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CLINICAL INVESTIGATION

Final Safety and Health-Related Quality of LIfe Results of the Phase 2/3 Act.In.Sarc Study With Preoperative NBTXR3 Plus Radiation Therapy Versus Radiation Therapy in Locally Advanced Soft-Tissue Sarcoma

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Data sharing statement: Nanobiotix has committed to sharing the data underlying this publication on request from qualified scientific and medical researchers, including patient-level clinical trial data, study-level clinical trial data, protocols from clinical trials in patients for NBTXR3, and indications approved in the United States and European Union by regulatory agencies as necessary for legitimate research. Interested researchers can request access to anonymized patient-level data and supporting documents from clinical studies to do further research that could help to advance medical science or improve patient care. Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel, which will ensure thorough scrutiny on the application of the global data protection regulation. Nanobiotix is not involved in the decisions made by the independent review panel. Nanobiotix takes all necessary measures to ensure that patient privacy is safeguarded. Contact: dataprivacy@nanobiotix.com.

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Purpose: Act.In.Sarc (NCT02379845) demonstrated that the first-in-class radioenhancer NBTXR3, activated by preoperative radiation therapy (RT), doubled the rate of pathologic complete response after resection compared with preoperative RT alone in adult patients with locally advanced soft tissue sarcoma of the extremity or trunk wall (16.1% vs 7.9%, $P = .045$), and more patients achieved R0 resections (77.0% vs 64.0%, $P = .042$). These are the toxicity and health-related quality of life (HRQoL) results.

Methods and Materials: Act.In.Sarc randomized eligible patients 1:1 to either NBTXR3 (single intratumoral injection, volume equivalent to 10% of baseline tumor volume, at 53.3 g/L) activated by external-beam RT (arm A) or external-beam RT alone (arm B) (50 Gy in 25 fractions), followed by surgery in both arms. Here, we report the safety analyses in the all-treated population with a long-term follow-up of at least 2 years, and HRQoL in the intention-to-treat full analysis set.

Results: During the on-treatment period, serious adverse events (SAEs) of all grades related to NBTXR3 occurred in 10.1% (9/89) of patients (arm A), and SAEs related to RT occurred in 5.6% (5/89) (arm A) versus 5.6% (5/90) (arm B); postsurgery hospitalization owing to SAEs occurred in 15.7% (14/89) (arm A) versus 24.4% (22/90) (arm B). During the follow-up period, posttreatment SAEs (regardless of relationship) occurred in 13.5% (12/89) (arm A) versus 24.4% (22/90) (arm B). NBTXR3 did not negatively affect HRQoL; during the follow-up period, there was an improvement in most mean Toronto extremity salvage, EuroQoL 5-dimension (EQ-5D), EQ5D02-EQ visual analog scale, reintegration to normal living index, and musculoskeletal tumor rating scale scores.

Conclusions: NBTXR3 did not negatively affect safety or HRQoL. Long-term safety results reinforce the favorable benefit−risk ratio of NBTXR3 plus RT.

Introduction

Patients with soft tissue sarcoma (STS) should be treated by a specialized multidisciplinary team.[1-4] The treatment goal is to maximize tumor control with minimal functional impairment.[1,2] For locally advanced STS, surgery with negative margins (R0) is the goal.[1,2] Pre- or postoperative radiation therapy (RT) is standard of care in high-risk STS,[5,6] and survival is not significantly different between pre- or postoperative RT.[7] An increased risk of surgery-related wound complications is associated with preoperative compared with postoperative RT, but postoperative RT has

a higher risk of long-term morbidity.[7,8] Modern RT dosimetry techniques and the use of flap reconstruction have reduced its toxicity.[9-11]

NBTXR3, a first-in-class radioenhancer comprising of functionalized hafnium oxide nanoparticles, is being evaluated in oncology.[12,13] NBTXR3 is administered as a one-time intratumoral injection that remains in the tumor in an "off-state" as it is chemically inert.[14,15] NBTXR3 is activated by ionizing RT.[14] In preclinical studies, NBTXR3 demonstrated potent radio enhancement and antitumor effects.[14,15]

In the first-in-human phase 1 study (NCT01433068), NBTXR3 activated by preoperative external-beam RT in adult patients with locally advanced STS demonstrated clinical activity, manageable safety, and no leakage of NBTXR3 nanoparticles into the surrounding healthy tissues.[12,13]

This phase 2/3 study (NCT02379845, Act.In.Sarc, n = 180) evaluated the efficacy and safety of NBTXR3 at the recommended dose of 10% of baseline tumor volume, activated by RT versus RT alone, followed by surgery, in the same patient setting.[13] The primary endpoint was met, with a greater pathologic complete response rate (pCRR) in the NBTXR3 plus RT group versus RT alone (16.1% [14/87] vs 7.9% [7/89] of patients, P = .045), further validating the radioenhancing properties of NBTXR3.[13] Furthermore, in the RT alone group, the pCRR was similar to previously reported results in STS.[16-18] The most common grade 3 to 4 treatment-emergent adverse event (TEAE) was postoperative wound complication of all types which occurred in 22.3% of patients in both groups (20/89 vs 20/90 patients in the investigational and control groups).[13] Here, we provide the final results with a long-term follow-up period of at least 2 years.

Methods and Materials

Patients

Act.In.Sarc is a multicenter, randomized, open-label, active-controlled two-arm phase 2/3 study. Eligibility criteria included: patient's written informed consent, age ≥18 years, locally advanced STS of the extremity or trunk wall, and a tumor volume <3000 mL at baseline. Further details on patient eligibility have been described previously.[13]

Protocol approval by the relevant ethics committees or institutional review boards was obtained. The study complied with the Declaration of Helsinki, International Conference on Harmonization-Good Clinical Practice, and participating country and institution regulations. An independent data monitoring committee monitored the study and reviewed the interim analysis of the primary efficacy endpoint and safety data.

Randomization and procedures

Randomization was described previously.[13] In brief, patients were stratified by histologic type (myxoid liposarcoma vs others). Eligible patients were randomized 1:1 to receive either arm A, NBTXR3 (Nanobiotix SA, Paris, France) administered as a single intratumoral injection (at a volume equivalent to 10% of baseline tumor volume), activated within 1 to 3 days post-NBTXR3 by RT (50 Gy, given as 25 fraction [2 Gy/fraction] for 5 weeks) followed by surgery or arm B, RT alone (same 50 Gy, given as 25 fraction [2 Gy/fraction] for 5 weeks), followed by surgery. Intensity modulated RT or 3-dimensional conformal RT were both allowed. NBTXR3 was supplied as a suspension of nanoparticles at a concentration of 64 g/L. From June 2, 2016, a protocol amendment adopted the use of premedication with oral steroids to reduce the risk of acute immune reaction. Wide resection was planned 4 to 8 weeks after completing RT. Patients were assessed for 14 days during the postsurgery safety period. The end of treatment was at day 86 to 93 (ie, estimated end of postsurgical safety assessment period). Patients were followed-up and the study cutoff date was defined as the date when primary and secondary endpoints and a follow-up period of at least 2 years had been achieved for all patients. Treatment assignment and masking were previously described.[13]

Objectives

Act.In.Sarc primary objective was described previously,[13] and it compared the pCRR (≤ 5% of residual malignant viable cells) of arm A with arm B, by a blind central review board.[19]

Main secondary objectives included: objective response rate by magnetic resonance imaging according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; status of resection margins; incidence of early and late TEAEs, post-TEAEs, serious adverse events (SAEs), and laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Exploratory endpoints included: local and distant recurrence rate at 24 months; and health-related quality of life (HRQoL).

The final safety results with a long-term follow-up of ≥2 years and the HRQoL are described in this report.

Statistical analysis

In Act.In.Sarc, a total of 180 patients were randomized to allow for 156 evaluable patients (78 patients per treatment arm) to detect a significant improvement (with 80% power for a one-sided test at the 5% level) in the primary endpoint.

Safety analyses were descriptive. The Toronto extremity salvage score (TESS), EuroQoL 5-dimension (EQ-5D), reintegration to normal living index (RNLI), and the musculoskeletal tumor rating scale (MSTS) questionnaires were used and scored for HRQoL assessments. HRQoL scores were described per arm, with changes from baseline presented for each score at defined timepoints.

The intention-to-treat (ITT) population included all randomized patients. The ITT full analysis set was a subset of the ITT population and included all patients who had given informed consent, with an allocated randomization number, and had no eligibility or randomization issues. Safety was assessed in the all-treated patient population (ie, all randomly assigned patients who received any amount of NBTXR3 [arm A] or ≥1 fraction of RT [arm A or B]).

Analyses were performed using SAS software (SAS statistical software via SAS Enterprise Guide version 8.2; copyright 2019, SAS Institute Inc, Cary, NC, USA). Further methodological and statistical details have been described previously.[13]

Results

Patient characteristics

These details have been described previously,[13] briefly: between March 3, 2015, and November 21, 2017, 32 sites in 11 countries randomized 180 eligible patients (ITT population) to receive study treatment (90 patients per arm) (Fig. 1). One patient in arm A did not receive the planned treatment of NBTXR3 with RT due to a medical decision. Thus, a total of 179 patients received treatment (all-treated population). Database lock was on May 22, 2018, and the primary analysis has been presented previously.[13] For the final analysis, database lock was on November 9, 2020, and this updated data with a follow-up of at least 2 years are presented here.

In the ITT full analysis set population, patients were well balanced across treatment arms at baseline (arm A versus arm B), and patient characteristics have been described previously.[13]

Treatment compliance

In the all-treated population, in arm A, 79.8% (71/89) of patients completed NBTXR3 injection and 20.2% (18/89 did not received the full injection volume; Table 1). In arm A, 11.2% (10/89) received <80% of the planned injection volume, with pain being the most common reason for not receiving the intended volume. The median volume injected of NBTXR3 was 50.0 mL (range, 2-450 mL).

In arm A, 98.9% (88/89) versus 97.8% (88/90) of patients in arm B completed their RT (Table 1). In arm A, 2.2% (2/89) versus 5.6% (5/90) of patients in arm B had at least 1 fraction of RT delayed due to an adverse event. The median total dose of radiation delivered was 50 Gy (range, 44-50) in arm A and 50 Gy (range, 14-50) in arm B. A greater percentage of patients in both groups received intensity modulated RT (67.4% on arm A, and 70.0% on arm B) compared with 3-dimensional conformal RT (32.6% on arm A and 30.0% on arm B). The median relative RT dose intensity (ie, actual dose intensity divided by planned dose intensity) was 97% in both groups. Median doses to organs-at-risk including femur, femoral head, and spinal cord were equivalent in both arms. RT planning target volume and clinical target volume minimum, mean, and maximum doses to respective volumes were equivalent in both arms.

In arm A, surgery was performed on 94.4% (84/89) of patients versus 96.7% (87/90) in arm B (Table 1). For resected patients, flap reconstruction was performed in 25.3% (21/83) of patients in arm A versus 15.1% (13/86) in arm B in the ITT full analysis set population.

Efficacy

Efficacy has previously been reported.[13] Briefly, arm A was significantly superior to arm B in terms of pCRR (16.1% [14/87] vs 7.9% [7/89], $P = .045$), tumor necrosis (median tumor necrosis: 20.0% [range, 0-95] vs 10.0% [range, 0-95], $P = .014$), and R0 resection (77.0% [67/87] vs 64.0% [57/89], $P = .042$). In arm A versus arm B, objective response rate was 6.9% (6/87) versus 10.1% (9/89) ($P = .863$) (Table 2).

The local recurrence rate at 24 months (cumulative rate) was 12.0% (9/75; 95% confidence interval [CI], 5.6%-21.6%) in arm A and 7.1% (6/84; 95% CI, 2.7%-14.9%) in arm B. The distant recurrence rate at 24 months (cumulative rate) was 33.3% (25/75; 95% CI, 22.9%-45.2%) in arm A and 26.2% (22/84; 95% CI, 17.2%-36.9%) in arm B, in the evaluable patient population.

During the whole study, 46 patients died, (24 patients in arm A and 22 patients in arm B). There were no treatment-related deaths, and the primary cause of death was progressive disease.

Safety

Safety is described both for the on-treatment period and the follow-up period of at least 2 years in the all-treated population.

Safety during the on-treatment period has been described previously.[13] Briefly, during the on-treatment period in arm A, 36.0% (32/89) of patients had at least 1 NBTXR3-related adverse event, with the most common being hypotension (all grades: 11.2% [10/89]), and grade 4 events included 1 hypotension and 1 anaphylactic shock (Table E1). In arm A, 46.1% (41/89) of patients had at least 1 adverse event related to the injection procedure, with the most common (all grades) being injection site pain (12.4% [11/89]), and 1 patient had a grade 4 pulmonary embolism. During the on-treatment period no grade 4 RT-related TEAEs occurred (Table E2). At least 1 adverse event related to RT was noticed in 78.7% (70/89) versus 80.0% (72/90) of patients in arms A and B, the most common being radiation skin injury (all grades, arm A 52.8% [47/89] vs arm B 63.3% [57/90] of patients; Table E2).

Postsurgical TEAEs are shown in Table E3. Grades 3 to 4 TEAEs (arm A vs arm B) for all wound complications after

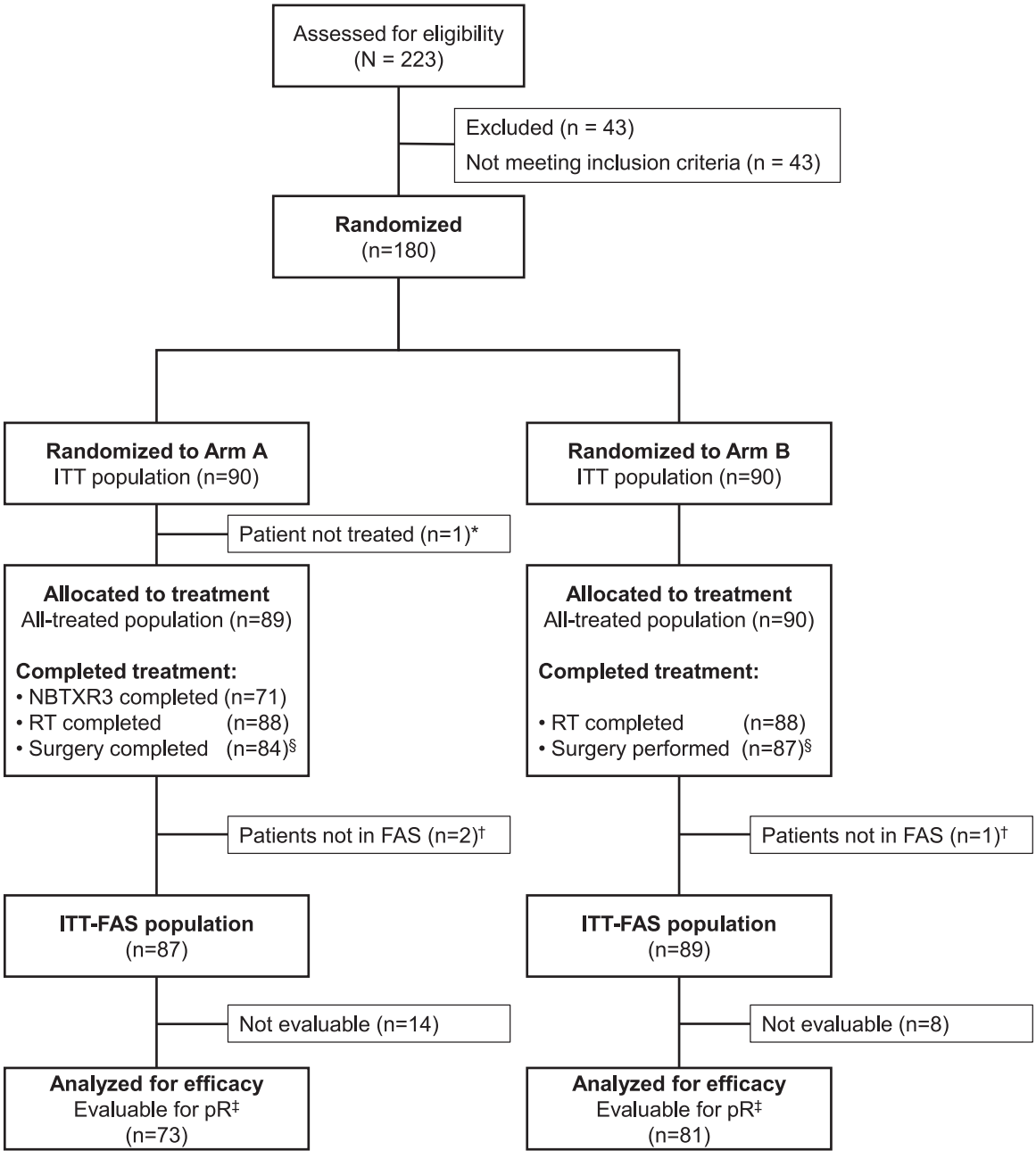

Fig. 1. Patient disposition. *Due to a medical decision. †Due to eligibility violations: 2 patients were ineligible in arm A (NBTXR3 activated by radiation therapy followed by surgery; 1 patient with myxoma and 1 patient with non-Hodgkin lymphoma), and 1 patient in arm B (radiation therapy followed by surgery) with melanoma was ineligible. §In arm A 6 patients did not complete surgery (3 patients withdrew consent, 2 patients had progressive disease, and 1 patient due to medical decision), and in arm B 3 patients did not complete surgery (1 patient withdrew consent, 1 patient had progressive disease, and 1 patient had an adverse event). ‡Evaluable patient population for pathologic response evaluations. The evaluable patient population was broken down as follows: evaluable patient population for pathologic response evaluation (n = 154 comprising of: arm A, n = 73; and arm B, n = 81); evaluable patient population for carcinologic resection margins evaluation (n = 155, comprising the following: arm A, n = 73; and arm B, n = 82); and evaluable patient population for imaging evaluation (n = 159, comprising the following: arm A, n = 75; and arm B, n = 84). *Abbreviations:* FAS = full analysis set; ITT = intention to treat; pR = pathologic response; RT = radiation therapy.

surgical resection occurred in 21.3% (19/89) versus 22.2% (20/90) of patients (Table 3).

During the follow-up period (of at least 2 years), 4.5% (4/89) of patients in arm A had at least 1 posttreatment adverse event related to NBTXR3 and RT, which included 1 grade 3 postoperative wound complication and 1 grade 3 osteonecrosis (Table 4). In arm A versus arm B, posttreatment RT related adverse events occurred in 24.7% (22/89) versus

Table 1 Treatment discontinuation and early withdrawals

		Arm A (n = 89)*	Arm B (n = 90)	Overall (n = 179)
Study treatment during the on-treatment period (all-treated population), n (%)				
NBTXR3 completed	Yes	71 (79.8)	-	71 (79.8)
	No	18 (20.2)†	-	18 (20.2)
RT completed	Yes	88 (98.9)	88 (97.8)	176 (98.3)
	No	1 (1.1)‡	2 (2.2)§	3 (1.7)
Surgery performed	Yes	84 (94.4)	87 (96.7)	171 (95.5)
	No	5 (5.6)‖	3 (3.3)#	8 (4.5)
		Arm A (n = 90)	Arm B (n = 90)	Overall (n = 180)
Patients completing the study with a follow-up period of at least 2 years (intention-to-treat population), n (%)				
Study completed until the study cutoff, September 20, 2020	Yes	37 (41.1)	36 (40.0)	73 (40.6)
	No	53 (58.9)	54 (60.0)	107 (59.4)
Reasons for not completing the study	Withdrawal of consent	5 (9.4)	6 (11.1)	11 (10.3)
	Lost to follow-up	1 (1.9)	1 (1.9)	2 (1.9)
	Medical decision	2 (3.8)	2 (3.7)	4 (3.7)
	Death	2 (3.8)	2 (3.7)	4 (3.7)
	Other	43 (81.1)**	43 (79.6)**	86 (80.4)

Abbreviation: RT = radiation therapy; Arm A = NBTXR3 activated by radiotherapy followed by surgery; Arm B = radiotherapy alone followed by surgery.

* One patient in arm A was randomized but not treated (ie, did not receive NBTXR3 or RT).

† Of the 18 patients who did not receive the whole dose of NBTXR3, the NBTXR3 injection was interrupted due to: adverse events for 10 patients, serious adverse events for 2 patients, for 2 patients the tumor configuration and poor visibility of the site rendered the injection difficult, for 3 patients the tumor was too hard, and for 1 patient there was a loss of a small amount of volume by dropping of the syringe.

‡ One patient in arm A stopped the RT due to clinical deterioration leading to death.

§ In arm B, 1 patient withdrew consent and 1 patient stopped due to progressive disease.

‖ In arm A, surgery was not performed in 3 patients who withdrew consent and in 2 patients with progressive disease.

In arm B, surgery was not performed in 1 patient due to an adverse event, in 1 patient who withdrew consent, and in 1 patient with progressive disease.

** The other reasons were comprised of: progressive disease (34 patients in arm A and 32 in arm B); further anticancer therapy (6 patients in arm A and 9 patients in arm B); 2 patients in arm A refused to visit the clinic due to COVID-19 and 1 patient in arm A was found to be no longer evaluable in the study (final diagnosis of intramuscular myxoma); 1 patient in arm B was abroad and unable to do a follow-up visit; and 1 patient in arm B refused to perform laboratory examinations, vital signs, and complete the questionnaire.

Table 2 Radiologic response by MRI according to RECIST 1.1 at the surgical visit and pathologic complete response rate (intention-to-treat full analysis set)

	Arm A: NBTXR3 activated by RT (n = 87)	Arm B: RT alone (n = 89)	*P* value
Type of radiologic response, n (%)			
Complete response	0	0	-
Partial response	6 (6.9)	9 (10.1)	-
Stable disease	72 (81.6)	71 (79.8)	-
Progressive disease	6 (6.9)	3 (3.4)	-
Not evaluable	3 (3.4)	6 (6.7)	-
Objective response rate	6 (6.9)‡	9 (10.1)	.863
Clinical benefit*	78 (89.7)	80 (89.9)	-
Primary endpoint: Pathologic complete response, n (%)†	**14 (16.1)**	**7 (7.9)**	**.045**

Abbreviations: MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1; RT = radiation therapy.

* Clinical benefit: includes complete response, partial response, and stable disease.

† Less than 5% of residual malignant viable cells.

‡ Intratumoral edema is more likely with nanoparticles within the tumor stroma, which determines the absence of tumor size decrease.

Table 3 Number of patients with wound complications after surgical resection, by worst NCI-CTCAE grade (all-treated population)

	Arm A (n = 89)			Arm B (n = 90)		
Preferred term	All grade	Grade 3	Grade 4	All grade	Grade 3	Grade 4
Postoperative wound complication	16 (18.0)	7 (7.9)	0	23 (25.6)	9 (10.0)	0
Postoperative wound infection	14 (15.7)	5 (5.6)	0	13 (14.4)	7 (7.8)	1 (1.1)
Postprocedural complication	16 (18.0)	1 (1.1)	0	10 (11.1)	0	0
Postprocedural infection	4 (4.5)	3 (3.4)	0	3 (3.3)	2 (2.2)	0
Seroma	1 (1.1)	1 (1.1)	0	5 (5.6)	2 (2.2)	0
Postprocedural hemorrhage	2 (2.2)	2 (2.2)	0	3 (3.3)	1 (1.1)	1 (1.1)
Postprocedural hematoma	0	0	0	2 (2.2)	0	0
Postprocedural edema	1 (1.1)	0	0	1 (1.1)	0	0
Skin flap necrosis	1 (1.1)	1 (1.1)	0	1 (1.1)	1 (1.1)	0
Arthritis bacterial	1 (1.1)	0	0	0	0	0
Lymphocele	1 (1.1)	0	0	0	0	0
Postprocedural discharge	1 (1.1)	0	0	0	0	0
Postoperative abscess	1 (1.1)	0	1 (1.1)	0	0	0
Wound complication	1 (1.1)	0	0	0	0	0
Wound infection	0	0	0	1 (1.1)	0	0
All	39 (43.8)	18 (20.2)	1 (1.1)	42 (46.7)	19 (21.1)	2 (2.2)

Data are shown for number of patients n (%) for a given category (preferred term). A patient may have more than 1 adverse event in the same category. Arm A, NBTXR3 activated by radiation therapy followed by surgery; arm B, radiation therapy alone followed by surgery.
Abbreviation: NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

25.6% (23/90) of patients, with the most common being radiation skin injury (all grades: 9.0% [8/89] vs 5.6% [5/90]); and the most frequent grade 3 was postoperative wound complication (3.4% [3/89] vs 4.4% [4/90]) with no grade 4 events (Table 4). Late onset radiation toxicities in arm A versus arm B included fibrosis (4.5% [4/89] vs 7.8% [7/90]) and edema (6.7% [6/89] vs 2.2% [2/90]).

Serious TEAEs during the on-treatment period are shown in Table E4. As previously reported,[13] during the on-treatment period (all grades): SAEs related to NBTXR3 occurred in 10.1% (9/89) of patients in arm A; SAEs related to the injection procedure occurred in 9.0% (8/89) of patients in arm A; SAEs related to RT occurred equally in 5.6% (5/89) and 5.6% (5/90) of patients in arm A and B, respectively; and in 2 patients in arm A there were 3 serious TEAEs related to NBTXR3 and RT. Postsurgery hospitalization due to SAEs occurred in 15.7% (14/89) versus 24.4% (22/90) of patients in arm A and B. During the follow-up period, posttreatment SAEs (regardless of cause) of any grade occurred in 13.5% (12/89) versus 24.4% (22/90) of patients in arms A and B.

For most hematology and biochemistry parameters, the proportion of patients with a change from grade 0 or 1 to grade 3 was similar between treatment groups during the on-treatment period (Tables E5 and E6), as well as the proportion of patients with a shift from grade 0 to 1 to grade 1 to 2 during the follow-up period (Tables E7 and E8).

HRQoL

NBTXR3 did not negatively affect patient HRQoL (Table 5). The mean change in baseline at 2-years follow-up (arms A vs arm B, respectively) for TESS were -3.4 versus -6.1; EQ-5D-5L were -0.093 versus -0.038; EQ5D02-EQ visual analog (VAS) were 6.5 versus 2.3; RNLI were 2.0 versus 0.0; and for MSTS were 1.7 versus 1.2 (Table 5). Over the follow-up period there was a gradual improvement in most HRQoL evaluations for the mean TESS, EQ-5D-5L, EQ5D02-EQ VAS, RNLI, and MSTS scores (Tables E9-E13). From the baseline score and end of treatment score, the mean TESS, EQ-5D-5L, EQ5D02-EQ VAS, RNLI, and MSTS scores mostly increased over the follow-up period in arms A and B.

Discussion

This phase 2/3 study demonstrated that NBTXR3 activated by RT resulted in statistically significant and clinically meaningful improvements in outcomes compared with RT alone, for patients with locally advanced STS, without jeopardizing safety and long term QoL. NBTXR3 increased the energy dose deposit within tumor cells, shown by the better pCRR compared with RT alone. Twice as many patients had

Table 4 Number of patients with posttreatment adverse events related to NBTXR3 and radiation therapy or related to radiation therapy, by worst NCI-CTCAE grade (all-treated population)

	Arm A (n = 89)			Arm B (n = 90)		
Preferred term	**All grade**	**Grade 3**	**Grade 4**	**All grade**	**Grade 3**	**Grade 4**
Posttreatment adverse events related to NBTXR3 and radiation therapy						
Peripheral edema	1 (1.1)*	0	0	-	-	-
Osteonecrosis	1 (1.1)	1 (1.1)	0	-	-	-
Postoperative wound complication	1 (1.1)	1 (1.1)	0	-	-	-
Thrombophlebitis superficial	1 (1.1)	0	0	-	-	-
Posttreatment adverse events related to radiation therapy						
Radiation skin injury	8 (9.0)	0	0	5 (5.6)	0	0
Postoperative wound complication	4 (4.5)	3 (3.4)	0	6 (6.7)	4 (4.4)	0
Radiation fibrosis	3 (3.4)	0	0	3 (3.3)	0	0
Fibrosis	1 (1.1)	0	0	4 (4.4)	0	0
Peripheral edema	3 (3.4)	0	0	2 (2.2)	0	0
Postoperative wound infection	1 (1.1)	1 (1.1)	0	2 (2.2)	2 (2.2)	0
Lymphedema	2 (2.2)	0	0	0	0	0
Neuralgia	2 (2.2)	0	0	0	0	0
Pain in extremity	2 (2.2)	0	0	0	0	0
Arthritis bacterial	1 (1.1)	0	0	0	0	0
Dyspnea	1 (1.1)	0	0	0	0	0
Fatigue	1 (1.1)	0	0	0	0	0
Osteonecrosis	1 (1.1)	1 (1.1)	0	0	0	0
Postprocedural complication	0	0	0	1 (1.1)	0	0
Postprocedural hemorrhage	0	0	0	1 (1.1)	1 (1.1)	0
Postprocedural edema	1 (1.1)	0	0	0	0	0
Pulmonary embolism	1 (1.1)	0	0	0	0	0
Staphylococcal osteomyelitis	0	0	0	1 (1.1)	1 (1.1)	0
Superficial thrombophlebitis	1 (1.1)	0	0	0	0	0

Data are shown for number of patients n (%) for a given category (preferred term). Arm A, NBTXR3 activated by radiation therapy followed by surgery; arm B, radiation therapy alone followed by surgery.

Abbreviation: NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

* One patient had 2 events of peripheral edema (1 grade 1 and 1 grade 2).

a pCRR with NBTXR3 activated by standard RT compared with the same RT alone (16.1% vs 7.9%, $P = .045$). pCRR was chosen as the primary endpoint because its assessment is less subject to variability than the partial response and it can provide a more rapid answer about the benefit of this new class of radioenhancer compared with overall survival (OS) endpoints. In retrospective series, pCRR is associated with an improved OS and disease-free survival, a lower risk of local and distant recurrence, and is a prognostic marker for survival for neoadjuvant treatment of STS.[20-23] In a report with 496 patients receiving neoadjuvant therapy for high-grade extremity STS, pathologic complete response (pCR) (≥95% pathologic necrosis) compared with <95% pathologic necrosis resulted in significantly higher 5- and 10-year OS (80% and 71% vs 62% and 55%, respectively) and significantly lower 5- and 10-year local recurrence rates (6% and 11% vs 17% and 23%, respectively).[21] In a systematic review and meta-analysis of 1663 patients with STS receiving neoadjuvant therapy, patients with <90% tumor necrosis had a significantly increased risk of recurrence at 3 years (odds ratio, 3.35; 95% CI, 2.27-4.92; $P < .001$) and death at 5 years (odds ratio, 2.60; 95% CI, 1.59-4.26; $P < .001$).[23] In an observational, retrospective analysis of 330 patients with locally advanced STS receiving neoadjuvant treatment, pCR (≤5% viable tumor cells or ≥95% necrosis/fibrosis) was predictive of survival outcomes, with a statistically significant improvement in 3-year disease-free survival in patients with pCR compared with patients without a pCR (76% vs 61%, $P < .001$). By multivariate analysis outcomes were significantly better, including local recurrence-free

Table 5 HRQoL evaluations over time (ITT-FAS)

HRQoL assessments	Statistics	Baseline value		Change from baseline at 2 years follow-up (follow-up visit 8)	
		Arm A: NBTXR3 activated by RT (n = 74)	Arm B: RT alone (n = 75)	Arm A: NBTXR3 activated by RT (n = 74)	Arm B: RT alone (n = 75)
Toronto extremity salvage score	n	55	61	27	26
	Mean (SD)	81.3 (20.6)	83.1 (19.1)	−3.4 (13.4)	−6.1 (17.4)
	Median	89.1	91.1	−0.5	−2.6
	Min; max	16; 100	23; 100	−38; 27	−58; 23
EuroQoL 5-dimension descriptive system single index utility score	n	57	62	31	28
	Mean (SD)	0.686 (0.257)	0.699 (0.305)	−0.093 (0.300)	−0.038 (0.312)
	Median	0.695	0.830	0.000	−0.008
	Min; max	0.03; 1.00	−0.31; 1.00	−0.76; 0.61	−0.86; 0.49
EuroQoL 5-dimension descriptive system visual analog scale score	n	57	63	31	28
	Mean (SD)	77.6 (19.7)	71.0 (21.3)	6.5 (15.9)	2.3 (22.7)
	Median	80.0	72.0	5.0	10.0
	Min; max	20; 100	0; 100	−28; 50	−80; 25
Reintegration to normal living index total score	n	47	53	25	24
	Mean (SD)	91.0 (26.2)	92.6 (21.2)	2.0 (27.4)	0.0 (26.7)
	Median	100.0	100.0	0.0	0.4
	Min; max	0; 110	20; 110	−69; 94	−56; 79
Musculoskeletal tumor rating scale total score	n	50	49	19	15
	Mean (SD)	26.9 (7.1)	27.8 (6.6)	1.7 (6.1)	1.2 (6.0)
	Median	29.0	29.0	2.0	2.0
	Min; Max	2; 35	8; 35	−14; 16	−8; 11

Abbreviations: Arm A = NBTXR3 activated by RT followed by surgery; Arm B = RT alone followed B; HRQoL = health-related quality of life; ITT-FAS = intention-to-treat full analysis set; Max = maximum; Min = minimum; QoL = quality of life; RT = radiation therapy; SD = standard deviation.

survival (95% CI, 1.23-5.92; P = .014) and 3-year OS (95% CI, 1.07-5.21; P = .033).[22] Thus, there is good rationale for the use of pCRR as an endpoint in clinical trials such as ours, as pCRR has prognostic significance for patient outcomes in this disease setting.[13,21-23] It is likely that a gain in OS related to a better pCRR by means of NBTXR3 could only be seen in patients with unresectable tumors. Similarly, the known low local relapse rate after a radio-surgical approach would require a very large number of patients to prove a hypothetic significant difference between treatment arms, which is unrealistic for such a rare disease.

NBTXR3 activated by RT was well tolerated in this patient population and demonstrated a safety profile that was comparable to RT alone. During the on-treatment period, NBTXR3 did not increase the incidence of adverse events related to RT (78.7% in arm A vs 80.0% in arm B), and the median relative RT dose intensity was the same in both the investigational and control arms of the study (97%). The number of patients with SAEs related to RT were similar (5.6% in both arms). During the follow-up period of at least 2 years, posttreatment SAEs (of any grade, regardless of relationship) were even less in the NBTXR3 arm, 13.5% versus 24.4% on arm B. Of particular importance is that no grade 5 toxicity (death) related to NBTXR3, or injection procedure occurred.

Postoperative wound complications (all grade/grades 3-4, 43.8% [39/89]/21.3% [19/89] vs 46.7% [42/90]/22.2% [20/90] in arm A and B, respectively) were similar between arms and to the work of O'Sullivan et al,[7] who reported them in 35.2% (31/88) of patients in the preoperative group, and Wang et al[24] reported 36.6% (26/71) on extremities-only STS groups. The use of flap reconstruction was more frequent and its use may have contributed to lower the incidence of wound complications.[11]

Our long-term safety evaluations demonstrated that NBTXR3 did not affect the postsurgical wound complications. In our study, similar results were observed in patients receiving NBTXR3 plus RT versus RT alone for late radiation toxicities such as fibrosis (4.5% [4/89] vs 7.8% [7/90]) and edema (6.7% [6/89] vs 2.2% [2/90]).[25] These late toxicities findings are also similar to other studies with the use of preoperative RT for STS patients: O'Sullivan et al[7] reported 9.3% (5/54) fibrosis and 11.1% (6/54) edema, although the longer follow-up reported by Davis et al[26] showed higher

incidences of edema 15.1% (11/73) and grade ≥2 fibrosis 31.5% (23/73) in the preoperative arm of their study, and Wang et al[24] reported 5.3% (3/57) fibrosis and 5.3% (3/57) edema.

NBTXR3 did not have a negative effect on the patients' HRQoL, notably in terms of late onset adverse effects such as fibrosis, edema and joint stiffness or presence of sequelae for those with STS in the extremity. Over the course of the follow-up period, there was an increase in most mean TESS, EQ-5D-5L, EQ5D02-EQ VAS, MSTS, and RNLI scores, with improvement in physical function and in normal social activities reintegration.

Limitations included the lack of the ability to use a placebo as control, and therefore it was not feasible to double-blind the study. There were more men in arm A than in arm B, which might favor arm B, as males classically have a worse prognosis.[3,13] The quality of the resection margins might be affected by the expertise of the study center; as no stratification by center was done, because most centers were either National-Cancer Institute designated or high-volume centers. The statistical hypothesis was not built to show an improvement on local control in this population with a small sample size. Different criteria of inclusion would be necessary to show an OS benefit. This could be evaluated in a new study intended for non resectable sarcomas, but enrollment could be challenging due to the rarity of the target population.

Conclusions

NBTXR3 plus RT increased the pCRR compared with RT alone, without increasing toxicity, and these long-term safety results reinforce the favorable benefit-risk ratio of NBTXR3 activated by RT in the treatment of locally advanced STS. NBTXR3 received CE marking approval in Europe on July 4, 2019, for the preoperative treatment of patients with locally advanced soft tissue sarcoma of the extremity, girdle, and trunk wall. The favorable therapeutic ratio of the Act.In.Sarc study results provides an opportunity for future research in different patient populations where obtaining local control with RT or combined therapy is more of an issue. Clinical trials are currently ongoing with NBTXR3 activated with RT as a treatment in other tumor types (eg, head and neck squamous cell carcinoma, prostate cancer, non-small cell lung cancer, esophageal adenocarcinoma, etc.), or in combination with chemotherapy or immune checkpoint inhibitors. In this context, the reassuring safety of NBTXR3 is particularly interesting.

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