



Case Report

NBTXR3, a first-in-class radioenhancer for pancreatic ductal adenocarcinoma: Report of first patient experience

Alexander F. Bagley, Ethan B. Ludmir, Anirban Maitra, Bruce D. Minsky, Grace Li Smith, Prajnan Das, Albert C. Koong, Emma B. Holliday, Cullen M. Taniguchi, Matthew H.G. Katz, Eric P. Tamm, Robert A. Wolff, Michael J. Overman, Shivani Patel, Michael P. Kim, Ching-Wei D. Tzeng, Naruhiko Ikoma, Manoop S. Bhutani^{*}, Eugene J. Koay^{*}

The University of Texas MD Anderson Cancer Center, Houston, TX, USA



A B S T R A C T

Background and purpose: Pancreatic ductal adenocarcinoma (PDAC) remains one of the leading causes of cancer-related deaths in the world. For patients with PDAC who are not eligible for surgery, radiation therapy improves local disease control, yet safely delivering therapeutic doses of radiation remains challenging due to off-target toxicities in surrounding normal tissues. NBTXR3, a novel radioenhancer composed of functionalized hafnium oxide crystalline nanoparticles, has recently shown clinical activity in soft tissue sarcoma, hepatocellular carcinoma, head and neck squamous cell carcinoma, and advanced solid malignancies with lung or liver metastases. Here we report the first patient with pancreatic cancer treated with NBTXR3.

Materials and methods: A 66-year-old male with unresectable locally advanced PDAC was enrolled on our clinical trial to receive NBTXR3 activated by radiation therapy. Local endoscopic delivery of NBTXR3 was followed by intensity modulated radiation therapy (IMRT). Follow-up assessment consisted of physical examination, laboratory studies including CA19-9, and CT of the chest, abdomen, and pelvis.

Results: The patient received NBTXR3 by local endoscopic delivery without any acute adverse events. Radiation treatment consisted of 45 Gy in 15 daily fractions using IMRT. The patient began radiation twelve days after NBTXR3 injection. Daily CT-on-rails imaging demonstrated retention of NBTXR3 within the tumor for the duration of treatment. At initial follow-up evaluation, the lesion remained radiographically stable and the patient did not demonstrate treatment-related toxicity.

Conclusion: This report demonstrates initial feasibility of local endoscopic delivery of NBTXR3 activated by radiation therapy for patients with pancreatic cancer who are not eligible for surgery.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains a major health-care challenge, as the third leading cause of cancer-related deaths in the developed world [1]. Surgery may be curative for patients presenting with early-stage disease, but 30% of all PDAC patients are diagnosed with locally-advanced (LAPC) or borderline resectable (BRPC) disease (without distant metastatic disease) and are not eligible for upfront surgery. These patients benefit from multimodality therapy including chemotherapy and radiation therapy to improve local disease control [2,3]. A key limitation of radiation therapy for PDAC is the potential for off-target toxicities in surrounding normal tissues. Systemic radiosensitizers make both tumors and normal tissues more radiosensitive, thus increasing toxicity. In contrast, NBTXR3, a novel radioenhancer composed of functionalized hafnium oxide crystalline nanoparticles directly injected into tumors, enhances the absorption of ionizing

radiation, resulting in increased tumor cell death without adding toxicity to adjacent normal tissues [4–6]. This approach has demonstrated clinical activity in soft tissue sarcoma, and is currently being investigated across multiple tumor types [7,8]. Here, we report the first patient treated with NBTXR3 activated by radiation therapy for PDAC, and reiterate the importance of multidisciplinary collaboration in advancing novel therapeutic avenues for this lethal disease.

The patient is a 66-year-old male who developed epigastric discomfort, dyspepsia, and an 8-pound weight loss in the preceding 10 months. He did not have a history of cancer or smoking and consumed 2–3 drinks containing alcohol per week. He was treated for *H. pylori* infection by his local physician, but his symptoms persisted prompting further evaluation. Imaging studies including an MRI and CT of the abdomen and pelvis with and without contrast demonstrated a 3.1 × 2.6 cm hypodense pancreatic neck mass at the junction of the pancreatic head and pancreatic body with infiltration of the celiac trunk, origin of

^{*} Corresponding authors at: 1515 Holcombe Blvd Unit 1422, Houston, TX 77030, USA (E.J. Koay); 1515 Holcombe Blvd Unit 1466, Houston, TX 77030, USA (M.S. Bhutani).

E-mail addresses: manoop.bhutani@mdanderson.org (M.S. Bhutani), ekoay@mdanderson.org (E.J. Koay).

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the splenic artery and common hepatic artery, with encasement and occlusion of the main portal vein. (Fig. 1a) He underwent an endoscopic ultrasound (EUS) and fine needle aspiration (FNA) biopsy confirming adenocarcinoma. Serum CA19-9 was 1,921 U/mL. Following review by our multidisciplinary team, the patient was staged as having unresectable LAPC and received FOLFIRINOX (5-fluorouracil, oxaliplatin, irinotecan, and leucovorin) chemotherapy. After 8 cycles of chemotherapy, CT of the chest, abdomen, and pelvis with contrast demonstrated a slight interval decrease in the size of the pancreatic mass (2.9×2.5 cm), and CA19-9 decreased to 170.3 U/mL. He received 3 additional cycles of chemotherapy, and imaging revealed a stable pancreatic mass without evidence of metastatic disease. In the absence of disease progression, the patient was approached to participate in our study (ClinicalTrials.gov NCT04484909) and receive NBTXR3 activated by radiation therapy.

At initial evaluation, the patient had recovered well from his chemotherapy and his ECOG performance status was 0. He had developed a small pulmonary embolus that was treated with enoxaparin. He reported bilateral peripheral neuropathy in his fingers and toes, and denied abdominal pain, nausea, vomiting, or shortness of breath. He had not received prior radiation therapy and had no history of gastric or duodenal ulcer disease. On physical examination, the patient was alert, had normal respiratory effort, and his abdomen was soft and non-tender to palpation. Notable laboratory values included hemoglobin 11.6 g/dL, platelets 138 K/uL, absolute neutrophil count 2.68 K/uL, creatinine 0.78 mg/dL, ALT 66 U/L, AST 56 U/L, total bilirubin 0.3 mg/dL, and CA19-9 80.8 U/mL.

Following trial enrollment on an IRB approved protocol and informed consent, pre-treatment planning meetings with the radiation oncologist, radiologist, and gastroenterologist were conducted. We used the most recent pancreatic protocol CT scan from diagnostic radiology to estimate the GTV volume for the dose calculation of NBTXR3. The gross tumor volume (GTV) was measured to be 15.7 mL. Review of available imaging led to consensus agreement on a suitable location for NBTXR3 injection. (Fig. 1b) The patient received premedication with prednisone 30 mg at 12 h and 2 h prior to NBTXR3 administration and levofloxacin 500 mg during the procedure. EUS was performed under general anesthesia. A 3.9×2.8 cm hypochoic oval mass was identified in the pancreatic neck, and FNA and core biopsies were obtained using a transgastric approach. A 22-gauge Cook needle was then inserted into the mass under color Doppler guidance to identify an avascular angle of approach, and 5.2 mL of NBTXR3 (33% of GTV) was slowly injected into the periphery and center of the tumor with three passes over >10 min, taking care to avoid blood vessels, necrotic regions, and areas <5 mm from the tumor margin. (Fig. 2; Supp. Fig. 1) Negative suction was

applied on the needle for 20 s prior to withdrawal. The patient tolerated the procedure well without any acute complications or adverse events, and he was discharged home in stable condition with prescription for levofloxacin 500 mg PO for two days following the procedure.

The patient underwent radiation simulation two days after NBTXR3 was injected. Respiratory-correlated breath-hold CT simulation was performed with the patient supine in a custom upper body cradle and arms positioned above his head. He was NPO for 3 h prior to simulation. Images were acquired with and without intravenous contrast, and acquisition was timed similar to a pancreatic protocol CT scan. Six breath-hold CT scans were obtained. The prescribed dose of radiation to the tumor was 45 Gy in 15 fractions, with surrounding regional lymph nodes treated to 37.5 Gy in 15 fractions using a simultaneous integrated boost technique with IMRT (6 MV photons). The CTV was defined as the GTV, celiac and SMA (from the origin of the aorta) with 1 cm margin. CT-on-rails was used for daily image guidance. All dose constraints related to target coverage (mPTV45: V45Gy > 95%; PTV37.5: V37.5 Gy > 95%) and organs at risk (Stomach: Dmax < 45 Gy; Duodenum: Dmax < 45 Gy; Small bowel: Dmax < 40 Gy; Large bowel: Dmax < 50 Gy; Heart: Dmax < 55 Gy, V40Gy < 10%, V50Gy < 1 cm³; Kidneys: V20Gy < 33%; Liver-GTV: Mean < 24 Gy; at least 700 cm³ spared below 24 Gy; Spinal cord: Dmax < 30 Gy; Spleen: Mean < 6 Gy; Chest wall: V40Gy < 150 cm³) were satisfied. (Fig. 3a-c) The proposed treatment plan was reviewed and approved at the weekly Radiation Oncology Gastrointestinal Section planning conference.

The patient received his first dose of radiation twelve days after NBTXR3 injection. Radiopaque NBTXR3 was well visualized using daily CT-on-rails and was retained within the GTV for the duration of therapy with negligible intratumoral redistribution. (Fig. 3d) We did not observe NBTXR3 redistributing or accumulating in surrounding non-malignant tissues. Radiation was administered without concurrent chemotherapy. The patient was evaluated weekly during his radiation therapy. Overall, his treatment was well tolerated. He developed Grade 1 fatigue (CTCAE Version 5) and one episode of vomiting after consuming a large meal shortly after completing his sixth fraction. The skin within the radiation field showed no evidence of erythema or desquamation. He denied abdominal pain, nausea, dysphagia, diarrhea, hematemesis, hematochezia, melena, fever, or respiratory symptoms.

At his initial follow-up visit four weeks after completing radiation, the patient reported ongoing mild fatigue and peripheral neuropathy, but he continued to exercise regularly, felt his appetite had improved, and he otherwise did not demonstrate any significant radiation-related toxicities. CT of the chest, abdomen, and pelvis with and without contrast showed a stable pancreatic neck mass (2.7×2.6 cm) by RECIST 1.1 criteria and no evidence of metastatic disease; however, decreased

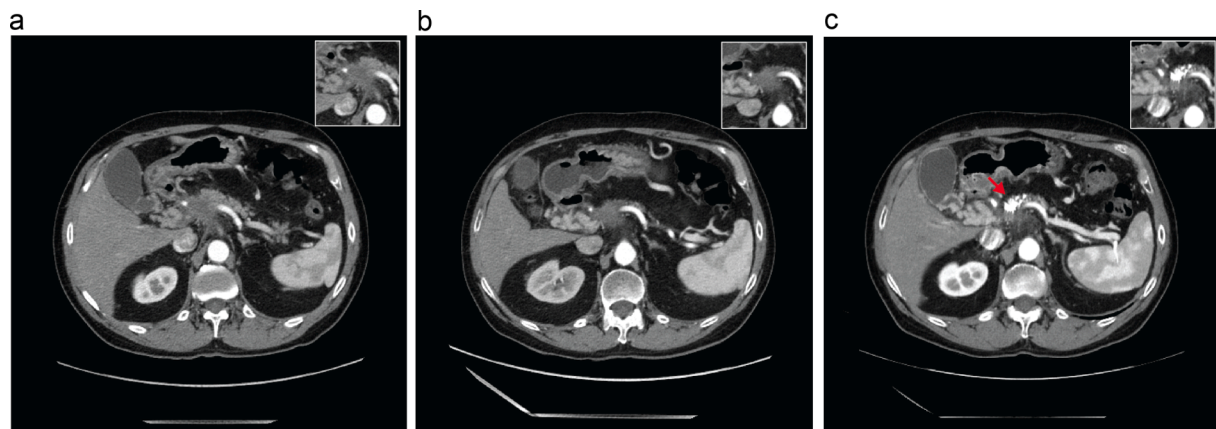


Fig. 1. (a) Initial staging CT of the chest, abdomen, and pelvis demonstrating an infiltrating hypodense mass in the pancreatic neck, with involvement of the celiac trunk and main portal vein. (b) Restaging CT scan after induction chemotherapy demonstrating stable disease in the pancreas. The portion of tumor shown here was determined to be a suitable area for NBTXR3 injection. (c) Restaging CT scan approximately 12 weeks after completing radiation shows a stable pancreatic mass with retained radiopaque NBTXR3. Insets in (a-c) highlight primary pancreatic tumor morphology.

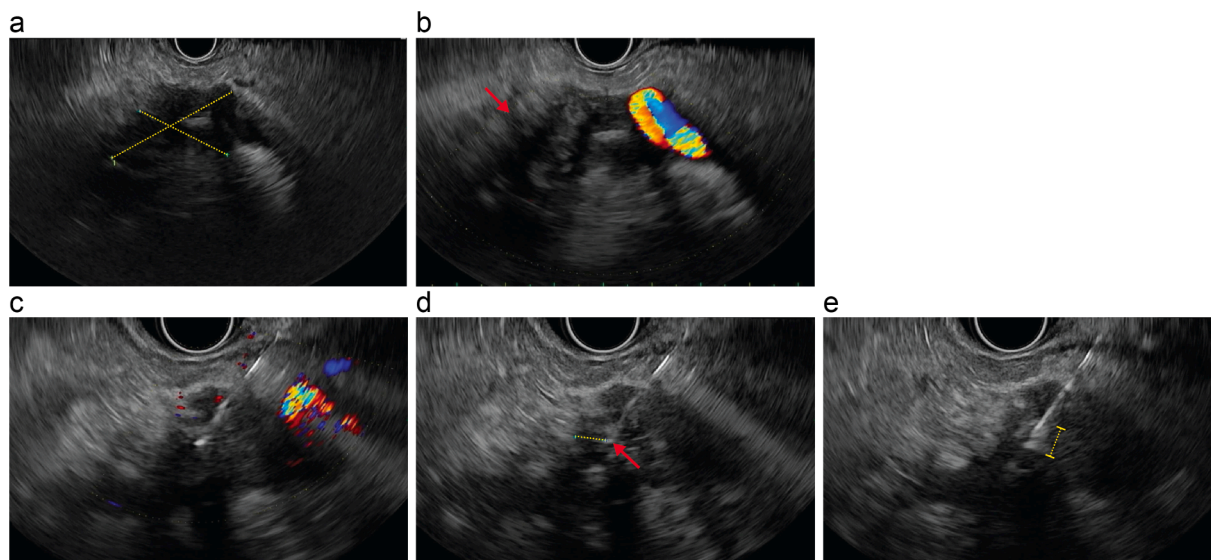


Fig. 2. EUS-guided intratumoral injection of NBTXR3. (a) Hypoechoic pancreatic mass measuring 3.9 cm × 2.8 cm in maximal cross-sectional diameter. Caliper dimensions shown as dashed yellow lines. (b) Mass demonstrated an irregular margin (red arrow) and encasement of the splenic artery and celiac axis. (c) An avascular plane was identified using color Doppler guidance, and needle was advanced into the tumor avoiding vascular and necrotic regions. (d) Tip of needle (red arrow) positioned at least 5 mm (dashed yellow line) from tumor margin. (e) Delivery of NBTXR3 by slow manual injection to tumor periphery and center visualized as an echogenic cloud surrounding the needle (dashed yellow line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

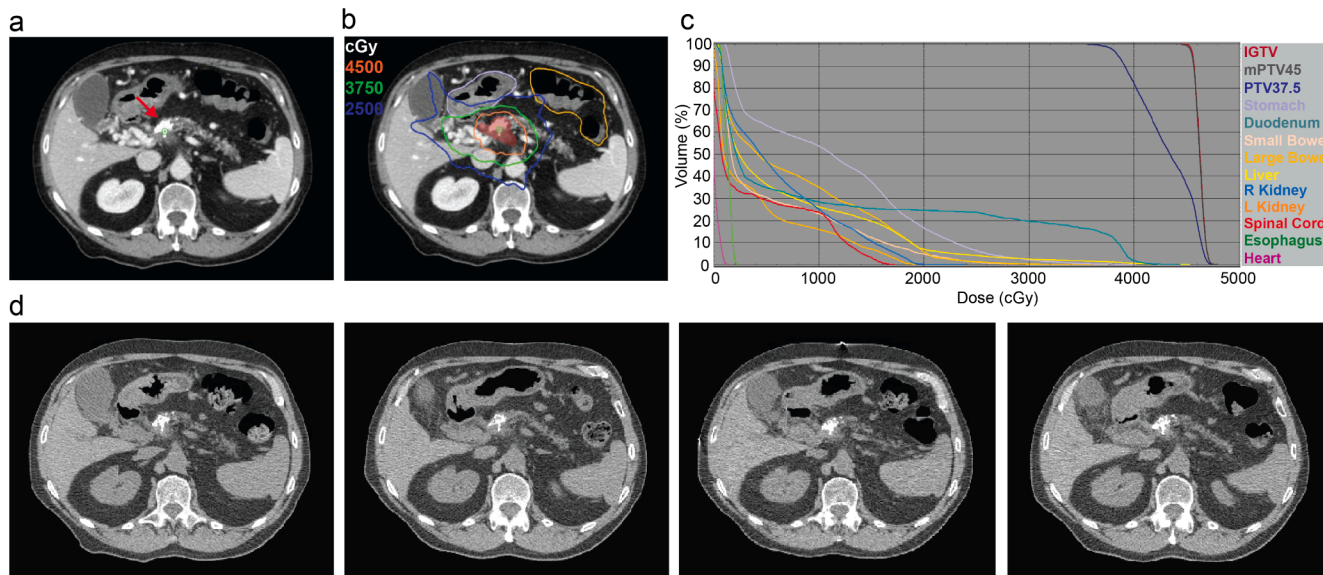


Fig. 3. Radiation planning and delivery. (a) Radiopaque NBTXR3 visualized on simulation CT image (red arrow). (b) Representative target volumes, organs at risk, and isodose lines (IGTV: Maroon shaded; Stomach: Purple; Large bowel: Yellow-orange; 45 Gy IDL: Orange; 37.5 Gy IDL: Green; 25 Gy IDL: Blue). (c) Cumulative dose-volume histogram. (d) CT-on-rails images from (left to right) fractions 1, 5, 10, and 15 (Days 12, 16, 23, and 30 post-NBTXR3 injection) demonstrate intratumoral retention of NBTXR3 for duration of treatment course. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

enhancement and regression along the blood vessels was suggestive of an early therapeutic response. CA19-9 was 93.2 U/mL, slightly elevated compared to pre-radiation therapy levels (74.9 U/mL). Approximately twelve weeks after completing radiation, the patient continued to report mild fatigue, mild mid-abdominal pain, and peripheral neuropathy, but he did not demonstrate any treatment-related toxicities. The pancreatic lesion remained stable radiographically (Fig. 1c), and CA19-9 decreased to 59.0 U/mL.

This report describes the first patient treated with NBTXR3 activated by radiation therapy for pancreatic adenocarcinoma. Our institution is

conducting a Phase I study to evaluate the safety, feasibility, and recommended Phase 2 dose for NBTXR3 in patients with LAPC or BRPC (ClinicalTrials.gov NCT04484909). We chose a hypofractionated regimen based on previously published data for locally advanced pancreatic cancer demonstrating that such regimens are safe, effective, and can be completed in a shorter time frame than conventional fractionation [9,10]. While the regimen we used has a similar biologically effective dose to conventional fractionation (50.4–54 Gy at 1.8 Gy per fraction), we did not consider higher doses such as 67.5 Gy in 15 fractions in this study due to the known amplification of local radiation dose

by NBTXR3. We believe these approaches may be feasible with SBRT, however the safety of this approach will need to be tested in a rigorous way. Planned correlative studies will evaluate biomarkers of response to treatment with NBTXR3 and radiation, including characterization of circulating tumor DNA and exosomes; quantification of immune activation (T- and B-cells, peripheral blood mononuclear cells, cytokines, T-cell receptor sequencing and repertoire); analysis of the tumor micro-environment using multiplex immunohistochemistry and hypoxia staining; and radiomics measurements of PDAC tumor morphology, including delta PDAC which measures the change in sharpness of the tumor/parenchymal interface after treatment and is associated with progression-free survival and overall survival [11,12]. Radiation enhancement using NBTXR3 relies on a physical mechanism of activation by ionizing radiation and therefore may have broad applicability across tumor types. The feasibility of local endoscopic delivery of NBTXR3 may provide a general framework for delivering other local therapeutics including injectable toll-like receptor agonists, STING agonists, and radioactive agents such as 32P-OncoSil to deeper visceral tumors [13]. Our initial experience illustrates the critical importance of multidisciplinary evaluation and management when treating PDAC or other tumors with NBTXR3. With highly integrated care provided by radiation oncologists, gastroenterologists, radiologists, clinical research nurses and staff, and other specialists, we believe that selected patients with PDAC can safely complete EUS-guided intratumoral NBTXR3 injection and radiation therapy. Future studies are necessary to evaluate the efficacy of NBTXR3 in this setting. This report presents initial feasibility for NBTXR3 activated by radiation therapy as a potential treatment for patients with PDAC who are not eligible for surgery.

Patient consent statement

All patients involved in this research were enrolled on an institutional review board (IRB)-approved protocol and informed consent was obtained.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: A. M. reports royalties for license from Cosmos Wisdom Biotechnology Ltd. and license for patent from Thrive Earlier Detection, all outside the submitted work. B.D.M. has served as the Co-chair of the Gastrointestinal Steering Committee at the National Cancer Institute (NCI) and has received grants from National Institutes of Health (NIH) and NCI (NIH/NCI 2U19CA021239-35, 1U10CA180858-01), all outside the submitted work. G.L.S. has received grants from NCI, Radiation Oncology Institute, and MD Anderson internal funding, all outside the submitted work. P.D. reports consulting fees from Leidos Biomedical Research, payment for

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