PD-0045

A PHASE I/II STUDY EVALUATING THE IMPACT OF NBTXR3 NANOPARTICLES ACTIVATED BY PRE-OPERATIVE RADIOTHERAPY IN LOCALLY ADVANCED SOFT TISSUE SARCOMA

C. Le Pechoux[1]; G. Kantor[2]; E. Deutsch[1]; P. Sargos[2] ; A. Levy[1];T. De Baere[1]; X. Buy[2]; F. Martinetti[1]; E. Stoeckle[2]; P. Terrier[1]; A. Le Cesne[1]; A. Italiano[2]; M. Dimitriu[3]; L. Levy[3]; J-C. Soria[1]; S. Bonvalot[1]

[1] Institut Gustave Roussy, Villejuif, France; [2] Institut Bergonié, Bordeaux, France; [3] Nanobiotix, Paris, France

OBJECTIVES

Patients with locally advanced soft tissue sarcoma of the extremities or trunk wall may be treated with neo-adjuvant treatment followed by wide resection. Pre-operative radiotherapy (RT) is one of these validated options.

To optimize outcome, NBTXR3, functionalized hafnium oxide nanoparticles, have been developed as selective radioenhancer, which may represent a breakthrough approach for the local treatment of solid tumors. The high electron density of NBTXR3 nanoparticles when exposed to radiotherapy, may allow absorption/deposition of a high energy dose within the cancer cell, and possibly improve outcome.

METHODS

The aim of this is open-label, single arm, feasibility and safety Phase I study with NBTXR3 intratumor implantation (by injection), activated by external beam radiation therapy (EBRT) in patients with soft tissue sarcoma of the extremity and trunk wall is:

Primary Objectives

To evaluate the feasibility of the NBTXR3 intratumor (IT) injection.

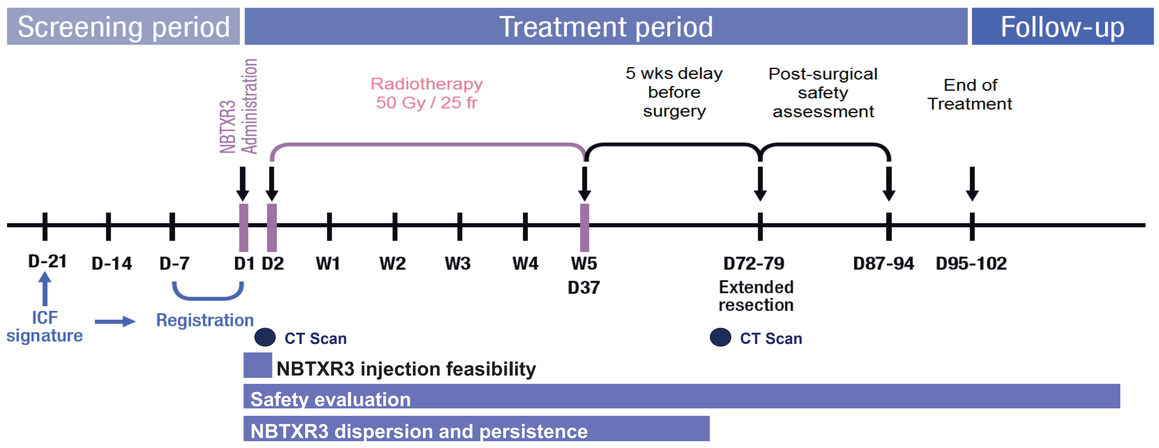
To determine the early dose limiting toxicity (DLT) and assess the safety profile.

Secondary Objectives

To evaluate the anti-tumor activity of NBTXR3 activated by EBRT in terms of pathological Response (pR) corresponding to % of residual malignant viable cells.

To evaluate the Response Rate (RR) of NBTXR3 activated by EBRT as per RECIST and Tumor Volume (TV).

Study Design



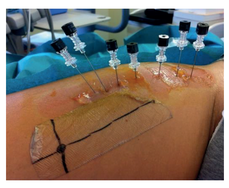
RESULTS

Baseline and disease characteristics

			Level 1 (N=6)	Level 2 (N=6)	Level 3 (N=8)	Level 4 (N=2)	Overall (N=22)
Sex	Female	N (%)	3 (50.0%)	3 (50.0%)	3 (37.5%)	2 (100.0%)	11 (50.0%)
	Male	N (%)	3 (50.0%)	3 (50.0%)	5 (62.5%)	0	11 (50.0%)
Age (Years)	Range		42; 78	31; 82	28; 57	65; 67	28; 82
	Median		(48.5)	(46.0)	(54.5)	(66.0)	(53.5)
Performance status WHO scale	0	N (%)	5 (83.3%)	5 (83.3%)	6 (75.0%)	2 (100.0%)	18 (81.8%)
	1	N (%)	1 (16.7%)	1 (16.7%)	2 (25.0%)	0	4 (18.2%)
Histology type	Liposarcoma ➢ *Myxoid liposarcoma*	N (%)	2 (33.0%) *0*	5 (83.0%) *2 (40.0%)*	2 (25.0%) *1 (12.5%)*	0 *0*	9 (41.0%)
	Undifferentiated Sarcoma	N (%)	1 (17.0%)	0	1 (13.0%)	1 (50.0%)	3 (14.0%)
	Synovial Sarcoma	N (%)	2 (33.0%)	0	0	0	2 (9.0%)
	Others	N (%)	1 (17.0%)	1 (17.0%)	5 (63.0%)	1 (50.0%)	8 (36.0%)
G Classification	G1	N (%)	1 (16.7%)	4 (66.7%)	2 (25.0%)	0	7 (31.8%)
	G2	N (%)	3 (50.0%)	2 (33.3%)	4 (50.0%)	1 (50.0%)	10 (45.5%)
	G3	N (%)	2 (33.3%)	0	1 (12.5%)	1 (50.0%)	4 (18.1%)
	GX – Unknown	N (%)	0	0	1 (12.5%)	0	1 (4.5%)
T Classification	T2 Superficial	N (%)	0	0	2 (25%)	1 (50.0%)	3 (13.6%)
	T2 Deep	N (%)	6 (100.0%)	6 (100.0%)	6 (75.0%)	1 (50.0%)	19 (86.4%)

Feasibility of NBTXR3 Intratumor Injection

NBTXR3 volume escalation at fixed concentration (53.3 g/L)		Tumor Volume (mL)	Volume Injected (mL)	Number of Punctures
		Total (N=6)	Total (N=6)	Total (N=8)
Volume 2.5%	Range	55-1814	1.4-45	2-10
	Median	291	4.7	4
Volume 5%	Range	85- 3682	4.2-184	2-11
	Median	567	27	6
Volume 10%	Range	130- 886	13-101	5-33
	Median	305	30	7.5
Volume 20%	Range	490-960	84-192	12-13
	Median	725	138	12.5



The injection procedure was performed under local anesthesia and premedication with analgesic. No sedative treatment was given.

This first step of the clinical development demonstrated the feasibility of the NBTXR3 intratumor injection at the 3 first volume levels, given as multiple punctures.

At 20%, two patients had grade 3 injection site pain. Thus, 10% volume has been chosen as the recommended volume for the phase II/III pivotal study.

Incidence of Adverse Events Related to NBTXR3

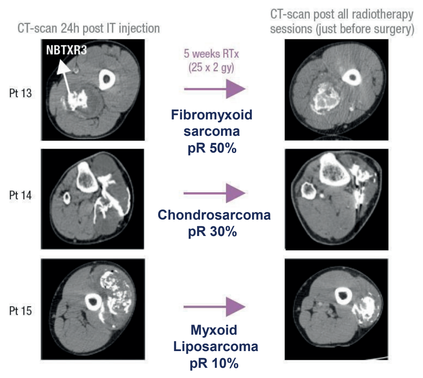
	NCI-CTCAE version 4					
	1	2	3	4	5	>= Grade 3
LEVEL 1 : N=6 (NBTXR3 2.5% baseline tumor volume)						0
Abdominal pain		1				
Hypotension	1					
Injection site reaction	1					
Paraesthesia	1					
Pyrexia	1					
LEVEL 2 : N=6 (NBTXR3 5% baseline tumor volume)						0
Headache		1				
Injection site pain	2					
Oedema peripheral		1				
Pyrexia	1					
LEVEL 3 : N=3 (NBTXR3 10% baseline tumor volume)						0
Injection site pain		1				
LEVEL 4 : N=2 (NBTXR3 20% baseline tumor volume)						2
Injection site pain			1			
Postoperative wound complication			1			

Main grade 1-2 toxicities related to NBTXR3 were injection pain/ reaction (5 pts), pyrexia (2 pts), pruritus (1 pt) and paresthesia (1 pt).

No adverse event caused radiotherapy delay or treatment discontinuation.

The intratumoral injection at the volume level 4 was considered non feasible due to the high volume injected in the tumor mass, as the two patients treated experienced grade 3 pain at the injection site.

Intratumor Bioavailability Of NBTXR3 At Volume 10%



Appropriate diffusion in the tumor with different histologies and sizes.

No leakage to the surrounding healthy tissues of NBTXR3.

Persistence of NBTXR3 during the whole duration of RT.

Efficacy Evaluation

		Number of patients	Pathological Response (% residual malignant viable cells)
Volume 2.5%	Range	6	07; 90
	Median		36
Volume 5%	Range	6	20; 100
	Median		84
Volume 10%	Range	8	10; 90
	Median		25
Volume 20%	Range	2	0; 2
	Median		1

← Recommended Volume

5/22 patients had ≤10% of residual malignant viable cells.

At 10% volume (recommended volume), the median residual malignant viable was 25%.

All patients treated in the study had a wide surgical resection of the tumor.

CONCLUSIONS

Feasibility of the NBTXR3 injection within the tumor mass combined to pre-operative radiotherapy across different tumor sarcoma and volumes was demonstrated.

Persistence of NBTXR3 during all sessions of radiation therapy with optimal bioavailability over time was demonstrated.

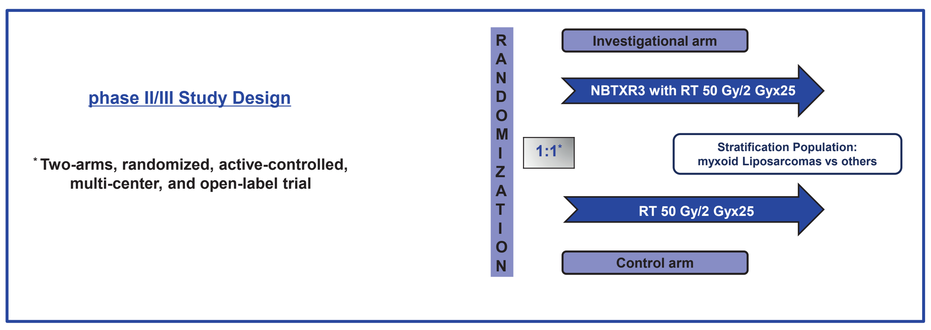
Appropriate dispersion of the product within the tumor: diffusion in the 3 dimensions was shown.

Very good tolerance and local safety of the product at volume 2.5%, 5% and 10% was observed.

The recommended volume for the pivotal study is 10%.

Promising signs of antitumor activity were observed in different sarcoma subtypes, such as liposarcoma, undifferentiated sarcoma, and synovial sarcoma.

An international phase II/III trial of NBTXR3 nanoparticles has already started comparing pre-operative radiotherapy (50 Gy / 25 fr) to the same RT regimen with a single NBTXR3 intratumoral injection[1].



References

[1] ClinicalTrials.gov Identifier: NCT02379845