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Feasibility and safety of endoscopic ultrasound-guided diffusing alpha emitter radiation therapy for advanced pancreatic cancer: Preliminary data

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Conflict of Interest: Corey S. Miller is a consultant for Alpha Tau Medical and Boston Scientific. Anand Sahai is a consultant for Boston Scientific. All other authors have no relevant conflicts.

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Trial registration: NCT04002479, ClinicalTrials.gov (http://www.clinicaltrials.gov/), Prospective

Abstract:
Background and study aims: Pancreatic cancer is a devastating disease with limited locoregional treatment options. Diffusing alpha-emitter radiation therapy (Alpha DaRT), a novel cancer treatment using alpha-particle interstitial radiotherapy, may help address this challenge. The aim of this study was to evaluate the feasibility and safety of endoscopic ultrasound (EUS)-guided Alpha DaRT for advanced pancreatic cancer.
Patients and methods: Patients with inoperable locally advanced or metastatic pancreatic adenocarcinoma were treated with EUS-guided Alpha DaRT insertion. The Alpha DaRT sources were delivered into pancreatic tumors using a standard EUS needle with a novel proprietary applicator. Adverse events (AEs) were assessed based on the Common Terminology Criteria for Adverse Events version 5.0. Tumor response was evaluated by imaging 4 to 6 weeks post treatment.
Results: The first five patients were treated between March and September 2023. The procedure was technically successful in all cases, with Alpha DaRT sources inserted into the target tumor. Estimated gross tumor volume coverage ranged from 8% to 44%. Fourteen AEs were reported among three patients. Four were serious AEs, none of which was associated with the treatment, but rather, with disease progression or medical assistance in dying. Only two AEs (mild) were deemed possibly related to the study device. At the 35-day visit, two patients had progressive disease and three had stable disease, with one of the latter showing partial response 2 months post procedure.
Conclusions: Preliminary results from this first-in-human trial indicate that EUS-guided Alpha DaRT treatment for unresectable pancreatic cancer is feasible and safe, with no device-associated serious AEs. Further investigation of this promising novel modality is underway.

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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related mortality, despite accounting for only 3% of new cancers diagnosed in the United States in 2021 [1]. It is associated with an extremely poor prognosis, reflected by a median survival of 5–8 months and a 5-year survival probability of less than 5% when all stages are combined [2-4]. Only 20% are eligible for curative surgical resection and, even of these, up to 85% recur [5]. Locoregional disease burden often causes obstruction of the gastric outlet and bile duct, as well as tumor-related pain, and is a major cause of morbidity and mortality.

Radiation therapy, which plays a pivotal role in treating many cancers, has demonstrated uncertain efficacy in both the neoadjuvant and locally-advanced settings [6]. Furthermore, the ablative dose prescribed to the target tumor is limited by the dose tolerance and tight dose volume constraints of nearby radiosensitive organs, risking normal tissue toxicity [7]. More encouraging results have been observed in the setting of ablative stereotactic body radiation therapy (SBRT) techniques, allowing for higher doses and more precise delivery of treatment. Studies suggest that SBRT is well tolerated and associated with improved local tumor control compared to conventional radiotherapy, presumably related to higher dose levels overcoming the inherent radio resistance of pancreatic tumor clones [8].

In recent years, endoscopic ultrasound (EUS) has become a key modality for accessing the pancreas and is considered the gold standard for diagnosing pancreatic cancer [9]; yet standard clinical practice has not adopted EUS-directed targeted therapies to treat pancreatic cancer. A few pilot studies have investigated EUS-guided brachytherapy for pancreatic cancer using iodine-125 seeds [10-12]. Although they reported promising feasibility and safety data over a decade ago, no further studies demonstrating efficacy have been reported. The absence of an accepted standard of care locoregional treatment for pancreas cancer represents an important unmet need.

Diffusing alpha-emitters Radiation Therapy (Alpha DaRT, Alpha Tau Medical, Jerusalem, Israel) is a novel method of delivering alpha radiation to solid tumors, using intratumoral placement of wires impregnated with radium-224 sources (3.7 days half-life). The decay of the primary isotope starts a decay chain of alpha-emitters inside the tumor, aiming to cause tumor cell death. The mechanism of action has been detailed in preclinical studies [13-16]. Alpha DaRT combines the advantages of local intra-tumoral irradiation with the destructive power of alpha particles, which

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is recognized to be significantly more potent than other forms of radiation. Additionally, due to the short range of alpha particles in tissue, most of the radiation absorption occurs within the tumor and the surrounding healthy tissue is spared. Pilot studies using Alpha DaRT for the treatment of skin cancer and head and neck cancer have demonstrated feasibility, safety, and high response rates [17, 18].

The present pilot study suggests a novel approach for the treatment of pancreatic tumors by employing EUS-guided intra-tumoral alpha radiation. We aim to evaluate the feasibility and safety of EUS-guided intra-tumoral alpha radiation-mediated therapy with Alpha DaRT sources for the treatment of advanced pancreatic cancer.

Patients and Methods

This is a prospective, single arm, open label study with a planned accrual of 37 patients (ClinicalTrials.gov Identifier NCT04002479). The study was approved by the Research Ethics Board (MEO-02-2023-3386), and patients provided written informed consent. Here we report on the first five patients enrolled as per a pre-planned interim analysis. The study population consists of patients with imaging confirmation by CT scan or by EUS of inoperable locally advanced or metastatic, biopsy-proven pancreatic adenocarcinoma or patients medically unfit for surgery. Tumor size was restricted to 4 cm in longest diameter. The required ECOG performance status was $\leq$ 2. Patients could not receive concomitant chemotherapy or immunotherapy. See Supplementary Table 1 for full list of eligibility criteria. Baseline CT scan was at most 30 days before screening and a maximum of 65 days prior to the study intervention.

A customized applicator was designed to backload the Alpha DaRT sources into an EUS needle, avoiding the need to directly handle the sources. Sources were inserted into the pancreas tumor under EUS guidance, similar to the established technique for inserting fiducial markers into the pancreas for image guidance during radiotherapy delivery [19]. The appropriate number of Alpha DaRT sources required to perform the procedure was determined from volumetric measurements of the pancreas tumor as seen on the baseline CT scan, based on the previously-described diffusion-leakage model to estimate the dose distribution of Alpha DaRT sources [20, 21] . Treatment was delivered using a linear echoendoscope (SU-1/EG-580UT, Fujifilm Medical Co., Tokyo, Japan). Alpha DaRT sources were inserted into the tumor using a standard 22-gauge EUS aspirate needle (Expect Slimline, Boston Scientific Co., Natick, MA, USA) with a novel

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proprietary applicator developed by Alpha Tau Medical to advance the sources. Standard biohazard gowns and gloves were used as protective equipment for the endoscopist and assisting staff, as alpha particles are generally unable to penetrate even the outer layer of skin. The sources contain 3 μCi of Ra-224 and were implanted at a targeted interval distance of 5 mm and at least 2mm from major blood vessels and vital organs. A pre-treatment plan was used to guide the optimal endoscopic source placement; however, as this is a first-in-human trial, investigators chose to take a conservative approach and increase the total activity and sources for successive initial patients to avoid any untoward safety issue. EUS procedures were performed under conscious sedation or monitored anesthesia care at the interventional team's discretion and peri-procedural antibiotics were administered. The position of the Alpha DaRT sources was documented by a post-insertion CT performed immediately after the insertion procedure.

Feasibility was determined by confirmation of Alpha DaRT source placement directly within the pancreas tumor or in the surrounding tissue, as noted on the post-procedure CT scan. Early tolerance was based on patient evaluations made at scheduled visits through 4 weeks post-procedure. Adverse events (AEs) were assessed as per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Tumor response was evaluated by imaging 4-6 weeks post treatment (RECIST V1.1, longest diameter of the target tumor). The need for biliary stent placement to address biliary obstruction was assessed over the course of Alpha DaRT treatment and follow-up as an indirect assessment of local tumor progression.

Results

The first five patients were treated between March and September 2023 at the Jewish General Hospital, Montreal, Canada. Baseline demographic and disease characteristics are provided in Table 1. Patients ranged in age from 68 to 84 years old and four out of the five were female. Cancer stage varied, with three patients having stage IV cancer according to UICC classification, 8th edition [22]. Location of tumor varied but four involved the pancreas head.

Feasibility of Alpha DaRT Source Placement

The Alpha DaRT procedure was deemed technically successful in all five cases included in this report, with Alpha DaRT sources inserted in or surrounding the pancreas tumor (Figure 1, Figure 2). Table 2 lists details of the procedures, including number of sources inserted, percent dose

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coverage and number of needle applicators used. With one source per needle deployed, the number of passes made ranged between three and 21. As noted, the total number of Alpha DaRT sources increased with each successive procedure.

Tolerance of Alpha DaRT Placement

A total of fourteen AEs were reported among three patients. Four of the AEs were considered serious (SAEs), all of which were either not related to the treatment or probably not related to treatment, but rather due to disease progression or medical assistance in dying. Of the two deaths, one was from a medically assisted death and the other due to gastrointestinal bleed thought to be related to tumor progression. The latter occurred over 80 days following Alpha DaRT insertion, in the context of progressive duodenal tumor invasion on therapeutic anticoagulation, and the nearest Alpha DaRT source was estimated to have been more than 5mm from the focus of bleeding. All other AEs were of mild (7) or moderate (3) severity and only two AEs (mild) were deemed possibly related to the study device. Table 3 lists the details of all AEs.

Regarding biliary stent placement, two patients had a previous metal stent, one of which underwent ERCP with coaxial stent placement due to suspected tumor ingrowth about one month following Alpha DaRT insertion. A third patient, who had no previous biliary stent, had a stent inserted 41 days following Alpha DaRT insertion. Notably this patient had partial biliary obstruction prior to the study intervention, with biliary dilation noted on pre-procedural CT scan. The remaining two subjects had no stent intervention reported at the time of this report.

Blood and urine radioactivity laboratory tests were performed at baseline, day 6 and day 35. Figure 3 shows the clear increase and subsequent return to baseline levels of radioactivity in blood and urine by day 35. Each line in the figures represents a single subject's levels of radioactivity over time.

Tumor Response

Tumor measurements for each patient as well as the response assessment according to modified RECIST criteria are listed in Table 4. At the 35-day visit, three patients showed stable disease and two had progressive disease. One patient with stable disease at 35 days showed partial response of the tumor on scan two months post procedure. Another patient with stable disease at 35 days remained stable on scan more than three months after intervention. Of note, the evaluation of

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RECIST was performed using CT scans from several days prior to the treatment (as many as 57 days prior). Baseline scans performed on the day of treatment were done without contrast and, as such, were not reliable for evaluating tumor size. At the time of this report, the surviving patients had documented survival through nine, eight and six months post procedure.

Discussion

Advanced pancreatic cancer represents one of the most formidable disease management challenges. Many patients present with bulky local disease with attendant morbidity associated with biliary obstruction, gastric outlet obstruction and pain, and ultimately disease-related mortality. The availability of alpha particle treatment may help address the significant unmet need for effective and safe locoregional pancreas cancer therapy due to its enhanced biologic potency coupled with its short range of activity, limiting radiation dose to adjacent heathy tissue.

Alpha DaRT therapy is a novel method to deliver alpha particles for solid tumor radiotherapy. Results from the first clinical study with Alpha DaRT for the treatment of squamous cell carcinoma of the skin and oral cavity were promising and demonstrated the safety of Alpha DaRT with no device-related SAEs [18]. In a follow-up pilot study in the U.S., treatment with Alpha DaRT resulted in few AEs, and no device or procedure related SAEs [17].

In the present first-in-human study for pancreatic cancer, Alpha DaRT is applied to the target tumor under EUS guidance. The current report of the first five patients treated indicates the feasibility of this novel approach. Only two mild device-associated AEs and no serious device-associated AEs were observed. Based on this analysis, the implementation of Alpha DaRT under EUS guidance in pancreatic cancer appears to be feasible and safe.

The initial efficacy results from this interim analysis are promising, with three of the five patients having stable disease at 1-month follow up and one of these showing partial response two months post procedure. Importantly, the baseline size measurement evaluation was performed prior to the date of the procedure. Given the relatively fast pace of growth of pancreatic tumors, it can be assumed that the tumors were larger at the time of the Alpha DaRT procedure than at the screening scan, thus potentially resulting in an underreporting of the true benefit of Alpha DaRT based on modified RECIST evaluation. At this early stage, these observations are hypothesis generating only.

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A few limitations should be mentioned. The present analysis includes few patients treated at a single tertiary care center by one endoscopist (CSM). The full study is currently underway which includes a larger sample size and patients treated at an additional center; yet results from the pre-planned interim analysis are important to disseminate given the novelty of the experimental treatment modality and its potentially major impact. The reported follow up duration, while suitable for the primary outcomes of feasibility and safety assessment, is inadequate for drawing meaningful conclusions about tumor response.

Should feasibility and safety be confirmed with the results of the full study, efficacy of Alpha DaRT for pancreatic cancer can then be further studied in select patient populations and in conjunction with different therapies. In addition to the potential for improved outcomes related to locoregional tumor symptoms, improved tumor control with EUS-guided Alpha DaRT could ultimately translate into higher conversion rates for patients with borderline unresectable disease into resectable disease or higher R0 resection rates. Further, combination therapies with chemotherapy or immunotherapy might yield an increased therapeutic benefit for patients. Concomitant checkpoint inhibitor therapy, for which emerging data are demonstrating enhanced tumor responses with the synergistic effects of such combined therapy approaches, may be explored. Indeed, a potent synergistic anti-tumor effect when Alpha DaRT is used in combination with immune check point inhibitors for various solid tumors has been previously demonstrated in animal models [23]. Future studies comparing Alpha DaRT to proposed locoregional EUS-guided therapies such as radiofrequency ablation will also help elucidate the role this novel modality has in the treatment of pancreatic cancer.

In conclusion, preliminary results from this pilot study indicate that EUS-guided Alpha DaRT treatment for unresectable pancreatic cancer is feasible and safe. Further investigation of this promising novel modality is underway.

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References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer Statistics, 2021. CA Cancer J Clin 2021;71:7-33.
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225-249.
3. Heinemann V, Boeck S, Hinke A, et al. Meta-analysis of randomized trials: evaluation of benefit from gemcitabine-based combination chemotherapy applied in advanced pancreatic cancer. BMC Cancer 2008;8:82.
4. Sultana A, Smith CT, Cunningham D, et al. Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 2007;25:2607-2615.
5. Bazeed AY, Day CM, Garg S. Pancreatic Cancer: Challenges and Opportunities in Locoregional Therapies. Cancers (Basel) 2022;14.
6. Ahn DH, Bekaii-Saab T. The Continued Struggle for Defining a Role for Radiotherapy in Pancreas Cancer. JAMA Oncology 2022;8:1257-1259.
7. Fegrachi S, Besselink MG, van Santvoort HC, et al. Radiofrequency ablation for unresectable locally advanced pancreatic cancer: a systematic review. HPB (Oxford) 2014;16:119-123.
8. Reyngold M, Parikh P, Crane CH. Ablative radiation therapy for locally advanced pancreatic cancer: techniques and results. Radiat Oncol 2019;14:95.
9. Gonzalo-Marin J, Vila JJ, Perez-Miranda M. Role of endoscopic ultrasound in the diagnosis of pancreatic cancer. World J Gastrointest Oncol 2014;6:360-368.
10. Sun S, Xu H, Xin J, et al. Endoscopic ultrasound-guided interstitial brachytherapy of unresectable pancreatic cancer: results of a pilot trial. Endoscopy 2006;38:399-403.
11. Jin Z, Du Y, Li Z, et al. Endoscopic ultrasonography-guided interstitial implantation of iodine 125-seeds combined with chemotherapy in the treatment of unresectable pancreatic carcinoma: a prospective pilot study. Endoscopy 2008;40:314-320.
12. Sun S, Ge N, Wang S, et al. Pilot trial of endoscopic ultrasound-guided interstitial chemoradiation of UICC-T4 pancreatic cancer. Endosc Ultrasound 2012;1:41-47.
13. Arazi L, Cooks T, Schmidt M, et al. Treatment of solid tumors by interstitial release of recoiling short-lived alpha emitters. Phys Med Biol 2007;52:5025-5042.
14. Arazi L, Cooks T, Schmidt M, et al. The treatment of solid tumors by alpha emitters released from (224)Ra-loaded sources-internal dosimetry analysis. Phys Med Biol 2010;55:1203-1218.
15. Cooks T, Arazi L, Schmidt M, et al. Growth retardation and destruction of experimental squamous cell carcinoma by interstitial radioactive wires releasing diffusing alpha-emitting atoms. Int J Cancer 2008;122:1657-1664.
16. Kelson I, Levy Y, Redmard E. Recoil implantation of alpha sources for thickness measurement of thin films. Journal of Physics D: Applied Physics 1995;28:100.

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17. D'Andrea MA, VanderWalde NA, Ballo MT, et al. Feasibility and Safety of Diffusing Alpha-Emitter Radiation Therapy for Recurrent or Unresectable Skin Cancers. JAMA Netw Open 2023;6:e2312824.
18. Popovtzer A, Rosenfeld E, Mizrachi A, et al. Initial Safety and Tumor Control Results From a "First-in-Human" Multicenter Prospective Trial Evaluating a Novel Alpha-Emitting Radionuclide for the Treatment of Locally Advanced Recurrent Squamous Cell Carcinomas of the Skin and Head and Neck. Int J Radiat Oncol Biol Phys 2020;106:571-578.
19. Sawhney MS. Role of Endoscopic Ultrasound in the Treatment of Pancreatic Neoplasms. Techniques in Gastrointestinal Endoscopy 2009;11:44-48.
20. Heger G, Roy A, Dumančić M, Arazi L. Alpha dose modeling in diffusing alpha-emitters radiation therapy-Part I: single-seed calculations in one and two dimensions. Med Phys 2023;50:1793-1811.
21. Heger G, Dumančić M, Roy A, Arazi L. Alpha dose modeling in diffusing alpha-emitters radiation therapy. Part II: Lattice studies. Medical Physics 2023;50:1812-1823.
22. Cong L, Liu Q, Zhang R, et al. Tumor size classification of the 8(th) edition of TNM staging system is superior to that of the 7(th) edition in predicting the survival outcome of pancreatic cancer patients after radical resection and adjuvant chemotherapy. Sci Rep 2018;8:10383.
23. Domankevich V, Cohen A, Efrati M, et al. Combining alpha radiation-based brachytherapy with immunomodulators promotes complete tumor regression in mice via tumor-specific long-term immune response. Cancer Immunol Immunother 2019;68:1949-1958.

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Figure Legend

Figure 1. a) EUS image of pancreas tumor with FNA needle (arrow) within; b) with Alpha DaRT seed (arrow) deployed. Note the previously placed Alpha DaRT sources (arrowheads)

Figure 2. CT image of pancreas tumor with Alpha DaRT sources in situ (arrow)

Figure 3. Plot per patient of Pb-212-Specific Activity Measured in a) urine, b) blood

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Table 1. Summary of Baseline Characteristics

Patient	Age (years)	Sex	ECOG Score	Tumor Stage	Tumor Location	Pancreatic cancer is inoperable due to	Prior Treatments
1	78	Male	1	IV	Pancreatic head/uncinate	Metastatic disease	Chemotherapy: Gemcitabine with paclitaxel; Gemcitabine
2	68	Female	2	III	Pancreatic head	Unresectability	Chemotherapy: Folforinox (fluorouracil+leucovorin+oxaliplating); gemcitabine+paclitaxel
3	69	Female	0	II	Pancreatic head/neck	Unresectability	Chemotherapy: Folforinox; Abraxane and Gemcitabine
4	84	Female	1	IV	Pancreatic head	Metastatic disease	Capecitabine
5	71	Female	0	IV	Pancreatic neck	Metastatic disease	None

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Table 2. Alpha DaRT Insertion Parameters

Patient	Number of 1cm Sources Inserted	Number of 2cm Sources Inserted	Total Sources Inserted	Equivalent No 1cm sources	Percent Coverage GTV* (%)
1	3	0	3	3	8
2	11	0	11	11	13
3	21	0	21	21	44
4	10	6	16	22	12.5
5	4	10	14	24	29.5

GTV, gross tumor volume

* Percent coverage GTV is corrected for overall dose of 16 Gy Alpha

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Table 3. Adverse Events

Patient	Adverse Event Description:	Relationship to Study Device?*	Severity Grade
1	Fatigue	Probably not related	Mild
	Loss of appetite	Possibly related	Mild
	Abdominal pain	Possibly related	Mild
	Medical assistance in dying	Not related	Death
2	Urinary tract infection	Not related	Mild
	Abdominal pain	Not related	Moderate
	Gastrointestinal bleed	Probably not related	Severe
	Cholangitis	Probably not related	Severe
	Loss of appetite	Not related	Mild
	Gastrointestinal bleed**	Probably not related	Death
4	Allergic reaction	Not related	Mild
	Constipation	Probably not related	Moderate
	Dizziness	Not related	Mild
	Biliary obstruction	Probably not related	Moderate

.

*An adverse event is considered associated with the use of the Alpha DaRT if the attribution is possible, probable, or very likely

** This occurred in an area removed from the Alpha DaRT insertion and was thought to be due to disease progression with duodenal invasion. Patient was on anticoagulant and also had external beam radiation after the first bleeding episode

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Table 4. Tumor Measurements and Response

Patient	Visit	Timing of CT (days from procedure)	Longest Diameter (cm)	Response	Metastases
1	Screening	-57	2.3		Yes
	Response Evaluation	40	3.1	Progressive Disease	Yes
2	Screening	-29	3.9		No
	Response Evaluation	31	5.6	Progressive Disease	Yes
3	Screening	-7	2.4		No
	Response Evaluation	28	2.4	Stable Disease	No
	Follow-up visit	69	1.6	Partial Response	Yes
4	Screening	-3	3.9		Yes
	Response Evaluation	28	3.7	Stable Disease	Yes
	Follow-up visit	98	4.3	Stable Disease	Yes
5	Screening	-25	3.9		Yes
	Response Evaluation	28	4.3	Stable Disease	Yes

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Supplementary Table 1. Eligibility criteria

Inclusion Criteria

- Histologically and/or cytologically proven locally advanced (Stage II or III) or metastatic (Stage IV) pancreatic adenocarcinoma
- Inoperable pancreatic cancer due to at least one of the following: a) unresectability, b) metastatic disease, c) medically unfit for surgery
- Single foci of tumor in the pancreas
- Platelet count ≥ 50,000/mm3
- International normalized ratio of prothrombin time ≤1.5
- ECOG performance status ≤ 2
- Measurable lesion per RECIST (version 1.1) criteria
- Maximum lesion of 4cm in the longest diameter (including primary tumor and regional lymph nodes)
- ≥ 18 years of age
- Estimated life expectancy of at least 12 weeks
- Women of childbearing potential (WOCBP) will have evidence of negative pregnancy test
- Subjects are willing to sign an informed consent

Exclusion Criteria

- Multifocal pancreatic adenocarcinoma
- Contrast medium sensitivity precluding the subject from undergoing contrast enhanced CT
- Prior abdominal radiation therapy
- Concomitant chemotherapy or immunotherapy
- Borderline unresectable pancreatic cancer and medically fit for surgery
- Connective tissue disease (scleroderma, lupus)
- Prior chemotherapy does not exclude the patient
- Patients with significant comorbidities that the treating physician deems may conflict with the endpoints of the study (e.g., poorly controlled autoimmune diseases, vasculitis, etc.)
- Patients undergoing systemic immunosuppressive therapy excepting intermittent, brief use of systemic corticosteroids
- Volunteers participating in another interventional study in the past 30 days which might conflict with the endpoints of this study or the evaluation of response or toxicity of DaRT
- High probability of protocol non-compliance (in opinion of investigator)
- Patients not willing to sign an informed consent form
- Women who are pregnant or lactating

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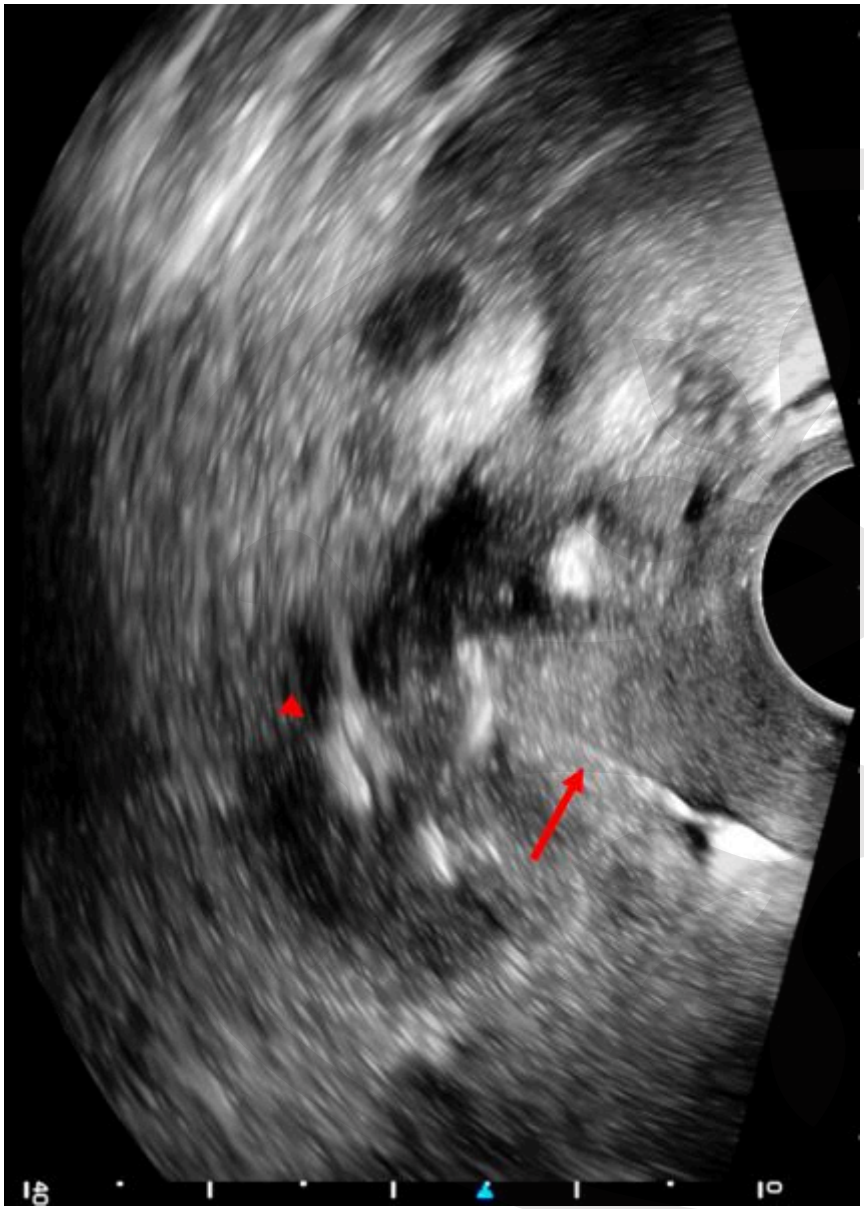

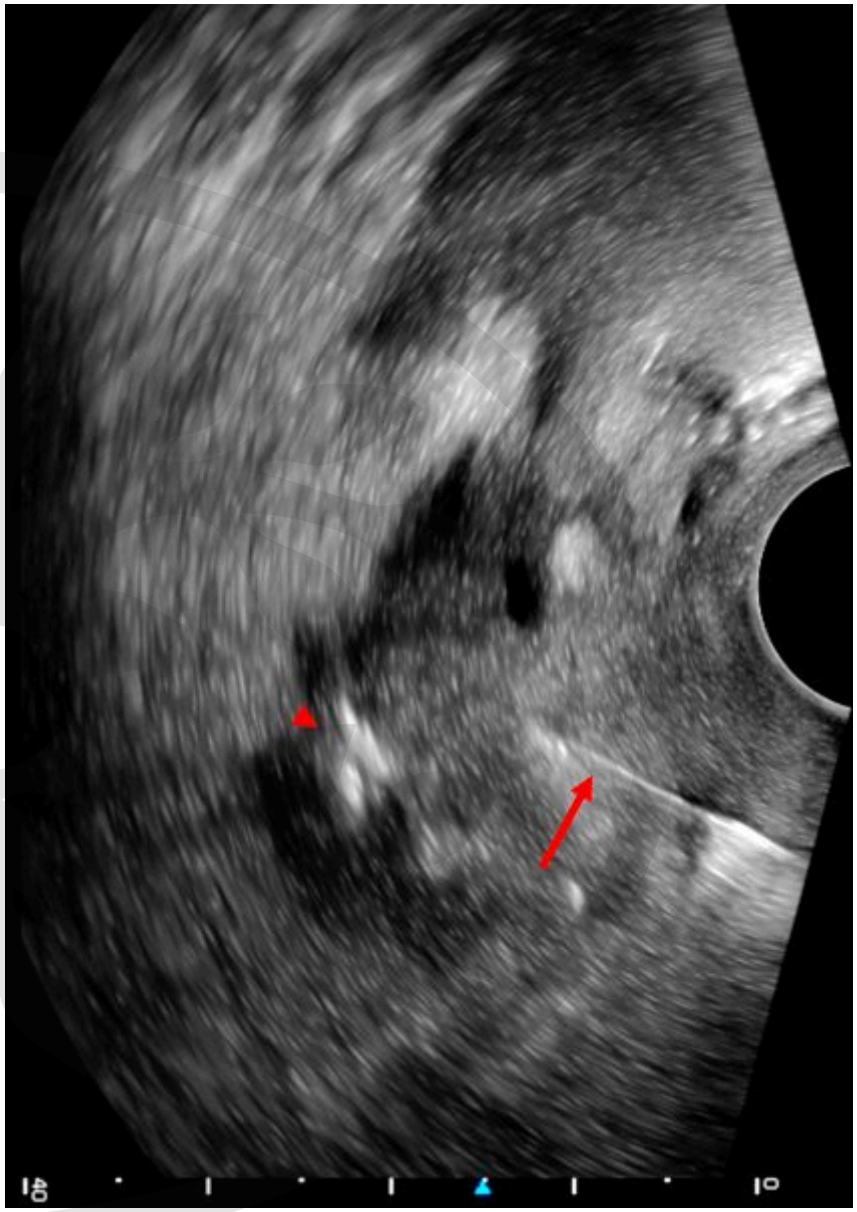

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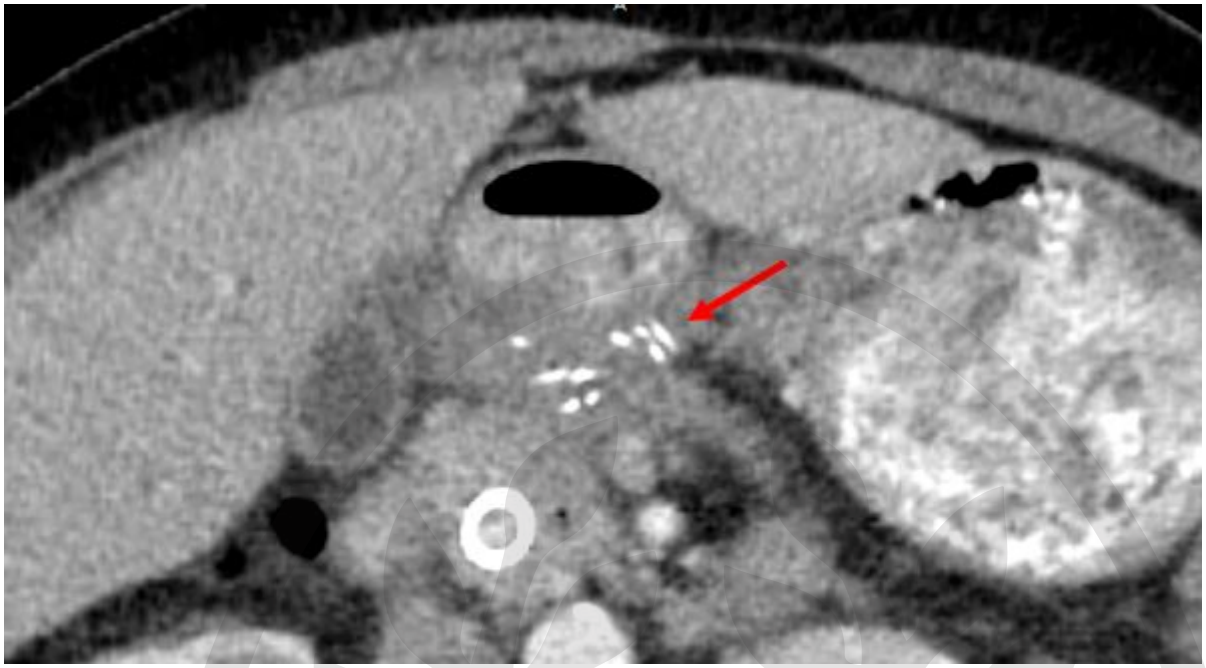

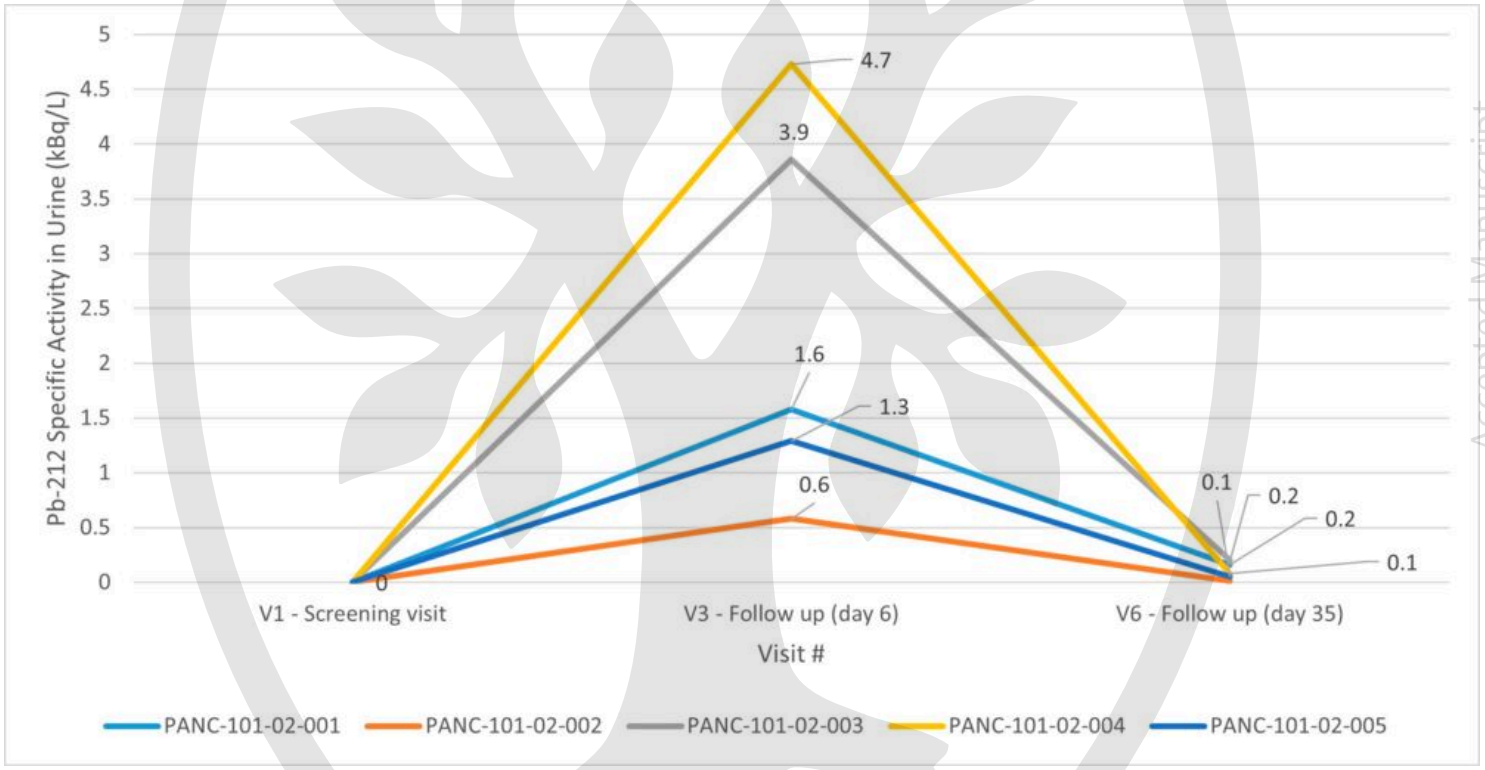

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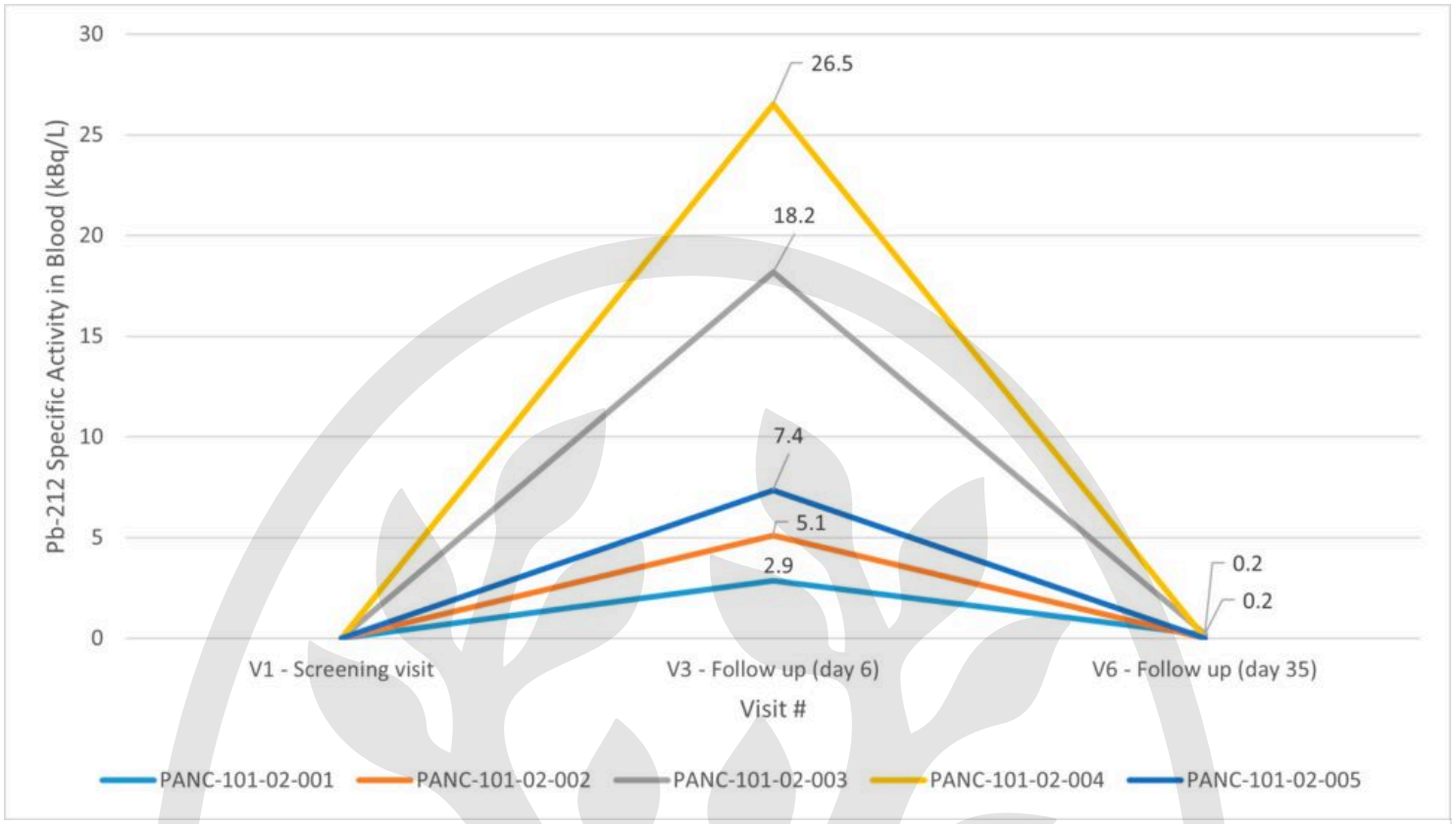

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