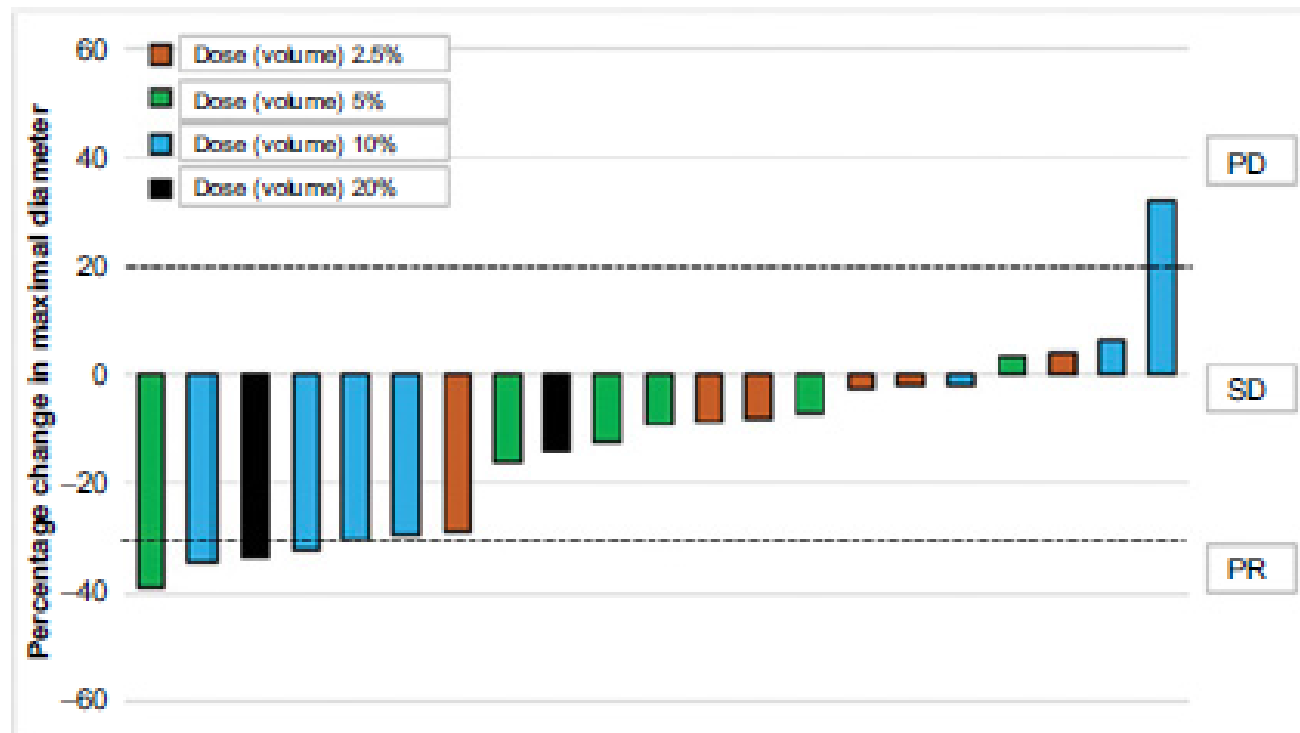


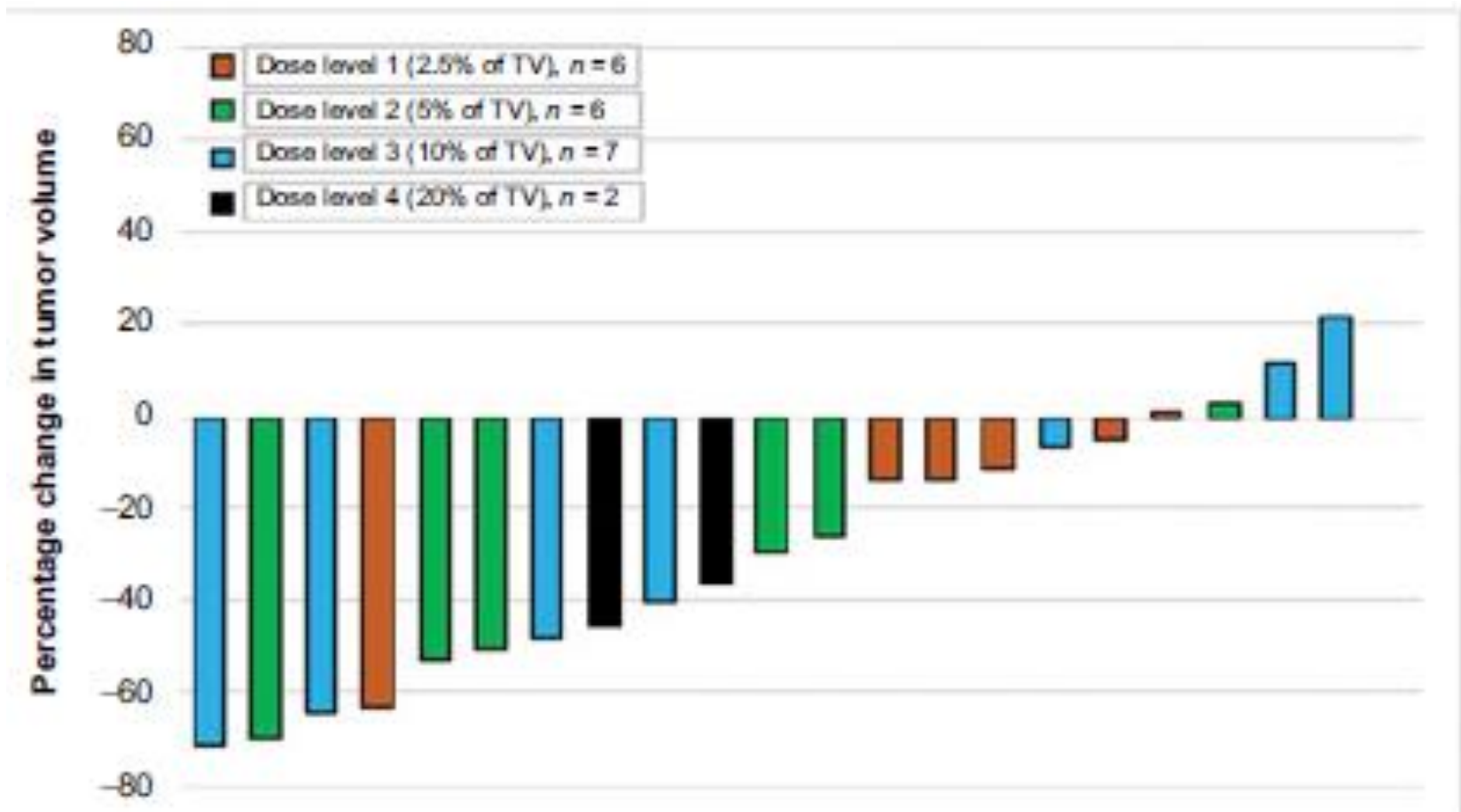
Figure 2.

Whole blood hafnium concentrations following NBTXR3 injection shown for each patient. The minutes for day 1 correspond to the time after completion of the injection procedure. Pt, patient; RT, radiotherapy.

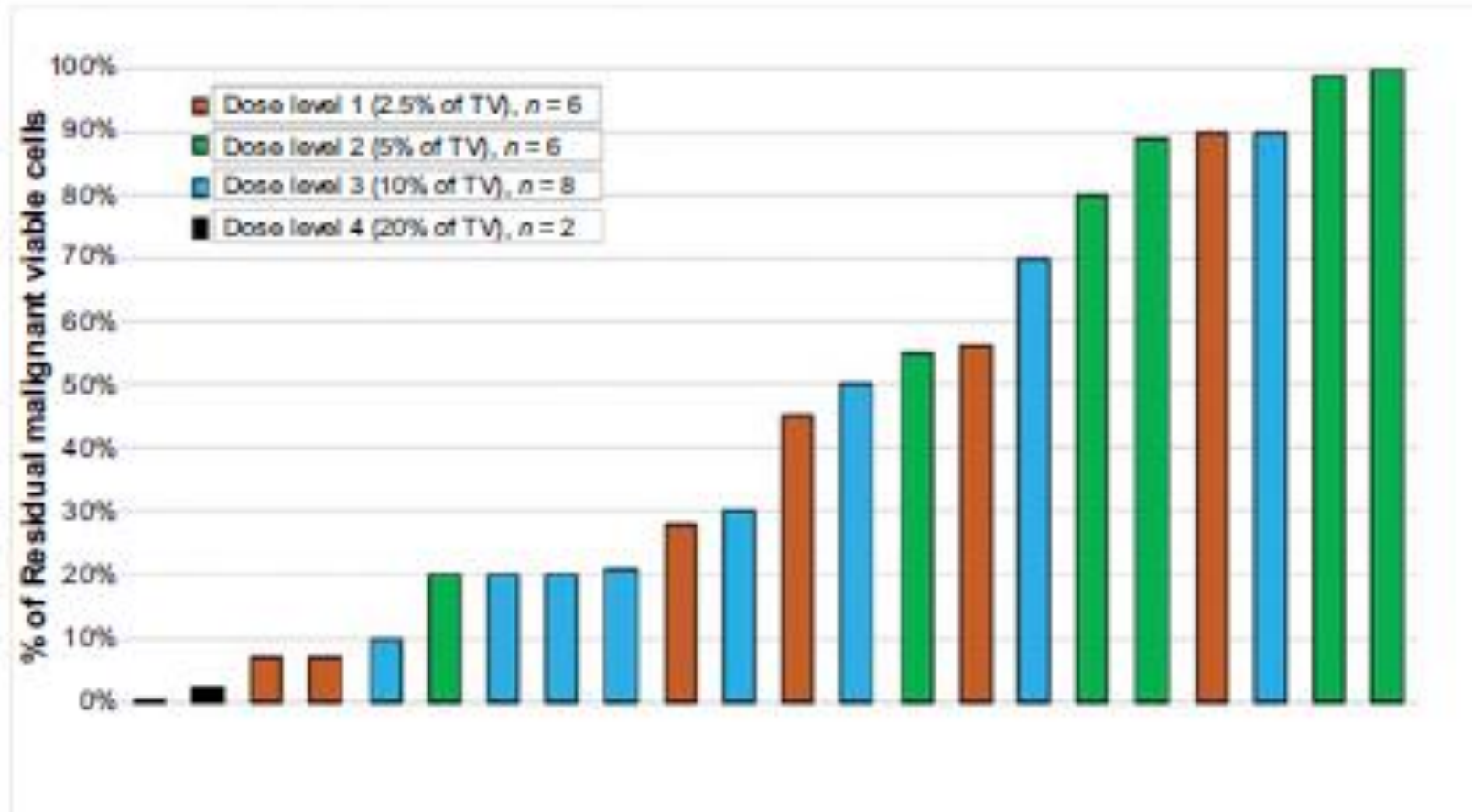
Percentage change in maximum diameter



NBTXR3 tumor volume evolution







% residual cells



NBTXR3 Pathological response and tumor volume evolution

Radiotherapy with NBTXR3



<i>NBTXR3 (level)</i>	2,5%	5%	10%	20%
				
Median tumor shrinkage	-13%	-40%	-41%	41%
Median pR (% malignant viable cells)	37%	85%	26%	1%
Complete tumorectomy (large margin)	6/6	6/6	8/8	2/2

Recommended
volume

Phase II/III registration study in Soft Tissue Sarcoma

Population: Patients with locally advanced soft tissue sarcoma of the extremity and trunk wall

End points

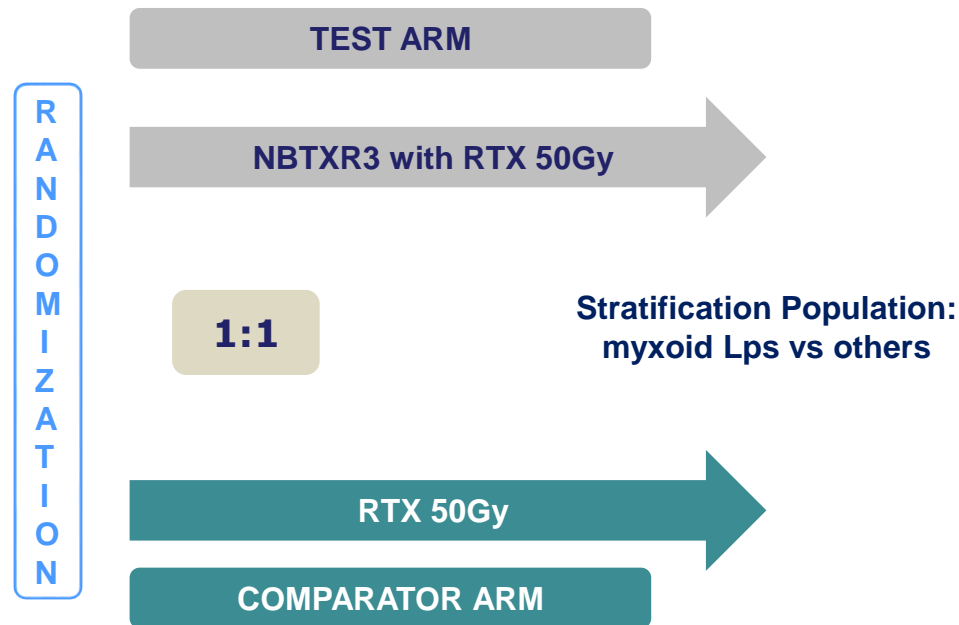
- 1) Complete path response rate pCR
- 2) Tumor shrinking rate and operability
- Progression free survival
- Amputation rate
- QoL

Number of patients Sites and countries

156 patients
30 sites
12 countries
EU, CAN, ASIA

Study Design

** Two-arms, randomized, active-controlled, multi-center, and open-label trial*

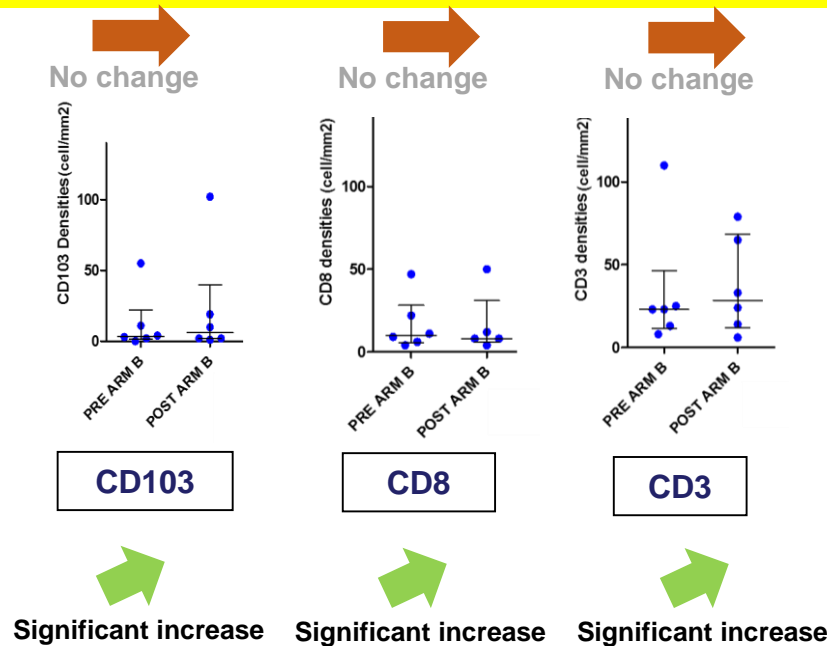


pCR
Primary endpoint
evaluation

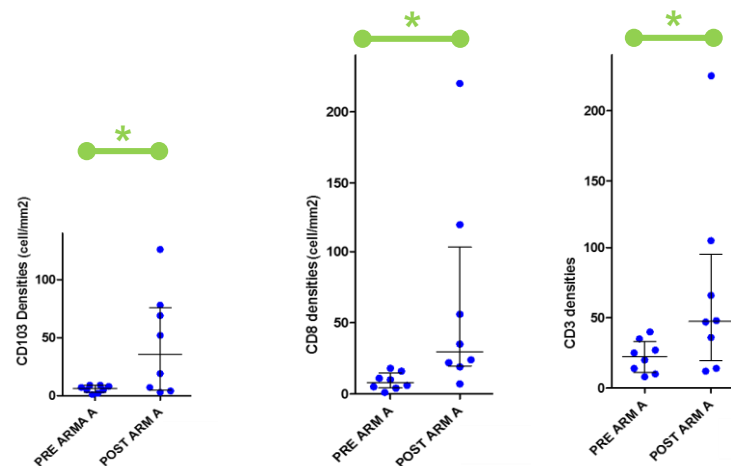
Implementation of guidelines for pathological response evaluation with:
International board including leaders from USA and EU
Central assessment reading of the treatment response

Patient tumor infiltration: 14 pts (RT + NBTXR3) /12 pts (RT) Pre and post treatment comparison

RTx alone

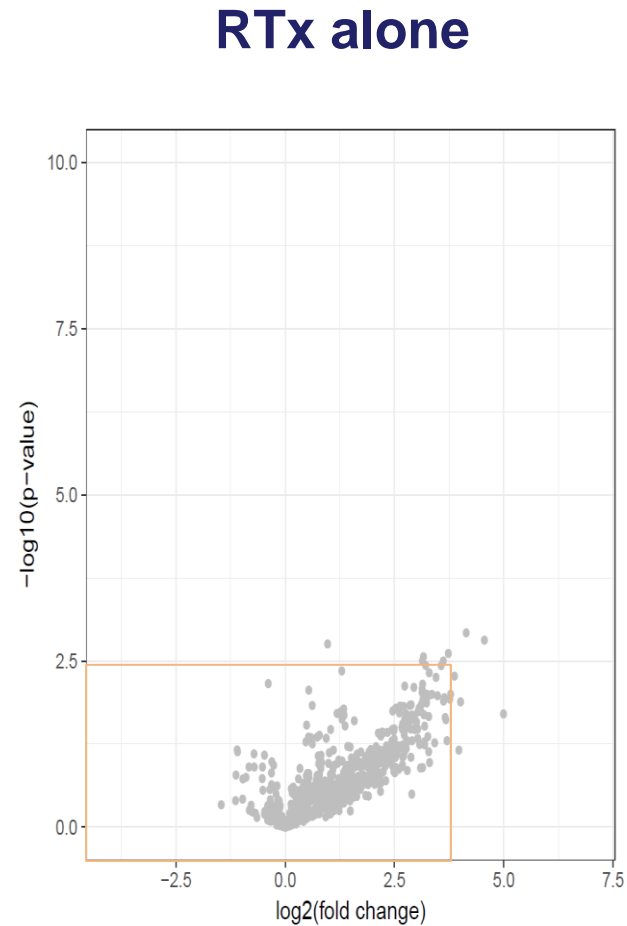
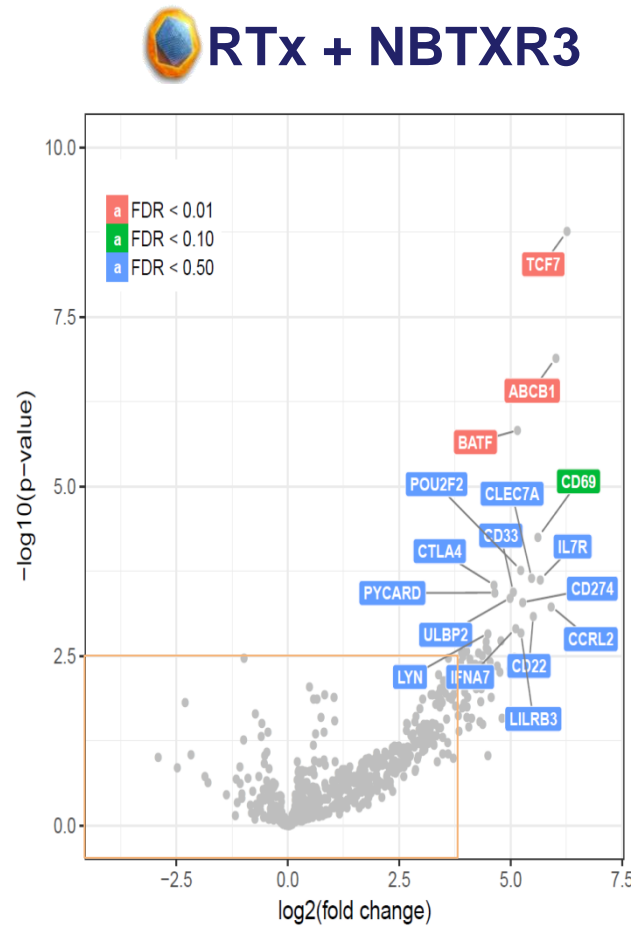


RTx + NBTXR3



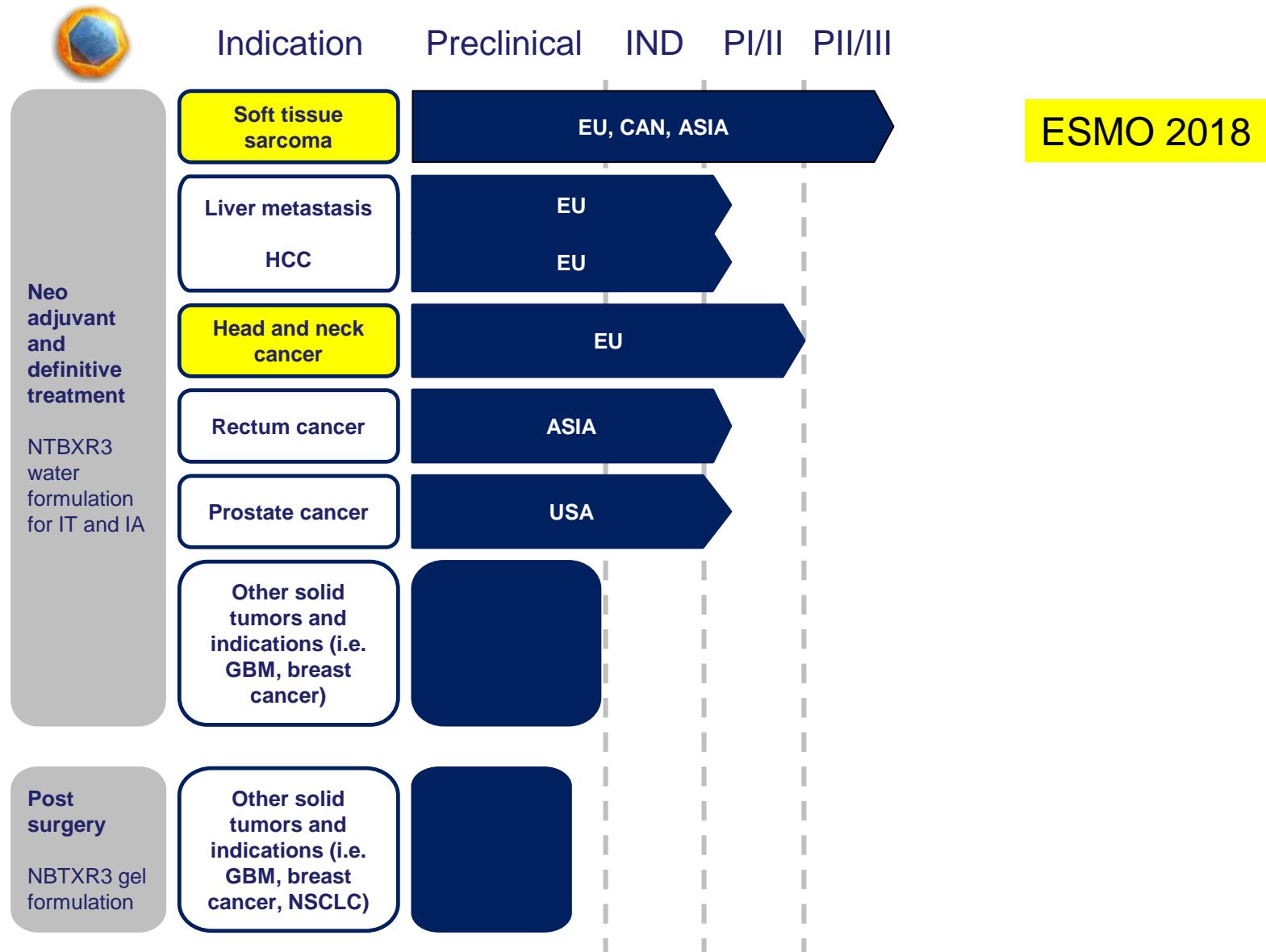
NBTXR3 allows higher infiltration in STS tumor
Transforming cold to hot

Genes Up-Regulation of adaptative Immune Response



- Asymmetrical volcano plot showing a trend to up-regulation of PanImmune genes in post-treatment NBTXR3 arm

NBTXR3 single agent combined with RTx



Conclusions

- A new mode of action: radio enhancement: the nanoparticle becomes the active principle / No drug
- Initial development with NBTXR3 in sarcomas showed promising results
- Results of the randomized study ESMO 2018
- Development included phases 1/2 in various tumors types (prostate, rectum, head and neck)