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Scientific Article

Radioenhancing Hafnium Oxide Nanoparticles (NBTXR3) Followed by Stereotactic Body Radiation Therapy in Patients With Hepatocellular Carcinoma and Liver Metastases (NBTXR3-103): Phase 1 Dose-Escalation Trial

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Purpose: Stereotactic body radiation therapy (SBRT) is a common treatment for unresectable liver cancers; however, delivering ablative doses while minimizing normal tissue toxicity is challenging. NBTXR3, a novel radioenhancer, demonstrated enhanced

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radiation therapy (RT) efficacy with minimal toxicity in healthy tissue. We evaluated NBTXR3 intratumoral injection followed by SBRT for hepatocellular carcinoma (HCC) or liver metastases.

Methods and Materials: This phase 1, multicenter, dose-escalation trial enrolled adults with unresectable HCC or liver metastases. Five dose levels of NBTXR3 were evaluated (3 + 3 design): 10%, 15%, 22%, 33% and 42% of gross tumor volume (GTV) determined by magnetic resonance imaging. Patients received RT (15 Gy × 3 or 10 Gy × 5 over 5-15 days) starting 1 to 5 days after NBTXR3 injection. Primary endpoints included: incidence of early dose-limiting toxicities (DLTs) and determination of the recommended phase 2 dose (RP2D) of NBTXR3.

Results: Between December 2015 and May 2020, 26 liver lesions in 23 patients with HCC (17 lesions in 15 patients) or liver metastases (9 lesions in 8 patients) were treated. No early DLTs were reported, and the maximum tolerated dose was not reached. The RP2D of NBTXR3 was 42% of GTV. During the treatment period, 6 patients experienced grade ≥3 toxicities; none were NBTXR3-related, one was RT-related (grade 3 fatigue), and 2 were injection procedure−related (grade 3 abdominal pain). During the follow-up period, 2 patients experienced treatment-related grade ≥3 AEs (grade 3 bile duct stenosis related to cancer/RT/NBTXR3, and grade 3 anemia related to cancer/RT/underlying liver disease). No treatment-related deaths were reported. The 12-week objective response rate in treated lesions was 58.3% (7/12) in patients with HCC, and 50.0% (4/8) in patients with liver metastases.

Conclusions: NBTXR3 + RT has a manageable safety profile with no DLTs identified during dose escalation. The RP2D for treatment of HCC or liver metastases is 42% of GTV. Future studies will further evaluate efficacy.

Introduction

In 2022, liver cancer was the sixth most common cancer and the third leading cause of cancer-related death around the world.[1] By 2040, the incidence and mortality of liver cancer will each increase by at least 50%.[2] Hepatocellular carcinoma (HCC) accounts for 75% to 85% of liver cancers,[1] arising frequently in the setting of severe chronic liver disease.[3,4] Risk factors include chronic infection with the hepatitis C virus, hepatitis B virus, excessive alcohol consumption, and nonalcoholic fatty liver disease.[2] The liver is also a common site for metastases from primary cancers such as breast, lung, and colorectal cancer.[5] Among patients who received diagnoses of de novo metastatic cancer, more than one-third will have liver metastases.[5]

Hepatic resection or ablation constitutes a definitive treatment option for early-stage primary liver tumors and limited liver metastases.[4] Liver transplantation is also an emerging treatment option for patients with unresectable disease.[6] In cases where underlying liver function, medical comorbidities, tumor size, or tumor location render the disease unresectable, other treatment strategies must be considered.[7] External beam radiation therapy (RT) has evolved as a promising therapeutic option.[4,8]

Treatment of liver malignancies with RT has historically been limited by the liver's tolerance for radiation.[8] Radiobiological and technological advancements, particularly stereotactic body RT (SBRT), have allowed radiation oncologists to revisit the potential for RT in the setting of liver disease.[8] SBRT offers the potential for precise delivery of an ablative dose to the lesion while minimizing exposure to noninvolved liver,[9,10] and is an emerging treatment option for patients with unresectable disease,[9,10] with local control rates exceeding 90%.[11,12] However, a compromise must frequently be made between the dose delivered to the tumor and the protection of functional liver and nearby organs, especially in the setting of large tumors.[13,14] In order to meet normal tissue dose constraints, the prescribed dose must often be reduced, which can lead to suboptimal tumor dosing.[10,13,14] Innovative solutions are needed to effectively deliver ablative tumor doses without surpassing organ at risk (OAR) constraints.

NBTXR3 is a novel radioenhancer composed of functionalized hafnium oxide (HfO_2) nanoparticles, which are intratumorally injected and subsequently exposed to RT.[15-17] NBTXR3 was designed to ensure optimal uptake, bioavailability, and persistence in cancer cells after a one-time procedure.[17] After intratumoral injection, NBTXR3 aggregates in intracellular locations via endocytic and lysosomal mechanisms.[18] These radiopaque nanoparticles enhance the effects of RT primarily through their high atomic number (Z) and associated electron density.[19] High-Z atoms such as hafnium (Z = 72) act as radiation enhancers by amplifying energy deposition and radiobiological effects, leading to cell death.[15] In a phase 2/3 clinical trial of neoadjuvant RT for soft tissue sarcoma, NBTXR3 exposed to RT doubled the pathologic complete response compared to RT alone.[20] This and other NBTXR3 clinical trials provide clinical support for the exploration of the tumor-agnostic NBTXR3 in additional indications, including liver cancers, where improvement in the therapeutic ratio could be beneficial.

In this report, we present safety and efficacy results of the phase 1 dose-escalation part of the NBTXR3-103 study of NBTXR3 followed by SBRT in patients with advanced HCC or liver metastases.

Methods and Materials

Study design and participants

NBTXR3-103 was a multicenter, noncomparative, open-label trial conducted to evaluate the safety and tolerability of

NBTXR3 followed by SBRT in patients with HCC or liver metastases (ClinicalTrials.gov registration number: NCT02721056). The phase 1 dose-escalation part was planned to assess the safety of NBTXR3, followed by SBRT.

Eligible patients were at least 18 years old with an expected life expectancy of >3 months for patients with HCC or >6 months for patients with liver metastases, had an Eastern Cooperative Oncology Group performance status of 0 to 1, had at least one tumor which was amenable to NBTXR3 injection and RT and measurable according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (modified RECIST [mRECIST] for HCC and RECISTv1.1 for liver metastases),[21,22] and had adequate hematologic and biochemical parameters. The total volume of targeted lesions was required to be <500 cc and <50% of the total liver volume.

Key inclusion criteria for patients with HCC included a disease that was not amenable to curative approaches (surgery or ablation) or other locoregional therapies and a Child-Pugh score (CPS) of A5 to B7. Key exclusion criteria included extrahepatic portal vein tumor thrombosis, extrahepatic metastases, and any concurrent anticancer therapy planned during RT (surgery, chemotherapy, immunotherapy, etc.).

Key inclusion criteria for patients with liver metastases included disease that was inoperable (because of medical comorbidities or tumor unresectability), a histologically confirmed primary cancer, and no growing extrahepatic disease.

For all histologies, patients who had received systemic therapy were allowed, provided that these treatments were discontinued at least 28 days prior to NBTXR3 injection. Patients with prior intra-arterial chemotherapy, radioembolization in the same hepatic lobe, or prior RT to the liver (mean dose >15 Gy) were not allowed in this trial. Prior transarterial chemoembolization (TACE) or radiofrequency ablation was permitted. Full inclusion and exclusion criteria are found in Table E1.

This study was conducted in accordance with the protocol, its amendments, the principles laid down by the 18th World Medical Assembly (Declaration of Helsinki, 1964), and all applicable amendments laid down by the World Medical Assemblies, and the applicable International Council for Harmonization Guideline for Good Clinical Practice. The study protocol was approved by relevant institutional review boards or independent ethics committees at each trial center. All patients provided voluntary written informed consent.

Treatment and planning

The study was divided into 3 periods: screening (preinjection), treatment (time of injection until approximately 12 weeks after treatment), and follow-up (Fig. E1).

Patients received intrahepatic, intratumoral injections of NBTXR3 (Table E2), administered as an aqueous suspension (at a final concentration of 53.3 g/L) after corticosteroid premedication. Corticosteroids were required because of systemic administration−related reactions observed in early NBTXR3 studies. NBTXR3 intratumoral injection was performed under image guidance (computed tomography [CT], ultrasound) with multiple needle positions in the tumor for better nanoparticle distribution. Based on a classical 3 + 3 phase 1 design, sequential patient groups received an NBTXR3 injection volume equivalent to 10%, 15%, 22%, 33%, and 42% of the gross tumor volume (GTV) measured on baseline magnetic resonance imaging (MRI).

One to 5 days postinjection, patients were planned to receive a radiation dose of 45 Gy in 3 fractions (biologically effective dose with α/β of 10 [BED_{10}] = 112.5 Gy) or 50 Gy in 5 fractions (BED_{10} = 100 Gy) delivered during a period of 5 to 15 days (Fig. E1). Megavoltage equipment with photons of at least 6 MV energy and capable of daily image guided RT was used. If needed, dose reductions to a minimum of 24 Gy in 3 fractions or 30 Gy in 5 fractions were allowed in order to respect the OAR constraints. Assessment of tumor and liver motion because of respiration was required with 4-dimensional CT, fluoroscopy, and/or cine MRI. Peritumoral fiducial markers were strongly recommended. Motion management (ie, abdominal compression, breath hold, respiratory gating) was required for respiratory motion greater than 5 mm.

For each dose level, once the first patient had been treated and reached a period of observation of 4 weeks post-RT, the next 2 patients were recruited. If no dose-limiting toxicities (DLTs) were observed in this 4-week time period—defined as any grade ≥3 adverse event (AE) which could be reasonably related to NBTXR3 and/or RT—the following level was recruited. If one patient experienced an early DLT, 3 more patients were to be recruited at that dose level. If 2 out of 3, or 2 out of 6 patients, experienced an early DLT, the study was to be stopped. If no more than 1 of 6 patients experienced an early DLT, the next level was recruited. The maximum tolerated dose (MTD) of NBTXR3 was defined as the volume at which the volume escalation was stopped (ie, the volume where at least 2 patients of 6 experienced an early DLT). The recommended phase 2 dose (RP2D) of NBTXR3 was defined as the highest dose level at which no more than 1 of 6 patients experienced an early DLT or the maximum planned dose if it was reached without DLTs.

Patients were assessed for safety, intratumor localization, and systemic passage of NBTXR3. The presence of NBTXR3 in the blood and urine was quantified by inductively coupled mass spectrometry. Whole blood was collected immediately after NBTXR3 administration at the end of the injection, and 5, 10, 15, 60, 120, and 240 minutes after completion of the injection. Urine samples were collected at first and second voids after NBTXR3 injection. Imaging of local NBTXR3 dispersion was performed prior to the onset of RT by CT scan without contrast 1 to 5 days postinjection. Treatment-emergent

adverse events (TEAE) and post-TEAE, defined as AEs occurring during (including approximately 12 weeks after treatment) or after the treatment period, respectively, were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0). In the follow-up period—defined as the time period from the end of treatment visit (3-4 months postinjection) until the end of the study—patients were seen every 2 months for 6 months and then every 4 months thereafter. At each follow-up visit, patients underwent an MRI of the liver and laboratory assessments (hematology, chemistry, tumor markers, liver function tests).

Clinical outcomes

The primary endpoints for the dose-escalation were the incidence of early DLTs and the determination of the RP2D of NBTXR3, followed by RT. Key secondary endpoints included the incidence of clinical and laboratory AEs, body kinetic parameters of NBTXR3 in whole blood and urine, tumor marker levels, and objective response rate (ORR).

For this study, target lesions were defined as liver metastases or HCC that were injected with NBTXR3 and irradiated. Although the full response criteria were not used, the guidelines of RECIST 1.1 (for liver metastases) or mRECIST (HCC) were used for assessment of target lesion response. Nontarget and new lesions were evaluated but not included in the target lesion response or determination of target lesion progression. ORR was defined as the percentage of evaluable patients with a target lesion complete response or partial response (complete response [CR] or partial response [PR], respectively) on MRI at 12 weeks after completion of RT

Statistical analysis

For the phase 1 dose-escalation part of the study, it was estimated that the study would enroll up to 24 patients. The sample size could vary depending on the incidence of early DLTs and the resultant dose level sizes.

Descriptive statistics were used to characterize safety analyses. Safety analyses were performed on the "All Treated" population, which included all screened patients who received an intratumoral injection of NBTXR3 (even if incomplete). The evaluable for safety population for DLTs included patients who received at least 80% of the planned dose of NBTXR3, at least one RT fraction, and a safety evaluation. The evaluable for efficacy population included patients who received at least 80% of the planned dose of NBTXR3, at least 15 Gy of RT (regardless of fractionation schedule), and completed 12-week post-RT imaging.

All analyses were performed using SAS version 9.4 (SAS Institute Inc).

Results

Baseline characteristics

Between December 15, 2015, and May 6, 2020, a total of 26 liver lesions in 23 patients with HCC (17 lesions in 15 patients) or liver metastases (9 lesions in 8 patients) were treated with NBTXR3 followed by RT at 9 medical centers in France. Twenty patients had 1 tumor irradiated, and 3 patients each had 2 tumors irradiated (2 with HCC and 1 with metastases). No patient had RT to a liver lesion that had not been injected with NBTXR3. Primary disease in patients with liver metastases included colorectal carcinoma (4/8, 50.0%), lung carcinoma (2/8, 25.0%), pancreatic carcinoma (1/8, 12.5%), and intrahepatic cholangiocarcinoma (1/8, 12.5%). Twenty-two patients were evaluable for early DLT assessments, and 20 patients were evaluable for efficacy. Reasons for nonevaluable status are shown in Table E3.

Patient demographics and baseline characteristics are presented in Table 1. The overall median age was 70 years (range, 55-80), 82.6% (19/23) of patients were male, 65.2% (15/23) of patients had HCC, and 34.8% (8/23) had liver metastases. Table 1 and Table E4 show that 87.0% (20/23) of patients had a CPS class A, one (4.3%) patient had a CPS class B7, and 2 (8.6%) did not have a baseline CPS. Thirteen patients (56.5%) had cirrhosis at baseline (HCC: 86.7%, liver metastases: 0%). Nine patients (39.1%) were treated with chemotherapy prior to study entry (Table E5). Overall, the median tumor diameter was 27.5 mm (range, 10.0-66.7 mm) and the median tumor volume was 12.3 cc (range, 2.0-66.7 cc). The median follow-up was 9.8 months (range, 1.7-33.6 months).

Treatments

Six patients were assigned to NBTXR3 dose level 10% of GTV, 4 patients to 15%, 4 patients to 22%, 3 patients to 33%, and 6 patients to 42%. Although the dose-escalation part was based on a classical 3 + 3 phase, more than 3 patients could be enrolled per cohort without DLT. The median duration of the NBTXR3 injection was 5 minutes (range, 2-17). The median number of punctures was 1 (range, 1-4). At least 80% (± 1%) of the calculated NBTXR3 volume was successfully injected in 22 of 23 patients (95.7%) (Fig. 1A-C, Table E6). One patient experienced grade 2 abdominal pain during the injection, resulting in a premature injection discontinuation.

On postinjection verification CT, NBTXR3 was observed within the tumor in 22 of 23 patients (95.7%). Two patients were noted to have NBTXR3 within the tumor and tumor-surrounding tissues, and one patient had NBTXR3 noted only in tumor-surrounding tissues, with no severe AEs reported in these 3 patients.

Table 1 Patient demographics and baseline characteristics

	Dose level 1 (10%) (N = 6)	Dose level 2 (15%) (N = 4)	Dose level 3 (22%) (N = 4)	Dose level 4 (33%) (N = 3)	Dose level 5 (42%) (N = 6)	Overall (N = 23)
Sex, n (%)						
Female	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)	4 (17.4)
Male	4 (66.7)	4 (100.0)	4 (100.0)	3 (100.0)	4 (66.7)	19 (82.6)
Age, y						
Median	66.0	69.0	79.0	69.0	68.0	70.0
Min; max	56; 78	55; 76	70; 80	68; 70	63; 74	55; 80
ECOG PS, n (%)						
0	2 (33.3)	4 (100.0)	0	1 (50.0)	4 (66.7)	11 (50.0)
1	4 (66.7)	0	3 (75.0)	1 (50.0)	2 (33.3)	10 (45.5)
2	0	0	1 (25.0)	0	0	1 (4.5)
Child-Pugh scores, n (%)						
A5	3 (50.0)	4 (100.0)	3 (75.0)	2 (66.7)	6 (100.0)	18 (78.3)
A6	0	0	1 (25.0)	1 (33.3)	0	2 (8.7)
B7	1 (16.7)	0	0	0	0	1 (4.3)
Not available	2 (33.3)	0	0	0	0	2 (8.7)
Cancer type, n (%)						
Primary cancer (HCC)	4 (66.7)	3 (75.0)	2 (50.0)	2 (66.7)	4 (66.7)	15 (65.2)
Secondary cancer (liver metastases)	2 (33.3)	1 (25.0)	2 (50.0)	1 (33.3)	2 (33.3)	8 (34.8)
Liver metastases—location of primary cancer, n (%)						
Liver	1 (50.0)	0	0	0	0	1 (12.5)
Lung	1 (50.0)	0	0	1 (100.0)	0	2 (25.0)
Colorectal	0	0	2 (100.0)	0	2 (100.0)	4 (50.0)
Pancreatic	0	1 (100.0)	0	0	0	1 (12.5)
Location (MRI), n (%)						
Segment I	0	0	1 (25.0)	0	0	1 (4.3)
Segment I/I	0	0	1 (25.0)	0	0	1 (4.3)
Segment III	1 (16.7)	0	0	0	0	1 (4.3)
Segment IV	2 (33.3)	3 (75.0)	1 (25.0)	1 (33.3)	0	7 (30.4)

(*continued on next page*)

Table 1 (*Continued*)

	Dose level 1 (10%) (N = 6)	Dose level 2 (15%) (N = 4)	Dose level 3 (22%) (N = 4)	Dose level 4 (33%) (N = 3)	Dose level 5 (42%) (N = 6)	Overall (N = 23)
Segment IV/V	0	0	0	1 (33.3)	0	1 (4.3)
Segment V/VI	1 (16.7)	0	0	0	0	1 (4.3)
Segment VII	1 (16.7)	1 (25.0)	1 (25.0)	0	1 (16.7)	4 (17.4)
Segment VII/VIII	0	0	0	0	1 (16.7)	1 (4.3)
Segment VIII	1 (16.7)	0	0	1 (33.3)	3 (50.0)	5 (21.7)
Segment VIII/VIII	0	0	0	0	1 (16.7)	1 (4.3)
Tumor/lesion volume (centralized reading), mL						
Median	16.8	21.5	9.1	26.2	8.2	15.7
Min; max	3.4; 66.7	3.3; 30.5	4.8; 45.9	19.5; 30.6	2.6; 31.7	2.6; 66.7

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; HCC = hepatocellular carcinoma; MRI = magnetic resonance imaging.

At the end of NBTXR3 injection, hafnium quantification in whole blood ranged from 61.2 ng/mL to 33032.0 ng/mL across all dose levels. At 1 hour post-end of injection, hafnium quantification in whole blood ranged from not detected to 119.0 ng/mL across all dose levels. From 2 hours after NBTXR3 intratumoral injection and onward, hafnium quantification in whole blood was not detected (ie, absence of leakage of NBTXR3 into the blood) (Fig. 1B, C).

All patients had fiducials placed prior to RT. The first 3 patients enrolled in dose level 1 were treated with a reduced dose of 24 Gy in 3 fractions because of OAR constraints. All other patients were treated with 45 Gy in 3 fractions, except for one patient in dose level 5, who received 50 Gy in 5 fractions. The RT course was delivered over a range of 3 to 12 days. Most patients (73.9%) were treated with robotic RT (Cyberknife).

Adverse events

No early DLTs attributed to NBTXR3 or RT were reported. An MTD was not reached.

In the "All Treated" population (N = 23), Table 2 shows TEAEs related to study treatment, and Table E7 shows TEAEs regardless of causality. During the treatment period, in the "All Treated" population, 6 grade ≥3 AEs of any cause were reported in 4 patients (Table E7). None were attributed to NBTXR3, 2 were attributed to the injection procedure (grade 3 abdominal pain), and one was attributed to RT (grade 3 fatigue) (Table 2). Three patients (13.0%) had NBTXR3-related TEAEs, all grade 1 to 2 (abdominal pain, asthenia, and fatigue).

Although 1 patient in dose level 5 had grade 2 abdominal pain during the injection procedure, which led to a NBTXR3 dose reduction (79% of planned volume), there were no NBTXR3-related TEAEs leading to delay of RT or permanent discontinuation of treatment. This patient was included in both the safety and efficacy analyses as the administered volume was within 1% of the 80% threshold.

In the follow-up period, 18 grade ≥3 AEs were observed in 8 patients (regardless of the relationship to study treatment); 2 were treatment-related. One patient in dose level 3 experienced a grade 3 bile duct stenosis attributed to cancer progression, possibly NBTXR3, and possibly RT. One instance of grade 3 anemia was attributed to RT, cancer progression, and liver dysfunction. Three grade 4 posttreatment AEs (hemorrhagic shock, intestinal obstruction, and sepsis) were attributed to progression of disease, and one grade 4 AE (respiratory distress) was attributed to a subsequent liver transplant. Two grade 5 posttreatment AEs were observed, including a cardiac arrest attributed to cancer progression and an episode of

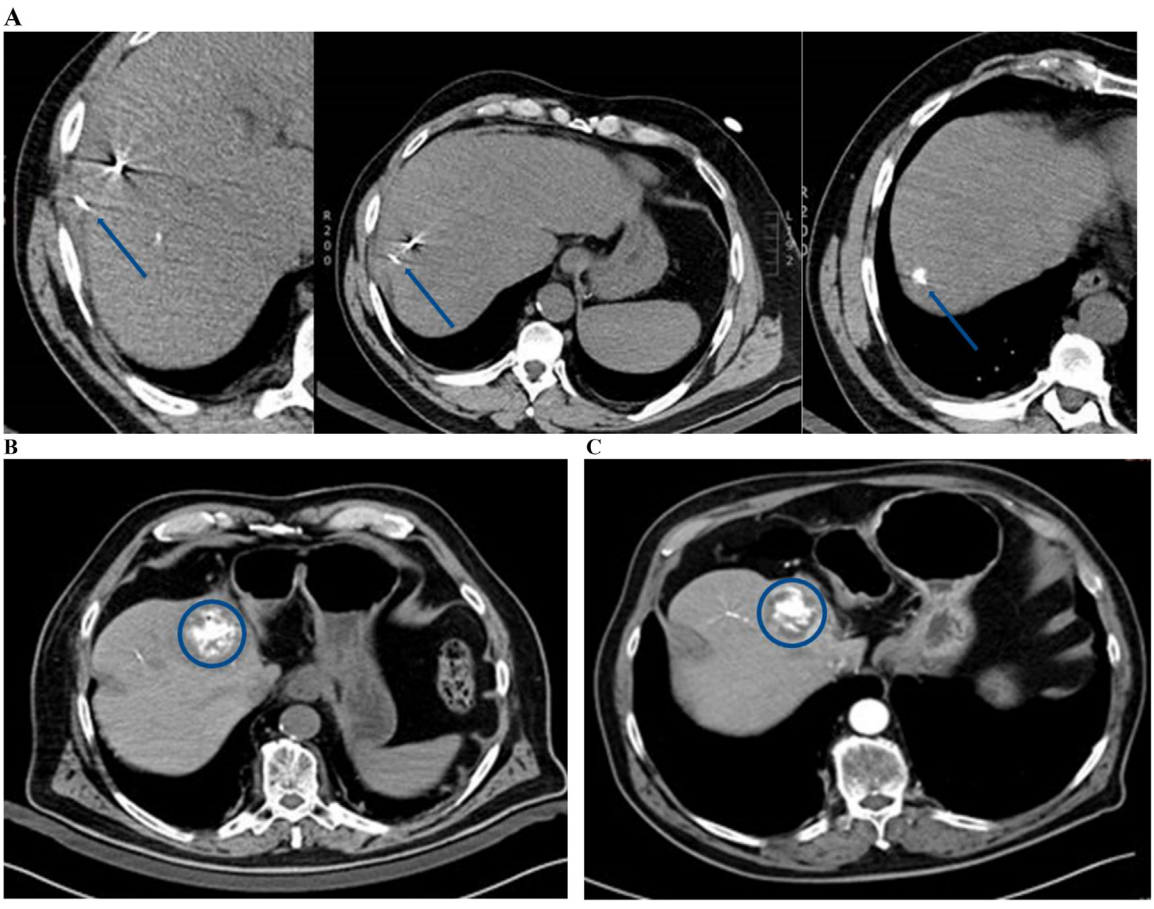


Figure 1 Computed tomography scan showing examples of: (A) intratumoral injection with arrow demonstrating needle position (left and middle panels) and NBTXR3 (right panel), (B) localization of NBTXR3 (dose level 15%) 24 hours after injection, and (C) post−radiation therapy.

hemorrhagic shock attributed to a duodenal ulcer. Of note, the duodenum was in close proximity to the irradiated volume. However, it is important to note that postinjection imaging did not reveal any deposition of NBTXR3 adjacent to the duodenum. Furthermore, all duodenal dose constraints were respected in the treatment plan, and the delivered dose to the duodenal wall remained within established SBRT safety limits. No grade 4 or 5 events were attributed to NBTXR3 or RT.

Among the 3 patients with NBTXR3 noted in the tumor-surrounding tissues, none experienced AEs greater than grade 2.

Twelve patients (52.2%) died while on study, 9 (75.0%) because of disease progression, and 3 (25.0%) because of other reasons (cardiac failure, possible heart attack, hemorrhagic shock). There were no NBTXR3-related deaths.

One patient had a CPS increase of >1 at the end of treatment visit (an increase from A5 to B8) (Table E4). The patient had underlying alcoholic cirrhosis and a known history of portal vein thrombosis. The planned target volume (PTV) was 35 cm^3 for a liver volume of 913 cm^3, with strict compliance with the mean dose constraints delivered to the entire nontumor liver. Shortly after the end of treatment visit, the patient received a diagnosis of G3 ascites associated with portal vein thrombosis. The investigator assessed the event as not related to NBTXR3, injection procedure, or RT. The event was attributed to previously reported underlying liver disease and portal vein thrombosis. No radiation-induced liver disease was observed in any of the dose levels.

Based on the results from the dose-escalation, a NBTXR3 dose (volume) of 42% was selected as the RP2D.

Efficacy

In the evaluable for efficacy population, at 12 weeks after treatment completion, the total number of patients was 20. No injected and irradiated lesion progressive diseases were reported.

For the 12 patients with HCC, the target lesion ORR was 58.3% (7/12) (Table 3). Four patients had a target lesion CR (33.3% [4/12]). The target lesion disease control rate (DCR: CR + PR + stable disease [SD]) was 83.3% (10/12).

Table 2 Number of patients with TEAEs related to study treatment in the "All Treated" population

	Dose level 1 (10%) (N = 6)		Dose level 2 (15%) (N = 4)		Dose level 3 (22%) (N = 4)		Dose level 4 (33%) (N = 3)		Dose level 5 (42%) (N = 6)		Overall (N = 23)	
Preferred term	**Grade 1-2**	**Grade 3**	**Grade 1-2**	**Grade 3**	**Grade 1-2**	**Grade 3**	**Grade 1-2**	**Grade 3**	**Grade 1-2**	**Grade 3**	**Grade 1-2**	**Grade 3**
NBTXR3-related TEAEs:												
All TEAEs	0	0	0	0	0	0	1	0	2	0	3	0
Abdominal pain	0	0	0	0	0	0	0	0	1	0	1	0
Asthenia	0	0	0	0	0	0	0	0	1	0	1	0
Fatigue	0	0	0	0	0	0	1	0	0	0	1	0
Injection procedure—related TEAEs												
All TEAEs	1	0	0	2	1	0	0	0	3	0	5	2
Abdominal pain	0	0	0	2	0	0	0	0	0	0	0	2
Injection site pain	0	0	0	0	0	0	0	0	1	0	1	0
Malaise	1	0	0	0	0	0	0	0	0	0	1	0
Transaminase increase	0	0	0	0	0	0	0	0	1	0	1	0
Pleural effusion	0	0	0	0	1	0	0	0	0	0	1	0
Pneumothorax	0	0	0	0	0	0	0	0	1	0	1	0
RT-related TEAEs												
All TEAEs	2	0	3	1	2	0	0	0	3	0	10	1
Abdominal distension	0	0	1	0	0	0	0	0	0	0	1	0
Abdominal pain	0	0	1	0	0	0	0	0	2	0	3	0
Abdominal pain upper	0	0	0	0	0	0	0	0	1	0	1	0
Diarrhea	0	0	0	0	0	0	0	0	1	0	1	0
Nausea	1	0	1	0	0	0	0	0	2	0	4	0
Vomiting	1	0	0	0	0	0	0	0	0	0	1	0
Asthenia	0	0	1	0	1	0	0	0	0	0	2	0
Fatigue	0	0	1	1	0	0	0	0	2	0	3	1
Portal vein thrombosis	0	0	0	0	1	0	0	0	0	0	1	0
Radiation skin injury	1	0	0	0	0	0	0	0	0	0	1	0
Decreased appetite	0	0	0	0	0	0	0	0	1	0	1	0

Abbreviations: RT = radiation therapy; TEAE = treatment-emergent adverse event.
Patients could have more than one TEAE.

Table 3 Target lesion response evaluation as per mRECIST for HCC at 12 weeks postradiation in the evaluable* for efficacy population

Response evaluation in target lesions (EOT—12 weeks postradiation)	Dose level 1 (10%)	Dose level 2 (15%)	Dose level 3 (22%)	Dose level 4 (33%)	Dose level 5 (42%)	All dose levels
As per mRECIST criteria for HCC	N = 3	N = 2	N = 1	N = 2	N = 4	N = 12
CR	1 (33.3%)	2 (100.0%)	0	1 (50.0%)	0	4 (33.3%)
PR	1 (33.3%)	0	0	0	2 (50.0%)	3 (25.0%)
SD	1 (33.3%)	0	1 (100.0%)	0	1 (25.0%)	3 (25.0%)
PD	0	0	0	0	0	0
NE†	0	0	0	1 (50.0%)	1 (25.0%)	2 (16.7%)
Objective response (CR + PR)	2 (66.7%)	2 (100.0%)	0	1 (50.0%)	2 (50.0%)	7 (58.3%)
Disease control rate (CR + PR + SD)	3 (100.0%)	2 (100.0%)	1 (100.0%)	1 (50.0%)	3 (75.0%)	10 (83.3%)

Abbreviations: CR = complete response; EOT = end of treatment; HCC = hepatocellular carcinoma; NE = not evaluable; PD = progressive disease; PR = partial response; mRECIST = modified Response Evaluation Criteria in Solid Tumors; SD = stable disease.

*Evaluable for efficacy population included patients who received at least 80% of the planned dose of NBTXR3, at least 15 Gy of stereotactic body radiation therapy, and completed 12-week post–radiation therapy imaging.

†NE indicates that the patient completed 12-week post–radiation therapy imaging, but the target lesion was not evaluable.

For the 8 patients with liver metastases, the target lesion ORR was 50.0% (4/8) (Table 4). No patient showed a CR (0%). The target lesion DCR was 87.5% (7/8).

In the "All Treated" population (ie, including those with no postbaseline imaging and who received less than 80% of the planned dose of NBTXR3), response evaluation in the injected target lesion is shown for HCC and liver metastases in Fig. 2A, B, respectively. The ORR was 47.8% (11/23) and the DCR was 78.3% (18/23) for HCC and liver metastases (Table E8). At study closure, 47.8% (11/23) of patients were alive.

For baseline tumor-specific markers in the "All Treated" population, 8 of 23 patients (7 HCC, 1 liver metastases) had high levels of alpha-fetoprotein (AFP), and 4 of 23 patients (3 HCC, 1 liver metastases) had high levels of carcinoembryonic antigen (CEA). Of patients with a high baseline AFP, 4 (50.0%) had AFP normalization at the first posttreatment measurement. One patient (25.0%) with a high baseline CEA level experienced normalization at the first posttreatment measurement.

Discussion

This study demonstrates that the radioenhancer NBTXR3, followed by RT, was safe and well-tolerated at all tested dose levels in patients with HCC or liver metastases. To our knowledge, NBTXR3-103 is the first study using an intratumoral radioenhancer in this setting. The MTD was not reached as no early DLTs related to NBTXR3 or RT were observed. The RP2D was determined to be 42% of GTV.

The absence of DLTs and the manageable safety profile indicate that NBTXR3 can safely be administered with RT in patients with HCC or liver metastases. The overall grade ≥3 toxicity rate across all time periods was 13.0% (HCC 13.3%, liver metastases 12.5%), attributed to RT or NBTXR3, and is comparable with historical liver SBRT safety data.[8,10,13] Grade ≥3 toxicities were experienced by 42% to 47% of patients treated with SBRT in RTOG 1112 (HCC),[23] and 17.4% of patients in RTOG 0438 (liver metastases).[24] Bile duct stenosis, the only grade 3 toxicity related to NBTXR3 in this study (posttreatment), has been documented as a toxicity from RT alone.[25-27] Our findings support those observed in the Act.In.Sarc phase 2/3 in soft tissue sarcoma comparing NBTXR3 + RT versus RT alone, which showed that NBTXR3 did not increase the incidence of RT-related AEs.[20]

SBRT has arisen as an effective treatment option for patients who cannot undergo surgery, providing excellent local control when ablative doses are delivered. However, ablative doses cannot always be delivered safely in the setting of large tumors, underlying liver dysfunction, or close tumor proximity to normal structures.[8,10,13,14] Multiple risk-mitigation strategies are used in these situations, including proton therapy, MRI guidance, heterogeneous

Table 4 Target lesions response evaluation as per RECIST 1.1 for liver metastases at 12 weeks postradiation in the evaluable* for efficacy population

Response evaluation in target lesions (EOT—12 weeks postradiation)	Dose level 1 (10%)	Dose level 2 (15%)	Dose level 3 (22%)	Dose level 4 (33%)	Dose level 5 (42%)	All dose levels
As per RECIST 1.1 criteria for liver metastases	N = 2	N = 1	N = 2	N = 1	N = 2	N = 8
CR	0	0	0	0	0	0
PR	1 (50.0%)	1 (100.0%)	0	1 (100.0%)	1 (50.0%)	4 (50.0%)
SD	1 (50.0%)	0	1 (50.0%)	0	1 (50.0%)	3 (37.5%)
PD	0	0	0	0	0	0
NE†	0	0	1 (50.0%)	0	0	1 (12.5%)
Objective response (CR + PR)	1 (50.0%)	1 (100.0%)	0	1 (100.0%)	1 (50.0%)	4 (50.0%)
Disease control rate (CR + PR + SD)	2 (100.0%)	1 (100.0%)	1 (50.0%)	1 (100.0%)	2 (100.0%)	7 (87.5%)

Abbreviations: CR = complete response; EOT = end of treatment; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

*Evaluable for efficacy population included patients who received at least 80% of the planned dose of NBTXR3, at least 15 Gy of stereotactic body radiation therapy, and completed 12-week post–radiation therapy imaging.

†NE indicates that the patient completed 12-week post–radiation therapy imaging, but the target lesion was not evaluable.

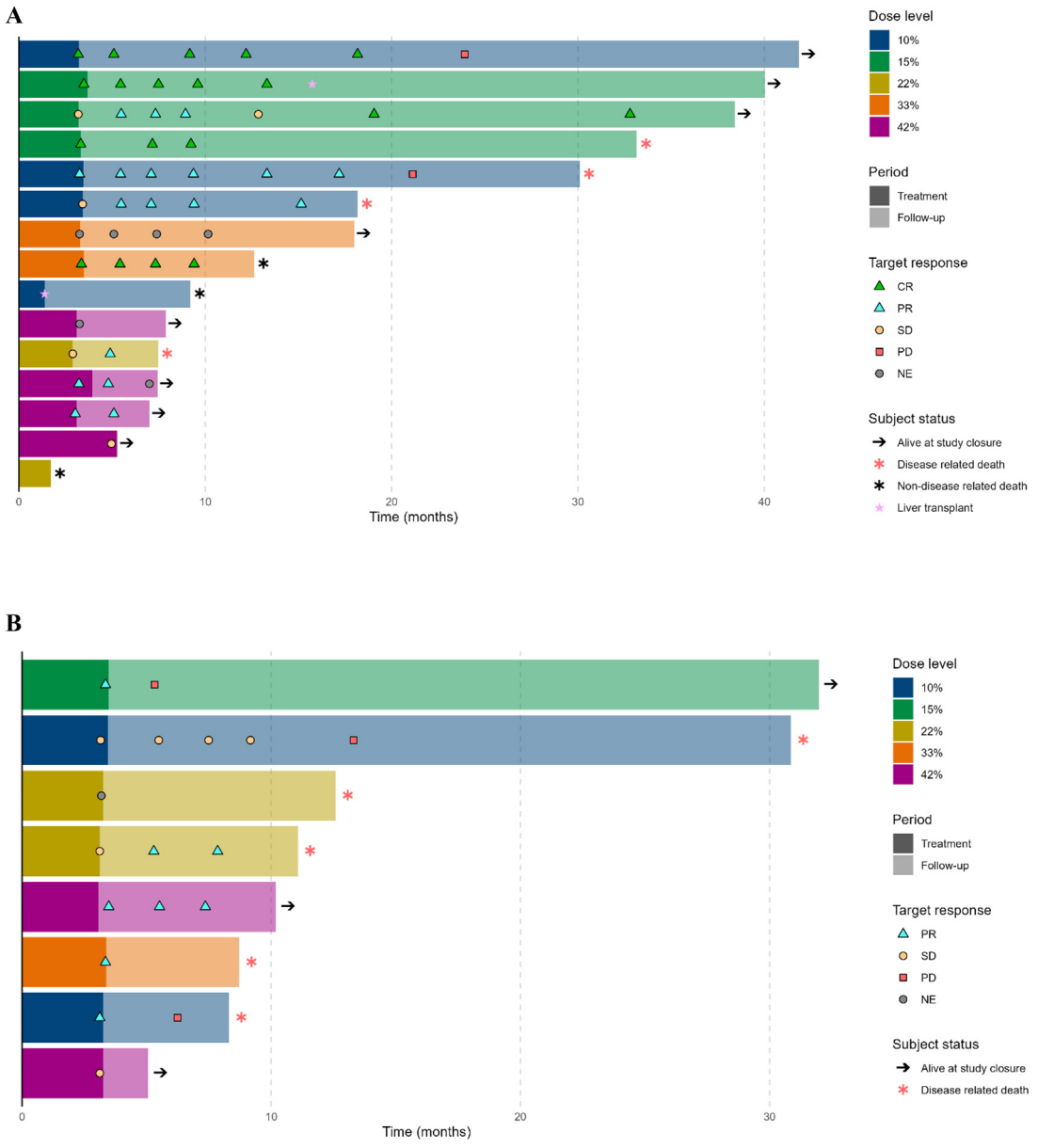
dose distribution, prolonged fractionation, and dose reduction.[28,29]

NBTXR3 is an innovative therapeutic option that has been shown to enhance RT without increasing toxicity.[20] Because of its one-time intratumoral delivery, NBTXR3 provides multiple potential advantages. With conventional techniques, large tumors or significant OAR exposure may require protracted courses or less biologically effective doses of RT. In the presence of NBTXR3, similar effects could theoretically be achieved when compared to a higher RT dose. This is attractive because out-of-field progression within the liver is the most common site of SBRT failure in HCC patients; using lower total doses for each SBRT course might make more room for future SBRT courses in nearby locations.[30,31]

An additional benefit of NBTXR3 is its radiopaque property on CT but not MRI. NBTXR3 can be visualized on the preradiation CT simulation scan and daily cone-beam computed tomography (CBCT). This allows investigators to confirm the proper placement of NBTXR3. In this study, as response was assessed by MRI, for which it is not radiopaque, NBTXR3 did not impact response assessment on MRI per RECIST.

Although not the primary focus of this phase 1 study, the available efficacy data are comparable to similar studies. A 33.3% CR at 3 months in the evaluable HCC population is similar to Wu et al,[31] and Yoon et al,[30] who reported 25.0% and 15.5% CR at 3 months, respectively, following SBRT in patients with HCC. Future phase 2 studies will further evaluate the efficacy of NBTXR3 followed by RT at clinically meaningful timepoints with or without immune checkpoint inhibition, which are now part of the standard of care.

Notably, although NBTXR3 enhances local radiation dose deposition within tumors and has shown promising early safety and efficacy results in our study (ORR in the target lesion of 58% and DCR of 83%), its mechanism differs substantially from multimodality approaches such as combining TACE with SBRT. For example, Chiang et al[32] reported in a retrospective evaluation of 72 patients with Barcelona Clinic Liver Cancer system stage B to C HCC (who were treated with a single dose of TACE followed by SBRT) a high ORR of 68%, but with SBRT-related grade ≥3 gastrointestinal toxicity in 2.8% of patients and treatment-related death in 1.4% of patients. Although NBTXR3 does not aim to compete with other locoregional therapies such as TACE, it could serve as a complementary approach in selected patients. Unlike lipiodol-based TACE,[33] which combines a therapeutic embolic effect with contrast enhancement but may be contraindicated in cases of portal vein thrombosis, advanced liver dysfunction, or poor performance status, NBTXR3 can be delivered independently of arterial patency and without compromising hepatic perfusion. Similarly, although combining TACE with SBRT has shown synergistic potential in certain settings, TACE-related toxicities (including postembolization syndrome, ischemic liver



CR, complete response; NE, not evaluable; PR, partial response; SD, stable disease; PD, progressive disease

Figure 2 Swimmer's plot of patient follow-up of response evaluation in target lesions, by dose level, in the "All Treated" population for: (A) hepatocellular carcinoma, and (B) liver metastases.
Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

injury, and risk of biliary complications) limit its applicability in frail patients or those with borderline liver reserve. In this context, NBTXR3 with SBRT offers an alternative means of enhancing local dose deposition that may be particularly valuable when other interventional techniques are contraindicated or impractical.

MRI-guided SBRT is evolving and has demonstrated feasibility and safety. The main limitation to delivering optimal doses of RT in liver tumors is tumor size and proximity to OARs. MRI-guided SBRT has been shown, in selected patients, to deliver up to 80 Gy in 5 fractions.[34] However, not all patients present with tumor sizes and locations ideally situated within the liver to achieve these dose levels. The combination of NBTXR3 with MRI-guided SBRT may offer an opportunity to optimize RT doses in complex cases.

Conclusions

NBTXR3, followed by RT, showed encouraging safety and efficacy results in patients with advanced HCC or liver metastases. There were no early DLTs, and the RP2D is 42% of GTV. Future studies will address NBTXR3's ability to improve the risk/benefit ratio of liver RT.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2025.101937.

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