(NASDAQ:DRTS)

R&D Update Day

Jan 27, 2025

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Today's Presenters

Raphi Levy
CFO
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Robert Den, MD
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Philip Blumenfeld, MD, MPH
Radiation Oncologist
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Corey Miller, MD, MSc
Endoscopist
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Agenda

1. **Introduction**
   Raphi Levy, CFO | Alpha Tau
2. **Updated Interim Pancreatic Cancer Data as of Jan 8, 2025**
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8. **Next Steps, Milestones and Q&A**
   Raphi Levy, CFO | Alpha Tau

The Alpha Tau Mission

Alpha DaRT

A novel approach using localized alpha particle radiotherapy designed to precisely destroy solid tumors while sparing surrounding healthy tissue

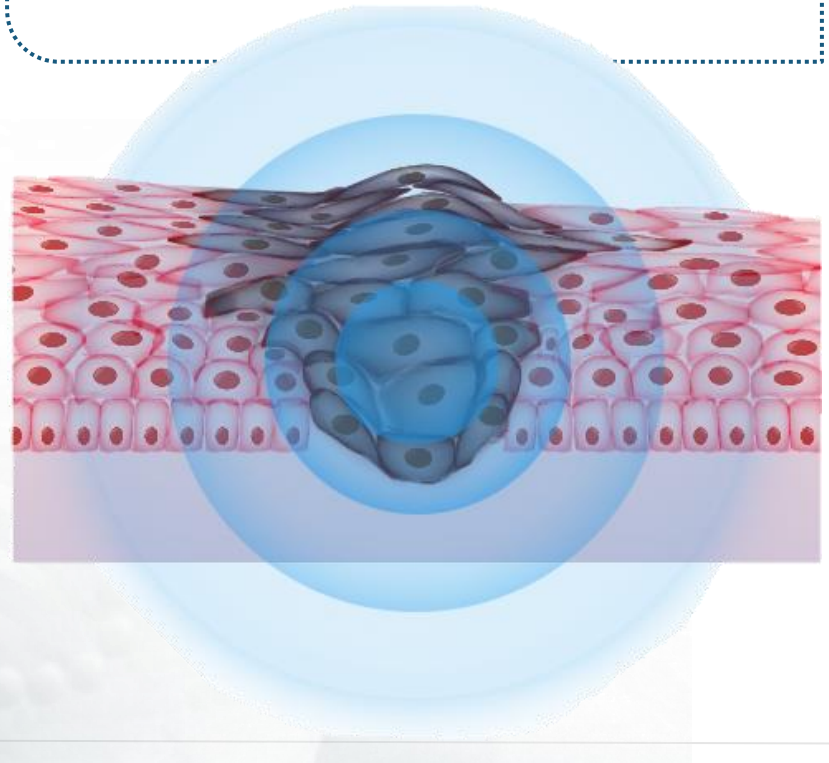
- Broad potential applicability for local tumor control, together with signs of compelling immuno-stimulatory activity
- Platform technology has the potential to be utilized alone or synergistically with other cancer treatment modalities
- Milestones and data from multiple clinical trials in various phases in different indications expected in 2025 and 2026
- 1st potential U.S. marketing authorization in 2026, with blockbuster market opportunity across multiple tumor types

Alpha Radiation is Focal - Short Range Limits Clinical Use

Whereas beta and gamma radiation can penetrate tissue with sufficient range to facilitate tumor coverage (while risking damage to healthy tissue), alpha radiation has short range in tissue (<100 µm), which limits its clinical usefulness in local delivery

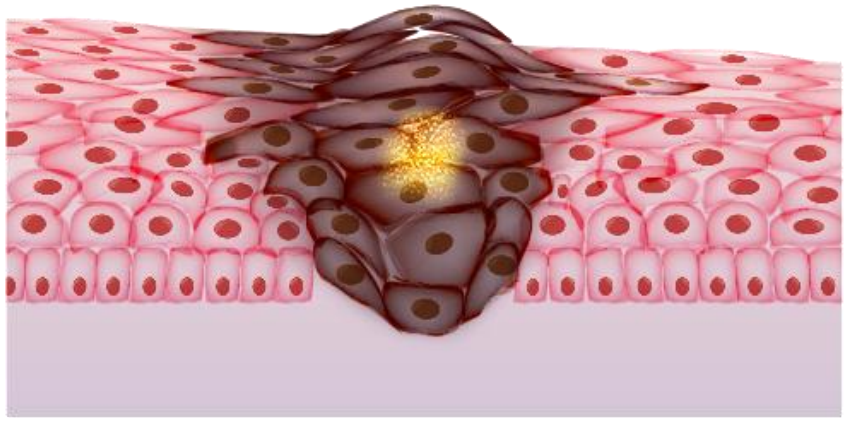
Beta/Gamma Radiation

Long therapeutic range with risk to surrounding organs



Alpha Radiation

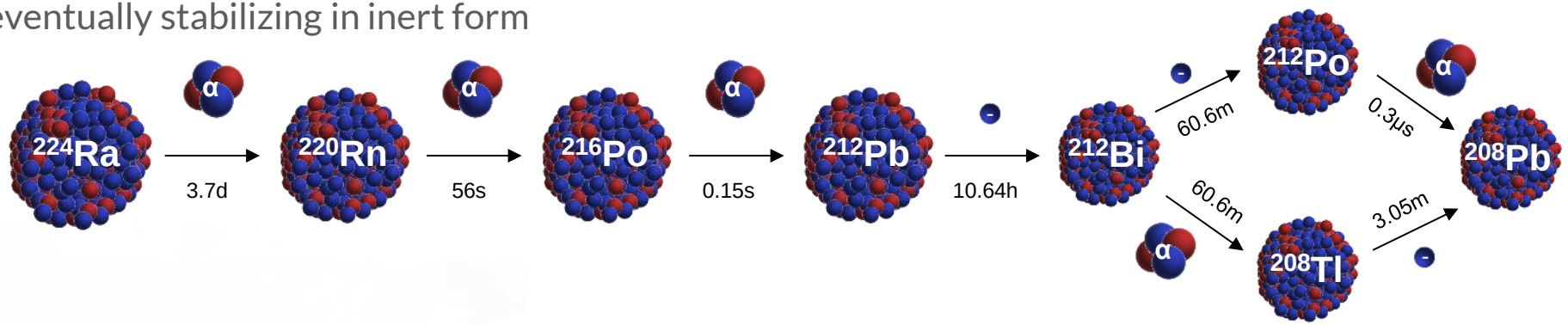
Short range in tissue limits damage to surrounding organs but also limits coverage



Mechanism of Action of the Alpha DaRT Technology

^{224}Ra Decay Chain

- Alpha DaRT leverages the innate decay chain of Radium-224
- The decay chain of Radium-224 includes four alpha particles
- Radium-224 has a half-life of ~3.7 days, while the remaining decay chain has a total half-life of approximately 12 hours, before eventually stabilizing in inert form



Alpha DaRT

- The Alpha DaRT utilizes stainless steel or titanium sources that are impregnated with Radium-224
- When the Alpha DaRT source is injected into the tumor, the radium remains attached to the source while its daughter atoms detach, emitting cytotoxic alpha particle payloads as they move deeper into the tumor until eventually stabilizing

Alpha DaRT is designed to overcome the range limitations of alpha particles through precise release of alpha emitters into the tumor, generating a potent and tight distribution of alpha radiation

Alpha DaRT - Diffusing Alpha-emitters Radiation Therapy

https://www.youtube.com/watch?v=nwfzJHm0fTQ

Therapeutic Focus

We are focused on delivering solutions to three markets that we believe would be best served by the unique characteristics of the Alpha DaRT

Localized & Unresectable

- Localized tumors that are not surgical candidates and tumors that recur after surgery and are resistant to other therapies, specifically radiotherapy
- Alpha DaRT to be evaluated as a later line therapy
- Tumor types we are targeting include SCC, H&N SCC and prostate

High Unmet Need

- Solid tumors that have limited treatment options with limited standard of care offering
- Alpha DaRT could potentially target broad patient populations
- Tumor types we are targeting include GBM and pancreatic cancer

Metastatic

- Alpha DaRT being evaluated for its potential to induce an immune response in metastatic tumors
- Alpha DaRT being evaluated in combination with checkpoint inhibitors as an adjuvant therapy
- Tumor types we are targeting include liver, breast and H&N (which includes lip, oral cavity, salivary glands, oropharynx & pharynx) cancers

Initial Foray into Superficial Tumors

Alpha DaRT first tested in superficial tumors – tumors of the skin or head & neck, due to:

- Ease of access
- Straightforward control
- Ongoing monitoring
- Strong initial preclinical data in Squamous Cell Carcinoma (SCC)

Treatment of hundreds of tumors to date :

- Indicated a mild safety profile
- Generated marketing authorization in Israel to treat SCC of the skin or oral cavity
- Allowed us to submit to PMDA in Japan for marketing authorization to treat recurrent head & neck cancer

Pivotal trial (“ReSTART”) underway in the U.S. for recurrent cutaneous SCC

Outline of The Multicenter Pivotal Recurrent SCC study

Primary / safety objectives:

- ORR based on Best Overall Response
- DOR 6 months after initial response
- Assess the safety based on statistics of device-related AEs (per CTCAE v5)

Secondary objectives: Evaluate O-DOR, local control, PFS and OS (all up to 12 months), and QoL Metrics

Key Eligibility Criteria

Recurrent non-metastatic cutaneous **SCC**

Patient with **no curative standard-of-care options**

No **previously untreated SCC**

Sample size N = 86 patients

Treatment and Procedure

Treatment plan based on CT-simulation

Sources 1cm length, 0.7mm diam.

Activity per source 3 µCi

Local anesthesia

Shifting focus to **Mohs surgeons**

Timeline and Follow-Up

Alpha DaRT sources insertion

Removal after 14 to 21 days

Weekly **follow-up** during the treatment period

Targeted Date of Completion: **Q3 2025**

Targeted Submission to FDA: **H1 2026**

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Overview of Trial Design

Three single-arm safety and feasibility trials treating pancreatic cancer patients in parallel:

- CTP-PANC-101 monotherapy treatment at 2 sites in Montreal, Canada – up to 37 patients total
- CTP-PANC-02 monotherapy treatment at 1 site in Jerusalem, Israel – up to 15 patients total
- CTP-ALL-00 flexible basket trial at 1 site in Jerusalem, Israel – no specified limit on number of patients

Following initial results, there are some situations where chemotherapy has been used in the first two trials

- CTP-PANC-101 allows chemotherapy 30 days after Alpha DaRT treatment
- CTP-PANC-02 was modified to allow concomitant chemotherapy

Therefore, after initially embarking on monotherapy exploration, **a small number of patients from all three trials have received chemotherapy treatment alongside or following Alpha DaRT treatment**

Due to the exploratory nature of the trials, they do not focus on a specific patient sub-population but rather a broad mix of patients with non-resectable pancreatic cancer

Patient Characteristics

Including the first five patients from the interim data released in late 2023, a total of **n = 41 patients have been treated** thus far with pancreatic cancer across the three trials

	Canada (n=24)	**Israel (n=17)**		
Characteristic (n)	PANC-101	PANC-02	ALL-00	Total
Gender				
Male	10	7	6	23
Female	14	2	2	18
Median Age	70	75	72	71
Cancer Stage				
2	4	1	0	5
3	4	3	2	9
4	16	5	6	27
Previous/concurrent lines of chemotherapy				
0	7	1	1	9
1	9	3	3	15
2	8	5	4	17

Highlights of Feasibility and Safety

100% success in delivering Alpha DaRT sources (feasibility)

Strong safety results

- Total of 151 adverse events (AEs) reported
- 38 were associated with Alpha DaRT (possibly, probably or definitely related), of which 29 were mild (Grade 1), five were moderate (Grade 2) and four were severe (Grade 3), of which three were SAEs
- Three related SAEs included:
  - Two cases of elevated liver functions:
    - One patient hospitalized and discharge
    - One patient declined to hospitalize and recovered at home
  - One case of sepsis – stabilized, hospitalized and discharge

Possibly-, Probably- or Definitely-Related Adverse Events (by CTCAE)

CTCAE Coded Term	1 – Mild	2 – Moderate	3 – Severe	4 – Life-Threatening	5 – Death	Total
Abdominal pain	6		1			7
Fatigue	5	2				7
Anorexia	3	1				4
Not yet coded	2	1	1			4
Nausea	3					3
Blood bilirubin increased	1		1			2
Gallbladder obstruction	1	1				2
Alkaline phosphatase increased	1					1
Back pain	1					1
Bloating	1					1
Chills	1					1
Gastroesophageal reflux disease	1					1
Sepsis			1			1
Stomach pain	1					1
Vomiting	1					1
Weight loss	1					1
Total	29	5	4	0	0	38

High Disease Control Rate Observed

Among the 41 patients treated, 33 had a measured objective response, with 5 patients awaiting response evaluation and 3 who discontinued prior to evaluation. Results are presented below using Best Overall Response (BOR) for those with a measured response.

Including first two patients (heavily underdosed / feasibility only)	**18%** Objective Response Rate (CR + PR)	**91%** Disease Control Rate (CR + PR + SD)
Excluding first two patients (heavily underdosed / feasibility only)	**19%** Objective Response Rate (CR + PR)	**97%** Disease Control Rate (CR + PR + SD)

Highlights of Overall Survival (OS) Data

Key Caveats:

- The data are still **relatively immature, but ongoing**
- Trial designs were **focused on feasibility and safety**, without the frequent monitoring visits common in studies focused on precise measurement of survival
- Five patients treated since Nov 25, 2024, and three patients who exited the study very shortly after treatment, in all cases with insufficient time to reach objective response measurement, were excluded from OS analysis for lack of data maturity
  - Therefore, a total of n = 33 patients are evaluated for OS using Kaplan-Meier analysis

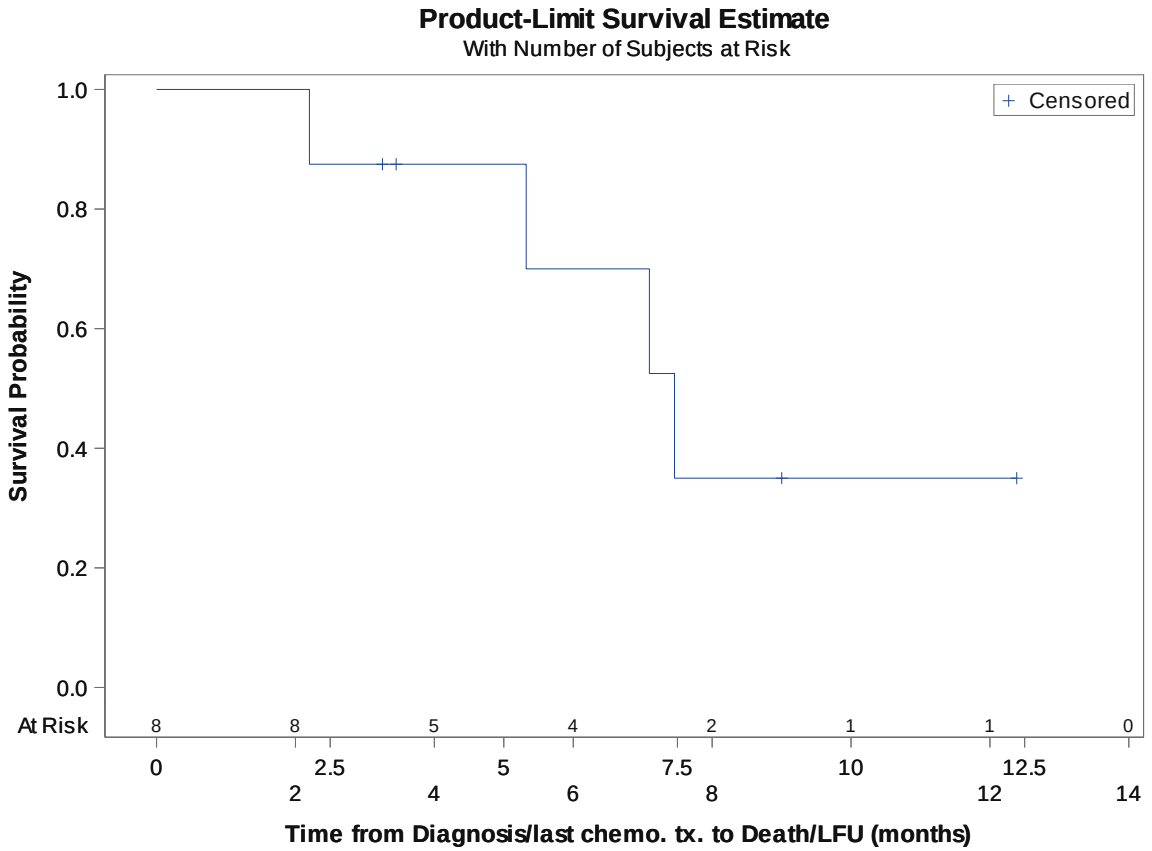
Population	OS Since Diagnosis / Initiation of Last Chemotherapy (mo)	OS Since Alpha DaRT Treatment (mo)
Overall Population (n=33)	18.6	10.9

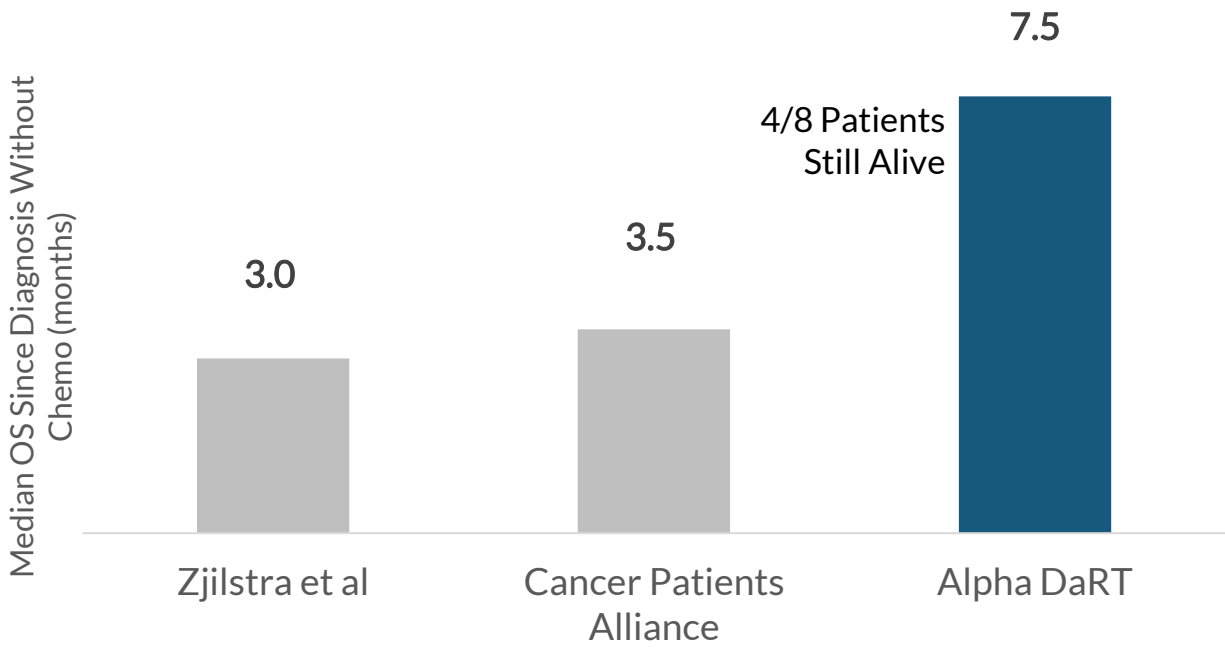
Of n=33 patients analyzed, 13 have died
The remaining 20 (and the five newer patients) remain alive

In light of the **heterogeneity of the population**, we conducted ad-hoc analyses **of key sub-groups** to offer context vs. expected OS for each group

Analysis of Overall Survival in Key Sub-Populations (1/3)

Newly Diagnosed / Not Eligible for Chemotherapy (n=8)





Note: Median follow-up in Alpha DaRT group of 6.3 months

For Illustrative Purposes Only - no head-to-head clinical study has been conducted comparing Alpha DaRT to other products or candidates. Differences exist between trial designs, subject characteristics and other factors, and caution should be exercised when comparing data across unrelated studies

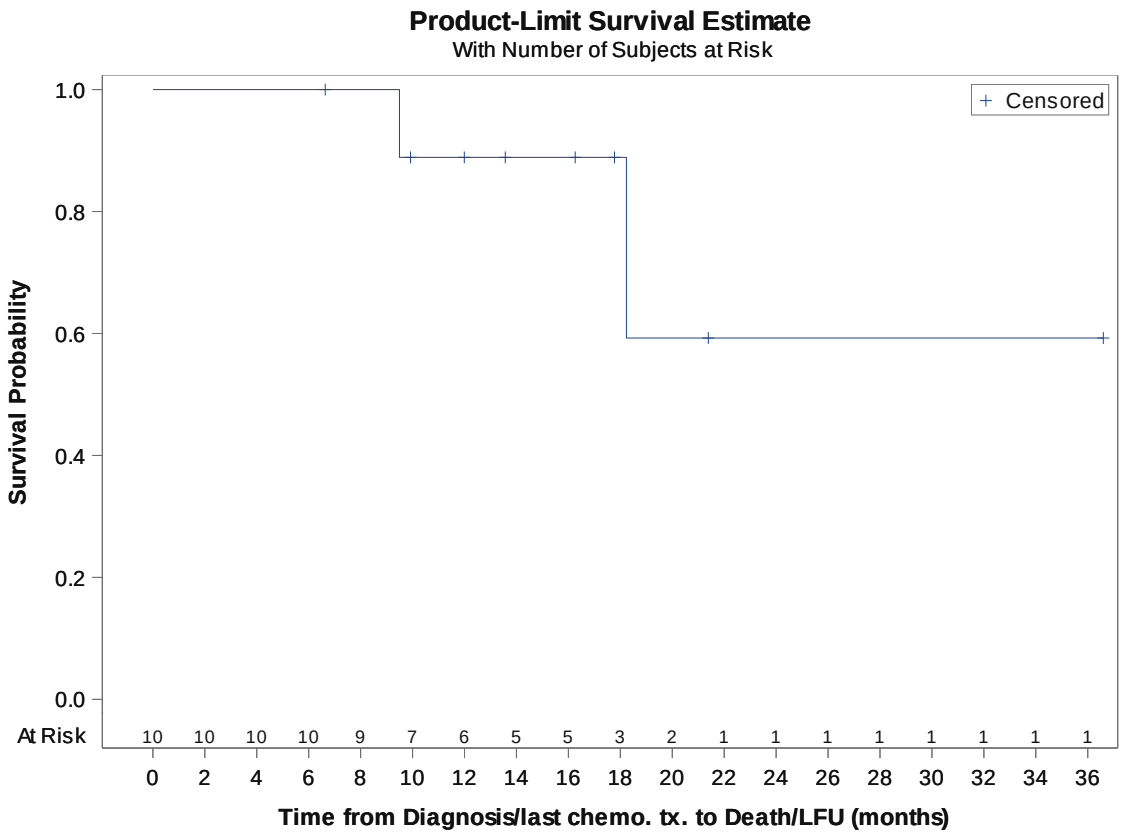
Sources:

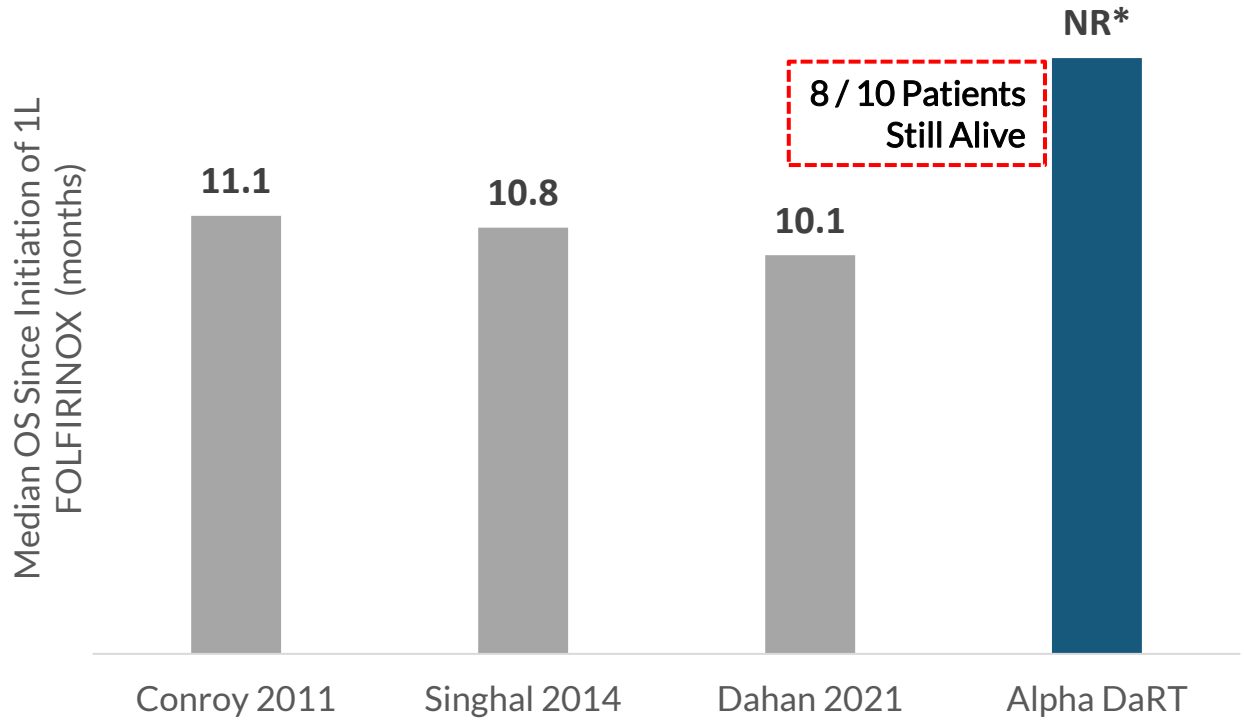
Zijlstra, M. et al (2018). Patient characteristics and treatment considerations in pancreatic cancer: a population based study in the Netherlands. https://doi.org/10.1080/0284186X.2018.1470330

https://pancreatica.org/pancreatic-cancer/pancreatic-cancer-prognosis/

Analysis of Overall Survival in Key Sub-Populations (2/3)

Metastatic (Stage IV) Patients After 1L FOLFIRINOX (n=10)





** Median Kaplan-Meier estimate was not reached (NR); median follow-up time was 15.1 months*

For Illustrative Purposes Only - no head-to-head clinical study has been conducted comparing Alpha DaRT to other products or candidates. Differences exist between trial designs, subject characteristics and other factors, and caution should be exercised when comparing data across unrelated studies

Sources:

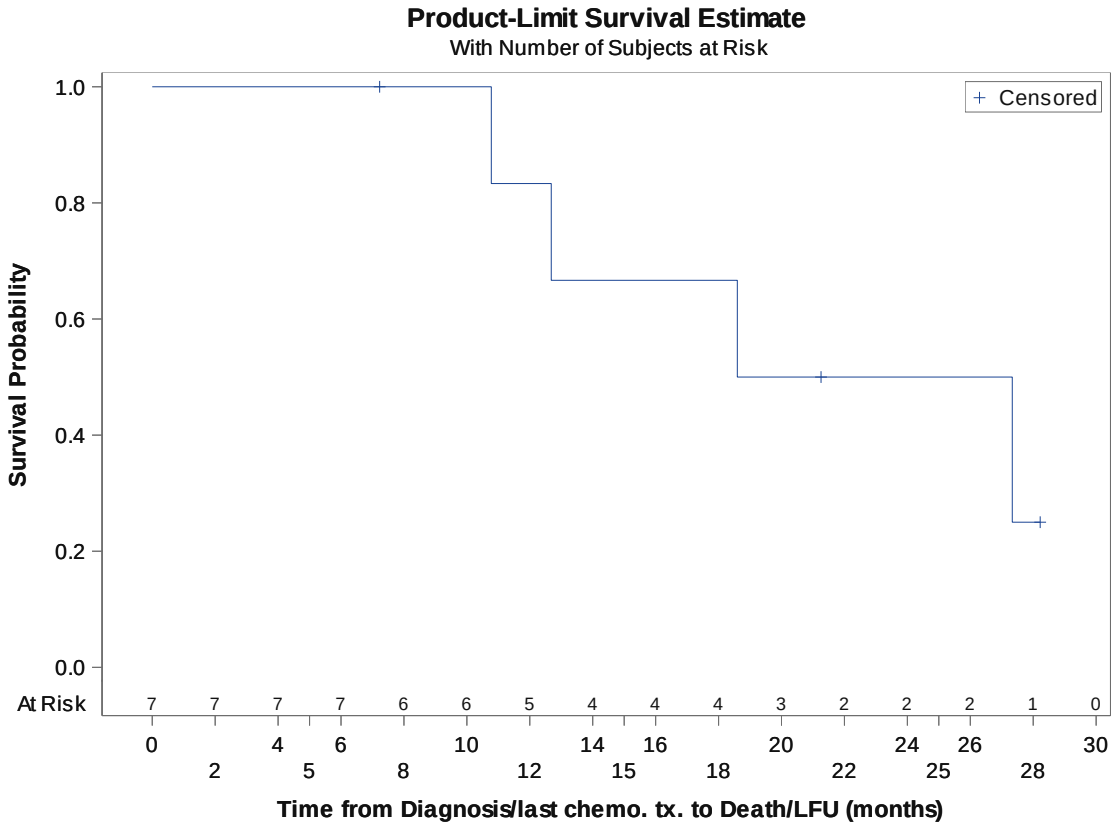
Thierry Conroy et al., FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer. New England Journal of Medicine (2011). DOI: 10.1056/NEJMoa1011923

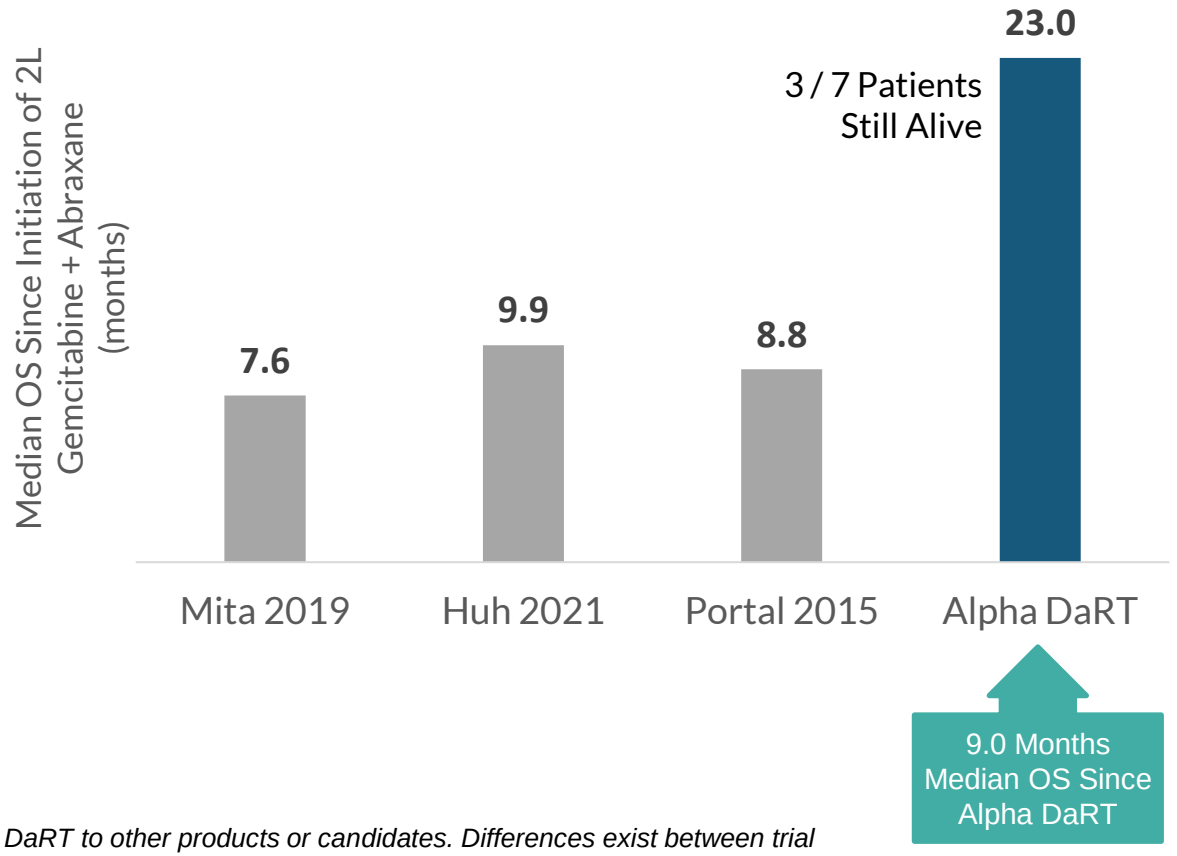
Singhal MK, et al. A phase III trial comparing FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. Ann Oncol. 2014;25(suppl 4):iv210–53.

Laetitia Dahan et al., Randomized Phase II Trial Evaluating Two Sequential Treatments in First Line of Metastatic Pancreatic Cancer: Results of the PANOPTIMOX-PRODIGE 35 Trial. JCO 39, 3242-3250(2021). DOI:10.1200/JCO.20.03329

Analysis of Overall Survival in Key Sub-Populations (3/3)

Progressed After 2L Gemcitabine-Abraxane (n=7)





Note: Median follow-up in Alpha DaRT group of 18.9 months

For Illustrative Purposes Only - no head-to-head clinical study has been conducted comparing Alpha DaRT to other products or candidates. Differences exist between trial designs, subject characteristics and other factors, and caution should be exercised when comparing data across unrelated studies

Source:

Mita N, Iwashita T, Uemura S, Yoshida K, Iwasa Y, Ando N, Iwata K, Okuno M, Mukai T, Shimizu M. Second-Line Gemcitabine Plus Nab-Paclitaxel for Patients with Unresectable Advanced Pancreatic Cancer after First-Line FOLFIRINOX Failure. J Clin Med. 2019 May 29;8(6):761. doi: 10.3390/jcm8060761. PMID: 31146420; PMCID: PMC6616879

Huh G, Lee HS, Choi JH, Lee SH, Paik WH, Ryu JK, Kim YT, Bang S, Lee ES. Gemcitabine plus Nab-paclitaxel as a second-line treatment following FOLFIRINOX failure in advanced pancreatic cancer: a multicenter, single-arm, open-label, phase 2 trial. Ther Adv Med Oncol. 2021 Nov 10;13:17588359211056179. doi: 10.1177/17588359211056179. PMID: 34790261; PMCID: PMC8591648.

Portal A et al. Nab-paclitaxel plus gemcitabine for metastatic pancreatic adenocarcinoma after Folfirinox failure: an AGEO prospective multicentre cohort. Br J Cancer. 2015 Sep 29;113(7):989-95. doi: 10.1038/bjc.2015.328. Epub 2015 Sep 15. PMID: 26372701; PMCID: PMC4651133.

Pancreatic Cancer Clinical Trial: USA Pilot

N=12

Newly Diagnosed
Metastatic Pancreatic Cancer

AlphaDaRT
Insertion
(During Cycles 1-4)

8-12 cycles of **mFOLFIRINOX**

1

Primary Endpoint:
Incidence of Treatment-Emergent Adverse Events

2

Secondary Endpoints:
Overall Survival
Progression-Free Survival
Pain Improvement

Pancreatic Cancer Clinical Trial: French Multicenter

N=40

LAPC
Treated with
mFOLFIRINOX

Screening

Alpha DaRT

Capecitabine
850mg/m² BID
(28 days)

FOLLOW-UP up to 12 months
until EOT or tumor progression*

1

Primary Endpoint
Safety

2

Secondary Endpoints

- Objective Response Rate based on Best Overall Response
- Overall Survival
- Progression Free Survival
- Resectability rate

Only patients with stable disease or tumor response according to RECIST 1.1 after mFOLFIRINOX are eligible for the trial

Blood samples for PBMC and ctDNA analysis before Alpha DaRT, and every 2 months EOT

CT-scan (RECIST 1.1) every 8 weeks

***Therapeutic options (investigator's choice):**
Tumor response/stability:

- Surgery if resectable disease
- Therapeutic pause

Tumor progression: 2nd line chemotherapy or Best Supportive Care

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Disclosures:
Consultant for Alpha Tau Medical

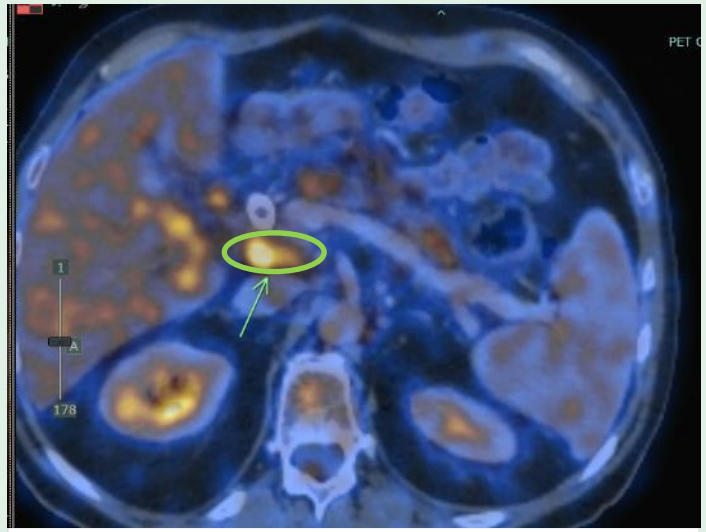
First Pancreatic Cancer Patient with CR – ALL-00-HA-006

- **Patient Background:**
  - 70yo male with pancreatic adenocarcinoma metastatic to the liver
  - Treated by FOLFIRINOX May-Nov 2023 but demonstrated progressive disease
  - Treated by Gemcibatine + Abraxane from Dec 2023, demonstrated progression at primary tumor but otherwise stable disease
  - Treated with Alpha DaRT in Jan 2024, together with continued chemotherapy

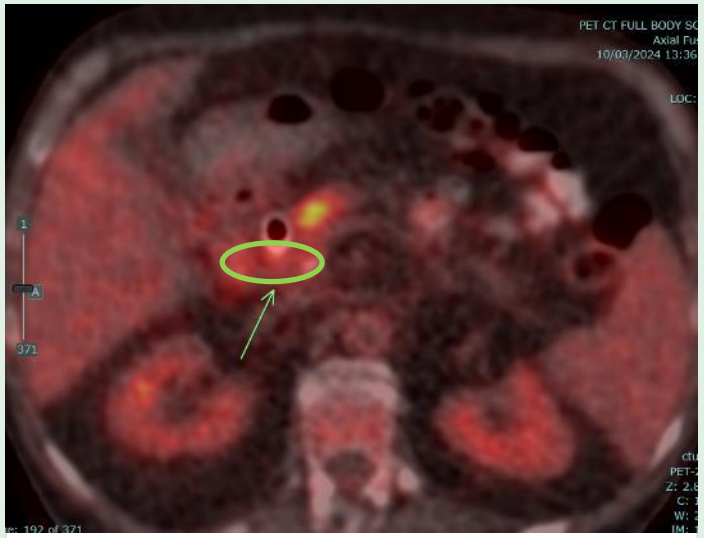
- **Observed Response:**
  - Interim 30-day PET scan demonstrated positive response in radiated tumor but seeming continued liver metastasis
  - **90-day PET showed complete response in primary tumor and resolution of liver metastasis**

First Pancreatic Cancer Patient with CR – Pancreatic Tumor Response

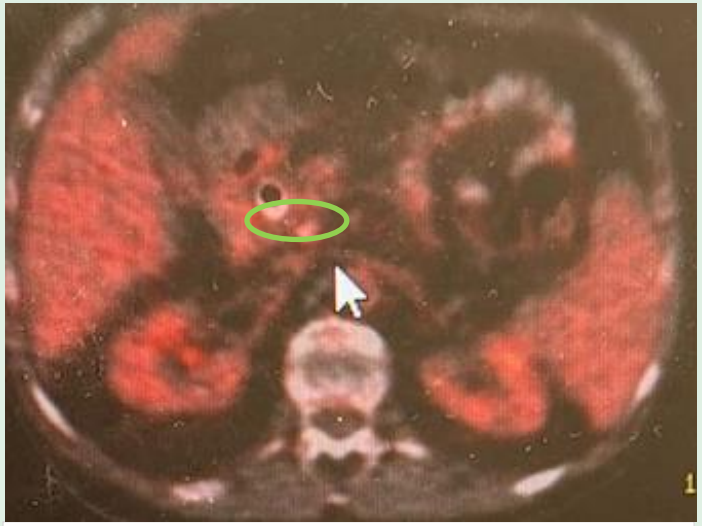
PET of the pancreatic tumor after 30 days demonstrates minimal SUV uptake at lesion, potential post-treatment inflammation distal to treated lesion. PET after 90 days demonstrates no PET activity and no further inflammation



Before
23-Nov-2023



>30 Days Post Treatment
10-Mar-2024



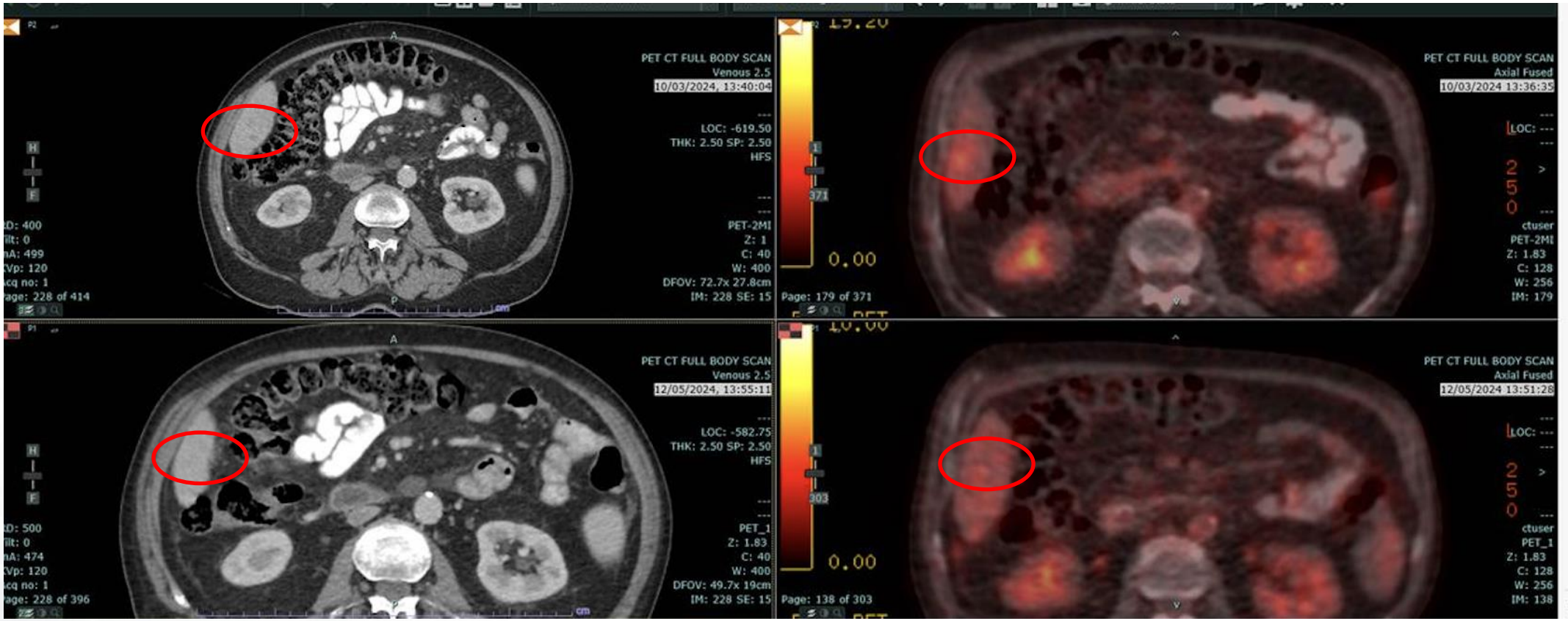
>90 Days Post Treatment
12-May-2024

First Pancreatic Cancer Patient with CR – Liver Metastasis Response

After 90 days post treatment, the lesion no longer remains evident on PET despite no change in systemic therapy, and cancer markers have dropped significantly

>30 Days Post Tx 10-Mar-2024

>90 Days Post Tx 12-May-2024



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EUS-Guided Alpha DaRT Insertion: A Novel Treatment for Pancreatic Cancer

Corey Miller, MD, MSc

Jewish General Hospital
Lady Davis Institute for Medical Research

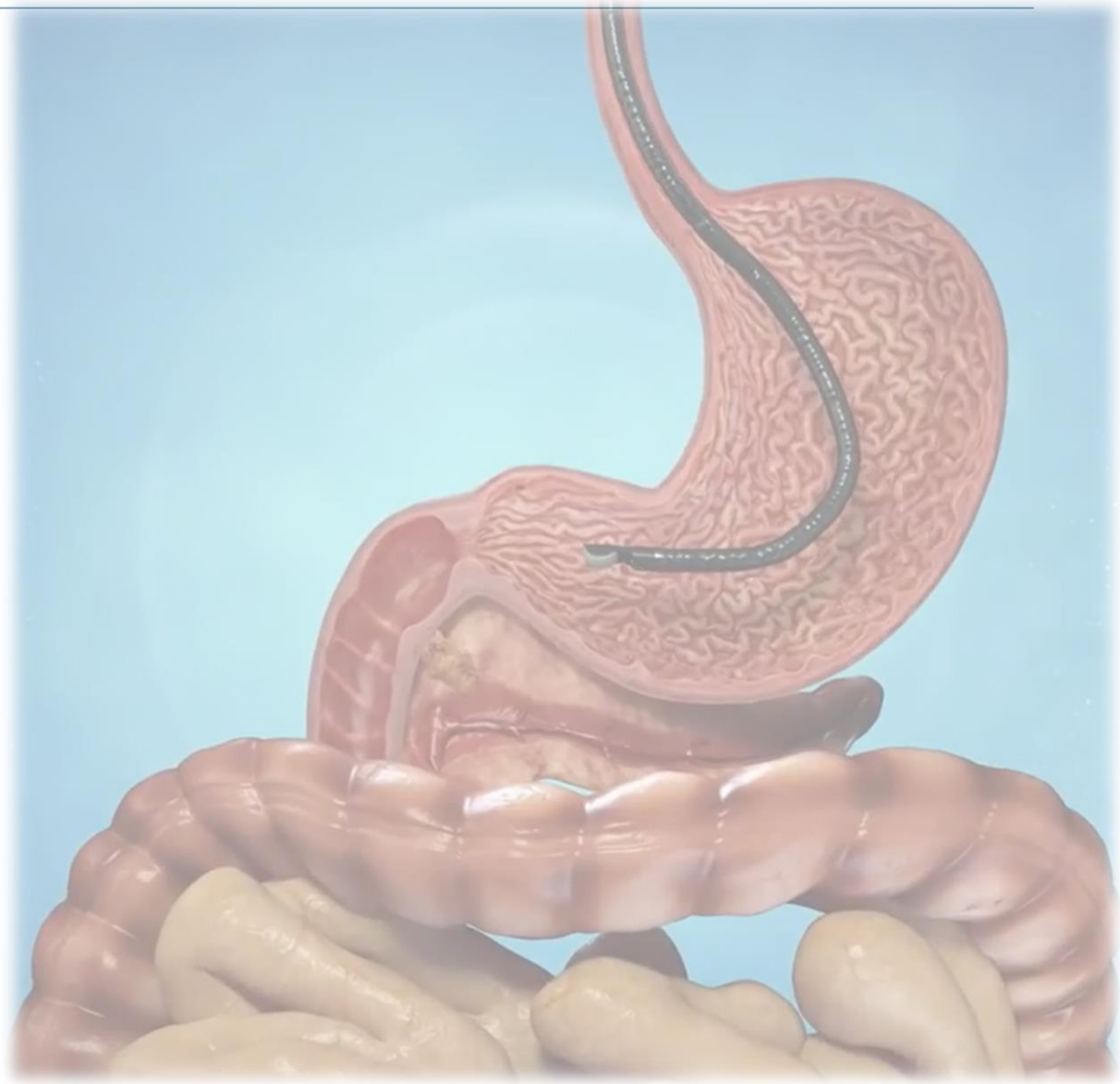
MCTRC
McGILL CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER

Disclosures:
Consultant for Alpha Tau Medical
Consultant for Boston Scientific

Background

PANCREATIC CANCER

- Endoscopic ultrasound provides best access to pancreas and provide pathologic diagnosis
- Currently, surgical resection is the only potentially curative treatment, but only 15-20% of patients are candidates
- **In non-resectable patients there is NO STANDARD LOCAL TREATMENT**
- Morbidity from local symptoms (blockages, **pain**)



Alpha Tau Loading Device

https://www.youtube.com/watch?v=Ws6ey-lvo38

Procedure Setup

Insertion

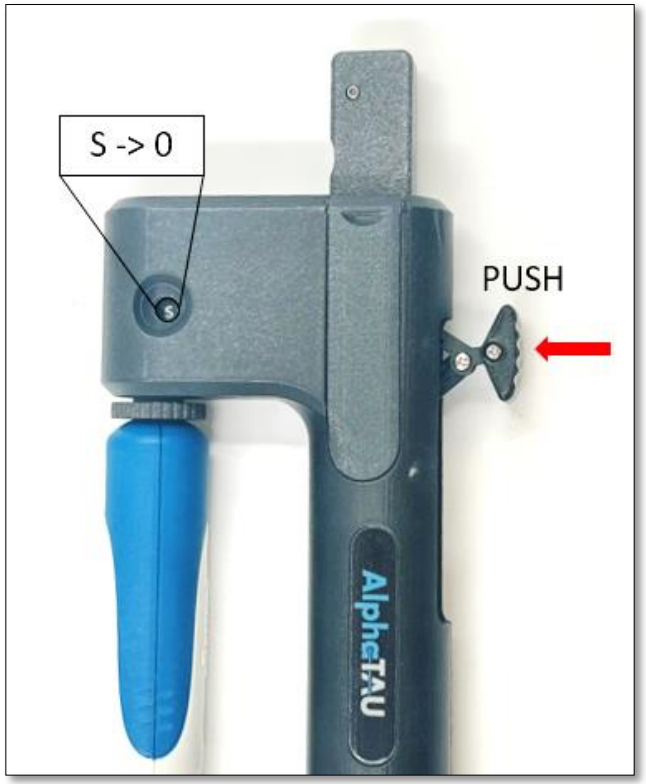
Image: Flaticon.com

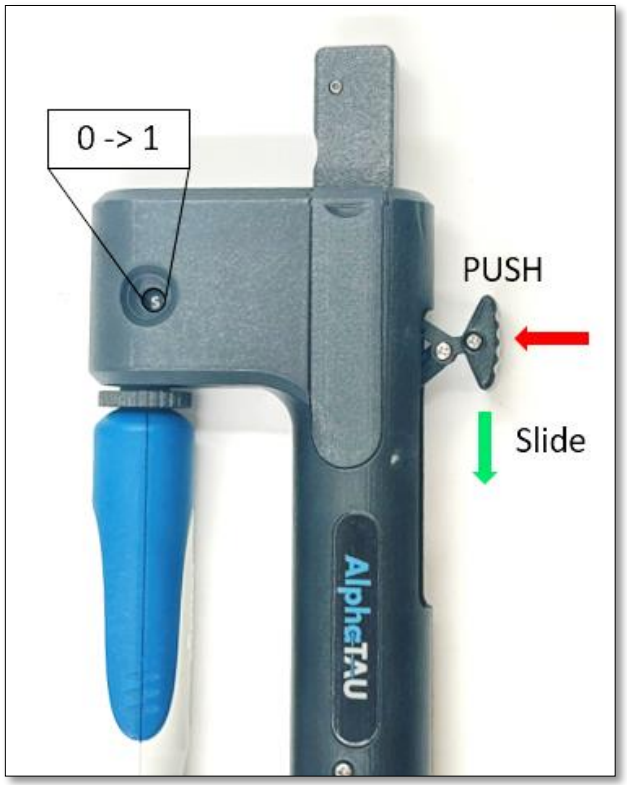
Adjustable Stopper

- “Standard” technique
- User-friendly
- Same “feel” as standard FNA

Retraction Handle

- Allows 4 Alpha DaRT sources to be delivered with one pass
- Time efficiency
- Especially when more challenging to reach





Endoscopist Experience

- Natural extension of the skillset of a trained EUS specialist
- EUS-guided biopsy, celiac plexus neurolysis
- Technique is intuitive
- Confidence in safety outcomes
- Procedure length not prohibitive ➔
- ~45 minutes
- Room setup only modestly longer after brief learning curve
- Barrier to adoption is low

A Word on Radiation Safety

For the **endoscopist** and **technologist** directly handling the scope, for the first 5 patients:

- The **max doses on skin** was between **0.8-1.6 µSv**
- The **max dose at 10 mm from skin** was between **0.2-0.7 µSv**

CNSC limits: Equivalent dose to the skin annual limit 500 mSv (i.e., 500,000 µSv) for nuclear energy workers and 50 mSv (i.e., 50,000 µSv) for the public

We could perform over 25,000 cases like these before reaching the annual limit for members of the public

Patient Experience

Outpatient procedure

Minimally invasive

Discharged Same Day

100% discharged after standard endoscopy recovery

Good Safety Profile

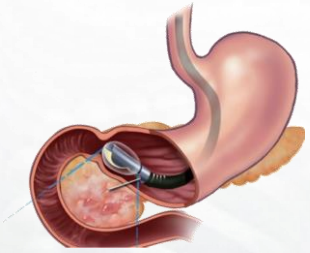
- Few important related adverse events
- Mostly minor discomfort
- Vast majority with no related symptoms

Lack of tumor growth in vast majority

Pain relief within a few days

Grant: Moving Forward

- Development of an **augmented reality-based navigation model** that allows the operator to visualize the anatomy of interest, thus **enhancing Alpha DaRT delivery**.
- In collaboration with Concordia University **computer science, bioimaging, engineering and Alpha Tau's Technology team**



Indication
Pancreatic cancer
Procedure
Endoscopic Ultrasound

MCTRC
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Jewish General Hospital
Lady Davis Institute for Medical Research

MEDTEQ+

Partenaire financier :
Québec

INSTITUT TRANSMEDTECH MONTRÉAL

Mitacs Accelerate

UNIVERSITÉ Concordia UNIVERSITY

Team Work Makes the Dream Work!

Final Thoughts

- Endoscopists engage pancreatic cancer patients early on the patient journey
- The Alpha DaRT insertion is straightforward to integrate into our clinical workflow
- Given the safety profile, the incorporation of Alpha DaRT insertion into non-resectable cases is quite promising to become standard of care
- Patient benefit through pain relief, stabilization of disease
- Need to consider incorporation of Alpha DaRT in management of metastatic lesions as primary tumor is under better local control

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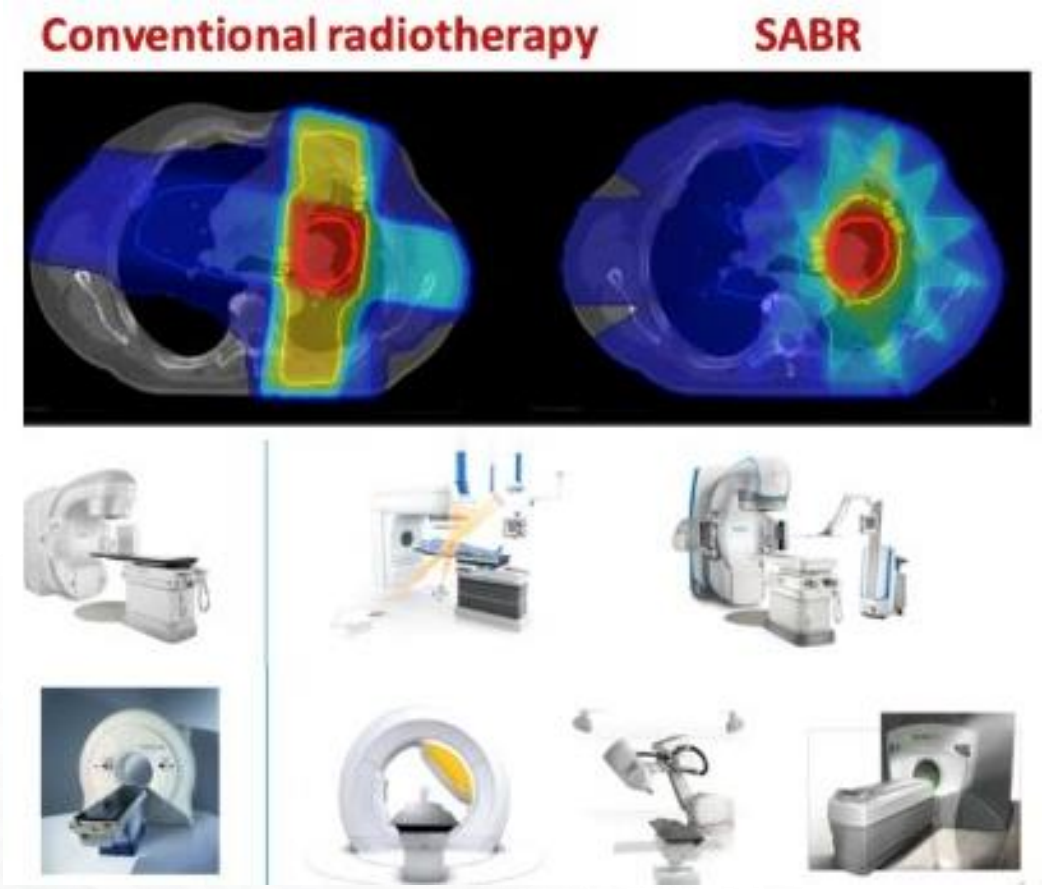
Clinical Challenges in Reirradiation

- **The treatment of recurrent or new primary cancers within or in close proximity to previously irradiated tissue is a clinically challenging problem due to tissue tolerance concerns:**
  - Reirradiation with SBRT for ultracentral lung tumors (such as the mediastinum) carries a high risk of severe toxicity, including pneumonitis, esophagitis, and fatal hemoptysis.
  - Reirradiation in the pelvis, such as rectum, carries high risk of rectal dysfunction, nerve damage, fibrosis

- **Balancing the need to *optimize tumor control* while *minimizing adverse effects* is much more difficult when dealing with prior radiation therapy.**

- **In such scenarios, options include non-curative systemic therapy or reirradiation with conventional or advanced techniques (SBRT or Proton Beam Radiotherapy)**

Current treatment options for recurrent thoracic cancers after previous radiation: SBRT

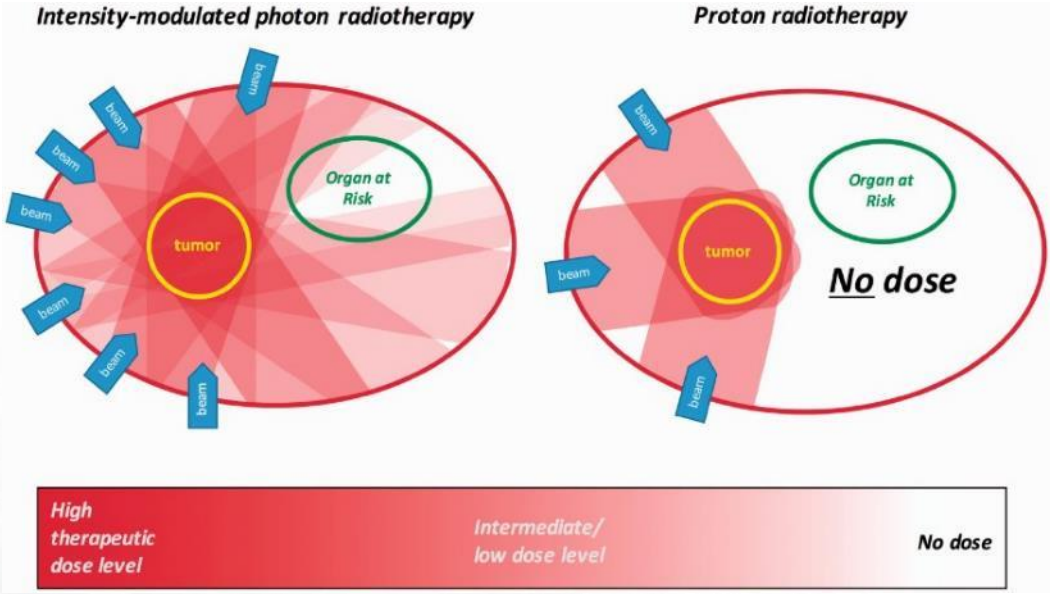


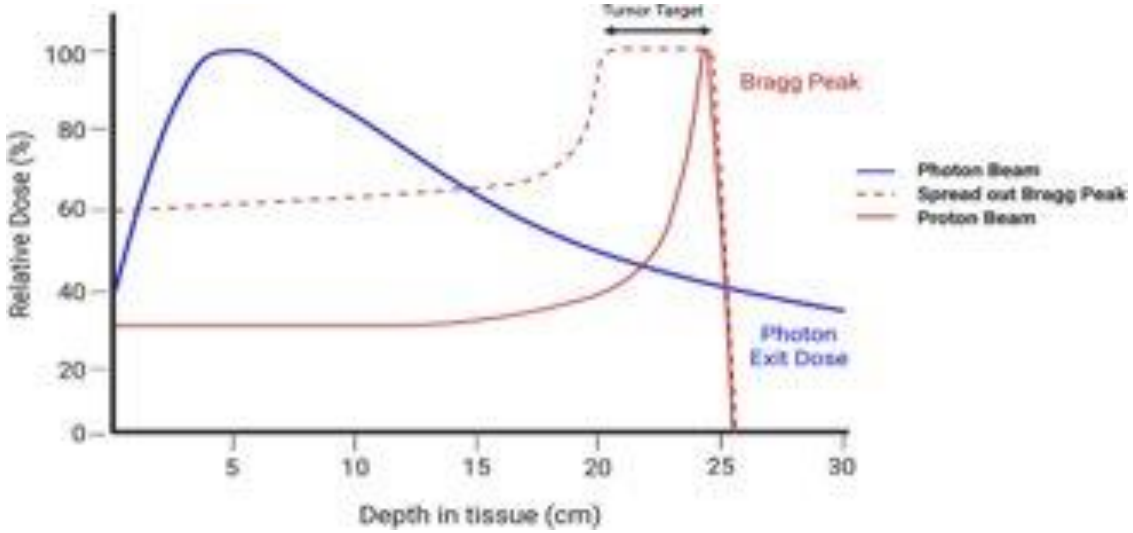
- Sood et al. reported 35% of patients experienced grade 2+ pneumonitis, and 10% had fatal hemorrhage, though likely unrelated to treatment.
- Rock et al. found 20% of patients had grade 2+ pneumonitis, and 12% experienced grade 3+ toxicity, including three cases of fatal hemoptysis.
- Peulen et al. linked SBRT reirradiation for central tumors to severe toxicity, including grade 5 massive bleeding.
- Despite good local control, reirradiation for ultracentral tumors requires cautious patient selection and meticulous dose planning.

- Ultra-Central Thoracic Re-Irradiation Using 10-Fraction Stereotactic Body Radiotherapy for Recurrent Non-Small-Cell Lung Cancer Tumors: Preliminary Toxicity and Efficacy Outcomes.Sood S, Ganju R, Shen X, Napel MT, Wang F. Clinical Lung Cancer. 2021;22(3):e301-e312.
- Ten Fraction Hypofractionated Stereotactic Body Radiotherapy for the Management of Ultracentral Lung Tumors: A Retrospective Analysis of Dosimetry, Outcomes, and Toxicity.Rock C, Sood S, Cao Y, et al. Radiation Oncology (London, England). 2023;18(1):128.
- Toxicity After Reirradiation of Pulmonary Tumours With Stereotactic Body Radiotherapy.Peulen H, Karlsson K, Lindberg K, et al. Radiotherapy and Oncology : Journal of the European Society for Therapeutic Radiology and Oncology. 2011;101(2):260-6.

Current treatment options for recurrent cancers after previous radiation: Proton Therapy

- Despite the advantages, proton therapy is not without risks. Chao et al. reported that 42% of patients experienced grade 3 or higher acute and/or late toxicity, with six grade 5 toxicities observed.
- Increased overlap with the central airway region and concurrent chemotherapy were associated with higher toxicity rates.
- Local failure following radiation remains a problem (close to 25-40%)



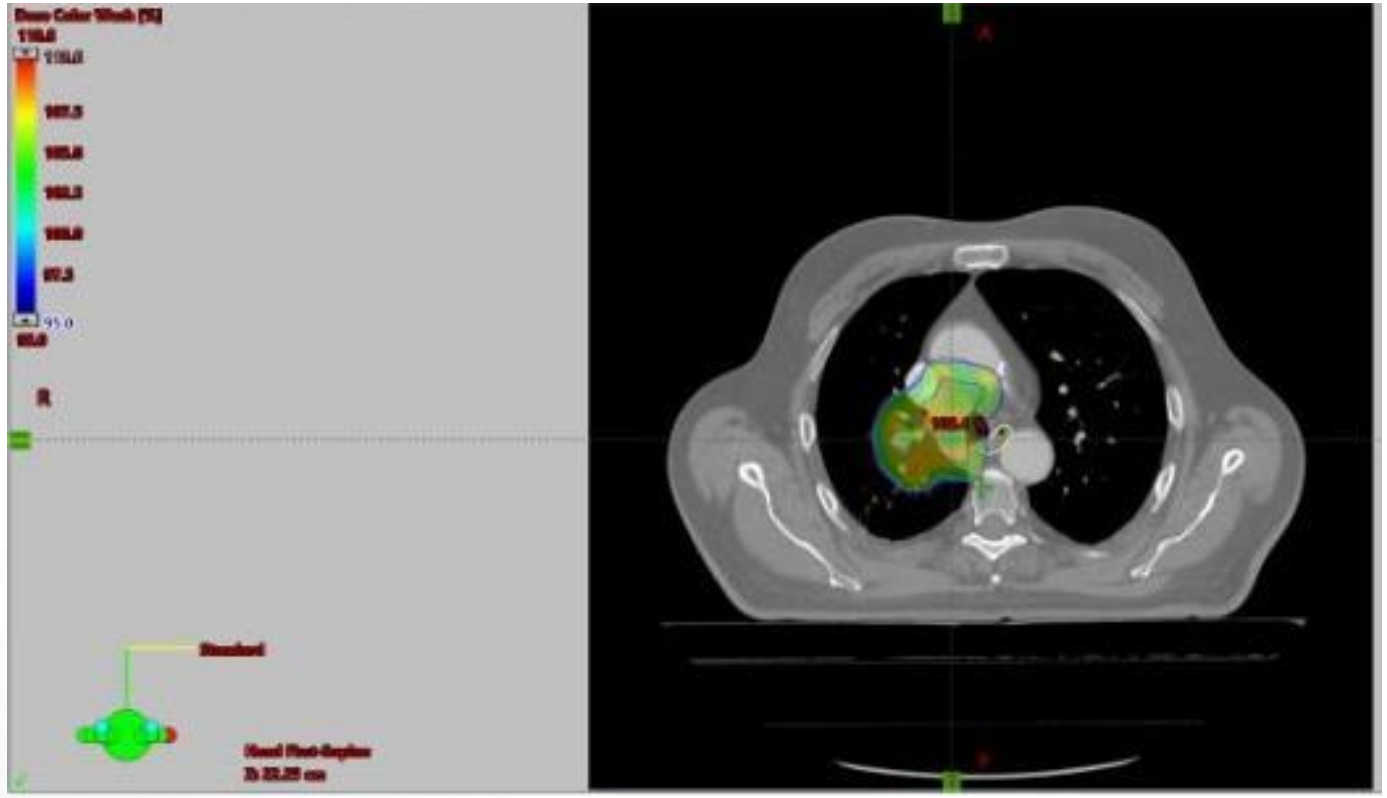


- Multi-Institutional Prospective Study of Reirradiation With Proton Beam Radiotherapy for Locoregionally Recurrent Non-Small Cell Lung Cancer.Chao HH, Berman AT, Simone CB, et al. Journal of Thoracic Oncology : Official Publication of the International Association for the Study of Lung Cancer. 2017;12(2):281-292.
- Feasibility of Proton Beam Therapy for Reirradiation of Locoregionally Recurrent Non-Small Cell Lung Cancer. McAvoy SA, Ciura KT, Rineer JM, et al. Radiotherapy and Oncology : Journal of the European Society for Therapeutic Radiology and Oncology. 2013;109(1):38-44.
- Definitive Reirradiation for Locoregionally Recurrent Non-Small Cell Lung Cancer With Proton Beam Therapy or Intensity Modulated Radiation Therapy: Predictors of High-Grade Toxicity and Survival Outcomes. McAvoy S, Ciura K, Wei C, et al. International Journal of Radiation Oncology, Biology, Physics.

Lung Cancer Case Study

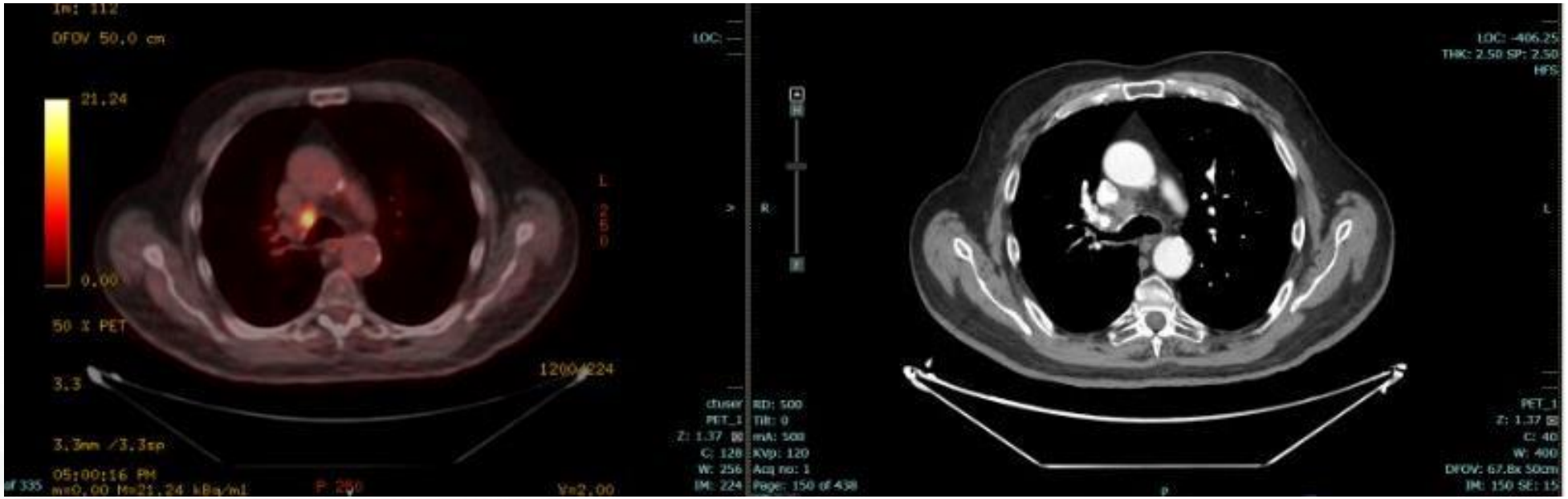
Locally Recurrent Lung Cancer Case Study (1/5)

70-year old male with limited stage small cell lung cancer received external radiation to the lung primary and mediastinum completing August 2023 with concurrent chemotherapy



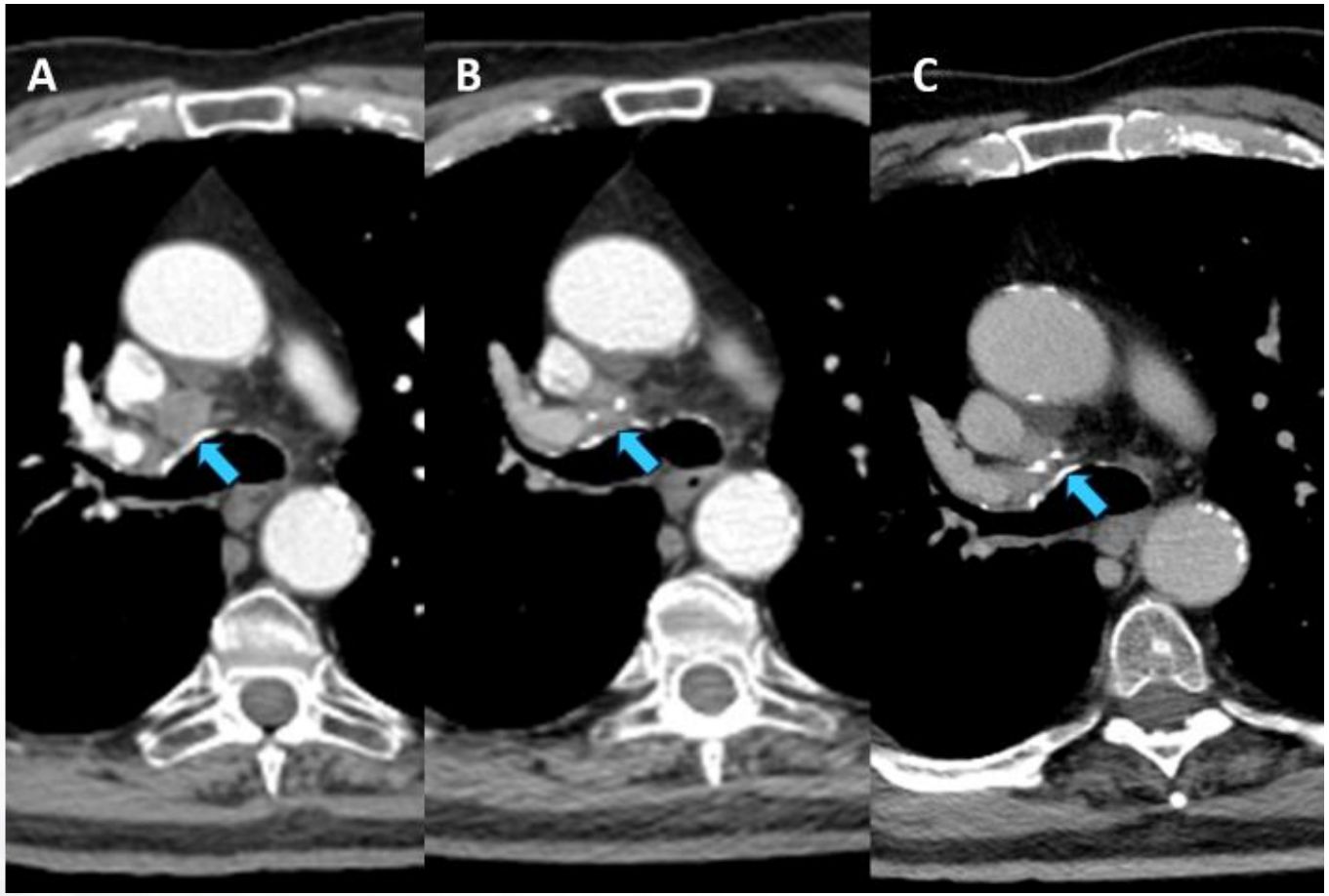
Locally Recurrent Lung Cancer Case Study (2/5)

- Metastatic progression 6 months post treatment s/p chemotherapy and palliative external radiation to several locations with good response
- PET-CT in August 2024 demonstrated enlarged and uptake of paratracheal node (mediastinum), SUV 9 which was in region of high dose radiation
- Patient referred for Alpha DaRT trial (NCT05632913)



Locally Recurrent Lung Cancer Case Study (3/5)

Scans of the first patient treated with Diffusing Alpha-emitters Radiation Therapy (Alpha DaRT) for recurrent lung cancer



A. Baseline B. 30-day follow-up C. 60-day follow-up

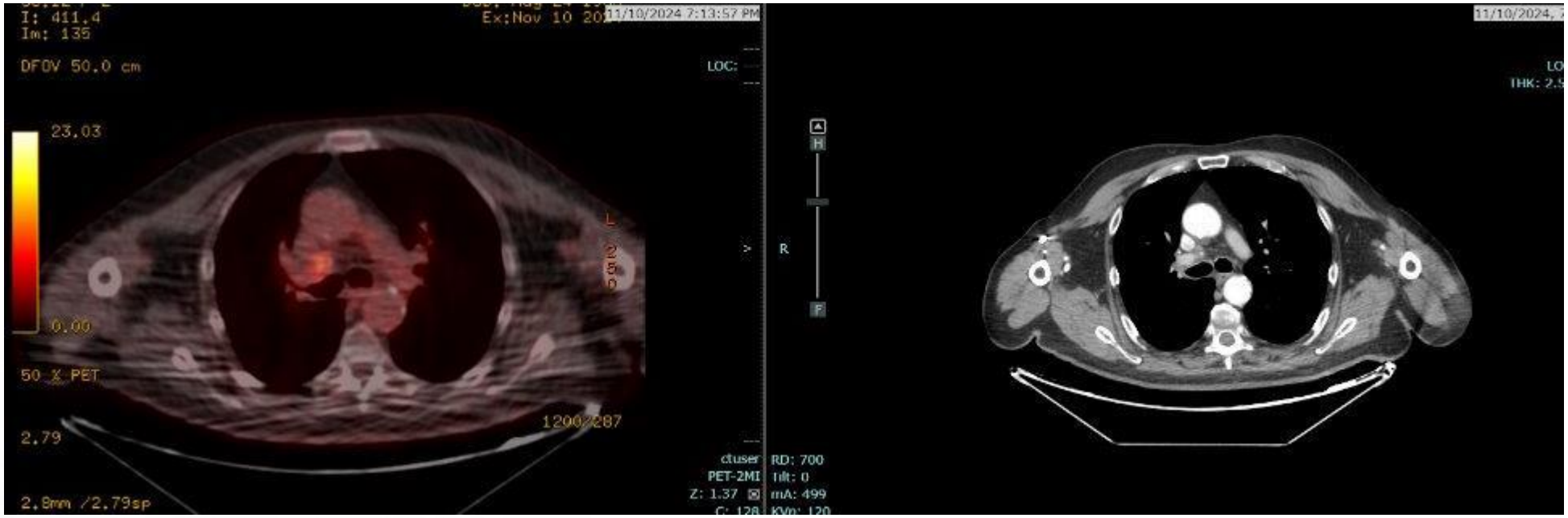
- 10 Alpha DaRT sources were implanted into the paratracheal lymph node (4R station, arrow)
- The lymph node's initial volume was 3.6 cm^3, which reduced to 2.1 cm^3 at 30 days and 1.7 cm^3 at 60 days post-procedure
- The Alpha DaRT sources are visible within the treated lesion as white region in panels B and C

Change in volume of irradiated lymph node metastasis		
Baseline	30-day follow-up	60-day follow-up
3.6 cm^3	2.1 cm^3	1.7 cm^3
Percent Change	**(41.6)%**	**(52.7)%**

52.7% Decrease in Tumor Volume at two months

Locally Recurrent Lung Cancer Case Study (4/5)

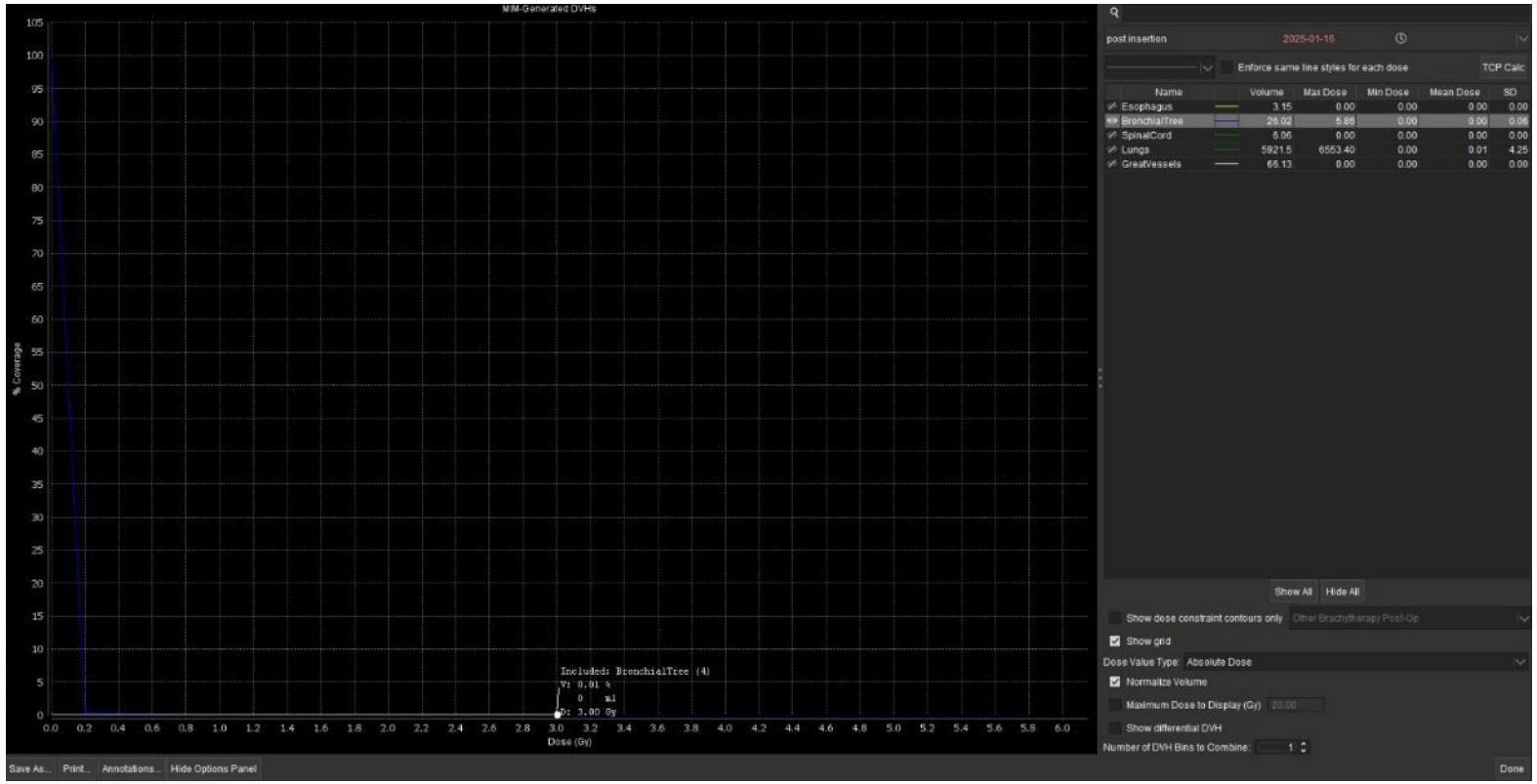
Post-treatment PET-CT (60 days)



Initial reduction in PET SUV to 7

Locally Recurrent Lung Cancer Case Study (5/5)

Dose to Normal Organs

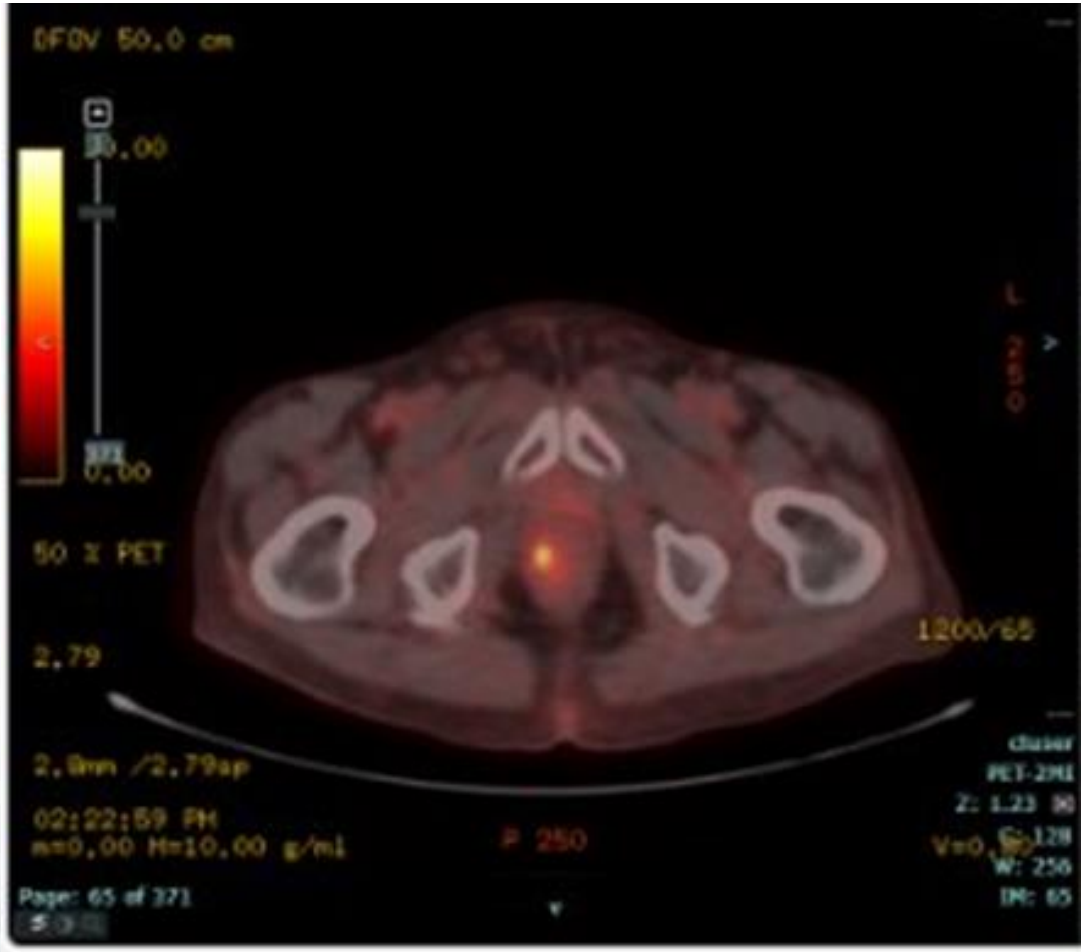


No treatment-related adverse events following the radiation treatment

Rectal Cancer Case Study

Locally Recurrent Rectal Cancer Case Study (1/2)

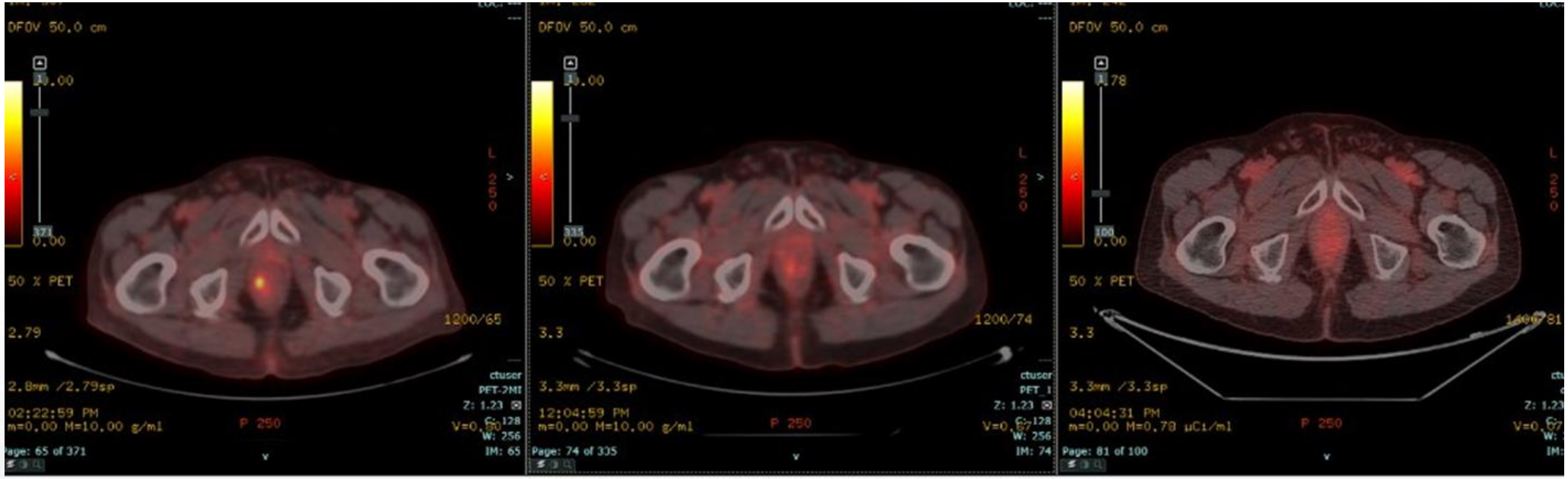
70-year old male presented to our institution after undergoing chemoradiotherapy followed by chemotherapy for a low-lying rectal adenocarcinoma



- PET and exam demonstrated residual tumor at the rectum, involving sphincter approximately 3 cm
- APR recommended, patient declined

Locally Recurrent Rectal Cancer Case Study (2/2)

- In September 2022, patient underwent Alpha DaRT insertion
- Exam was normal in March 2023
  - PET-CT SUV uptake: 4
- Exam was normal in March 2024
  - PET-CT SUV uptake: none
- Patient denies any bowel or bladder issues



No treatment-related adverse events

Conclusion

Despite the high risk associated with reirradiation, initial cases of reirradiation of internal organs (lung, rectum) using **Alpha DaRT demonstrate high efficacy potential and minimal toxicity**

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Outline of Liver Metastases Study - CTP-LIV-00

Primary objectives: Evaluate feasibility & safety of Alpha DaRT implanted in liver metastases

Secondary / exploratory objectives: Evaluate pathological and radiological response, determine immunological impact, stratify differences in response by histopath. growth patterns (vascular / immuno.)

Key Eligibility Criteria

Referred for a **two-staged hepatectomy** to resect liver metastases of colorectal cancer

No prior use of **systemic investigational agents** for primary cancer

Sample size N = 10 patients

Treatment and Procedure

Treatment plan based on CT scan or MRI

Sources 0.7 mm in diameter and 1 cm in length

Activity per source 3 µCi

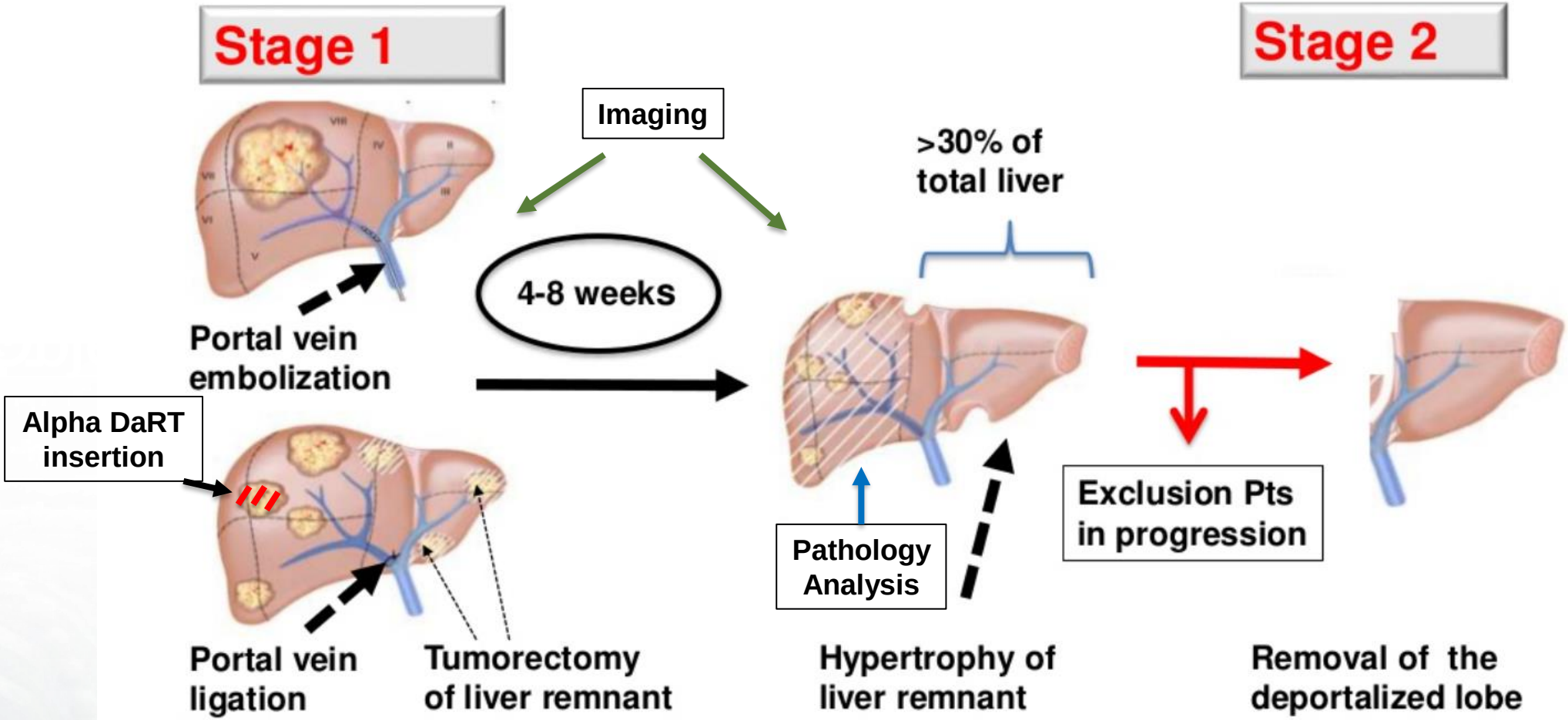
General anesthesia

Timeline

- **1st operation:** one side of the liver is cleared from its metastases & Alpha DaRT sources are implanted in the other side of the liver
- 3 - 4 cycles of **chemotherapy** (6 - 8 weeks)
- **2nd operation:** The liver lobe containing the metastasis with the sources is resected, to leave the patient with a disease-free liver

Study Schema

Liver study



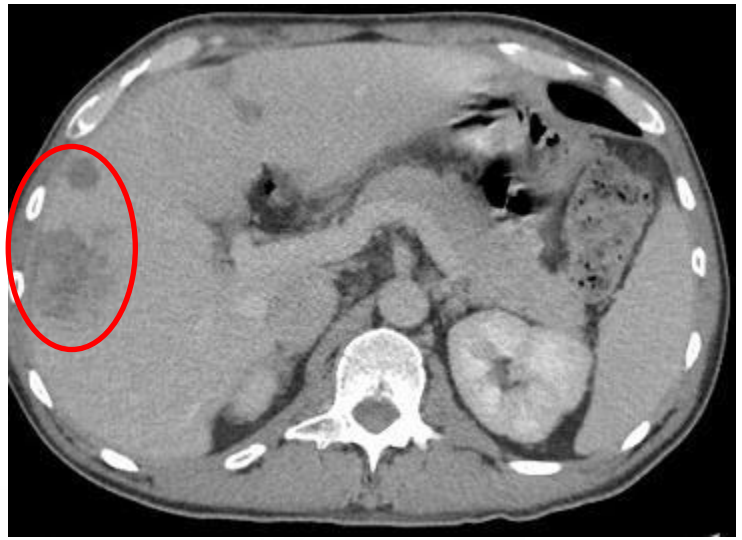
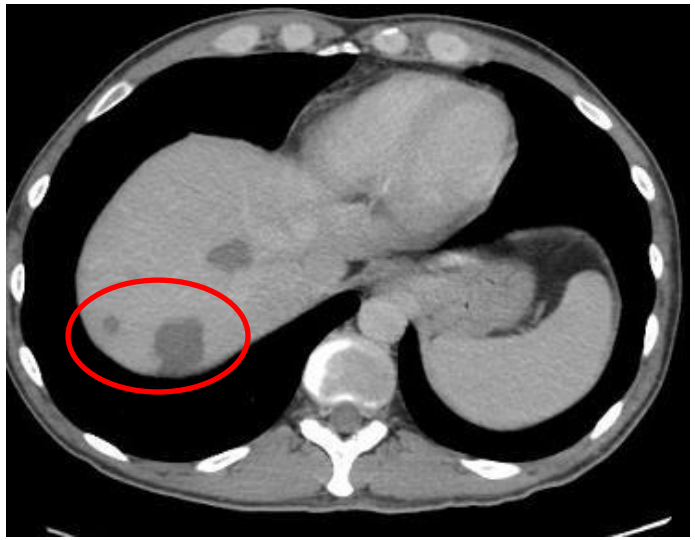
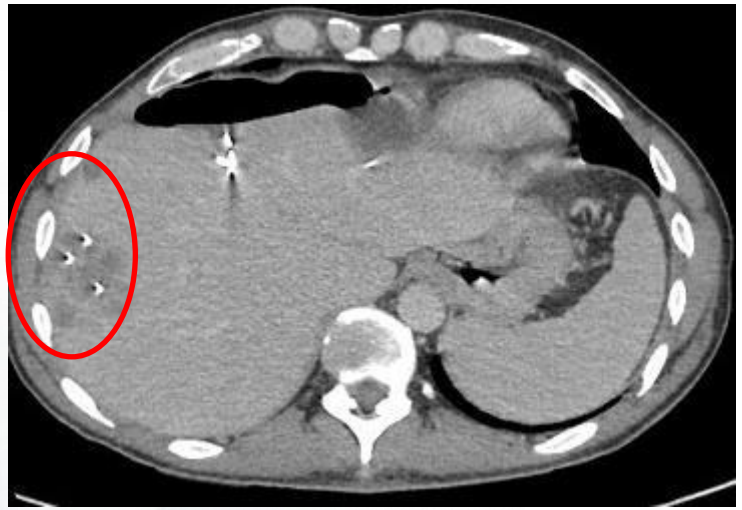
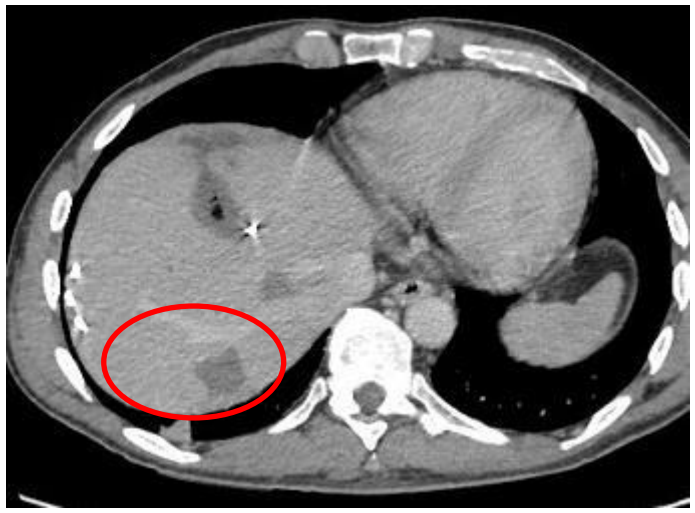
Clavien et al. Strategies for safer liver surgery. NEJM, 2017

First Patient Treated for Liver Cancer

- **Patient Background:**
  - 48yo male with bilateral liver colorectal metastases
  - The patient was off chemotherapy for 8 weeks prior to surgery
  - First stage of two-stage hepatectomy performed on May 9, 2024, with resection of primary colorectal tumor (sigmoidectomy), colorectal liver metastases resected from liver segments 2 and 4, and 25 Alpha DaRTs implanted into a lesion in liver segment 8 (~6% coverage of GTV)

- **Observations at Day 7 scan and follow-up:**
  - Patient doing well, no signs of distress or dyspnea, no clear jaundice
  - **Treated lesion in segment 8 reduced in dimension from 6.0 cm length to 4.9 cm length**
  - **Largest untreated lesion also regressed – the largest hepatic metastatic lesion in segment 7 reduced in dimension from 4.0 cm to 2.9 cm**
  - No newly developed hepatic lesions, portal and hepatic veins remain patent

First Patient Treated for Liver Cancer – CT Scans

	Treated Lesion	Untreated Lesion
Before Tx 24-Apr-2024		
Post Tx 23-May-2024		

Post-Treatment Clinical Course

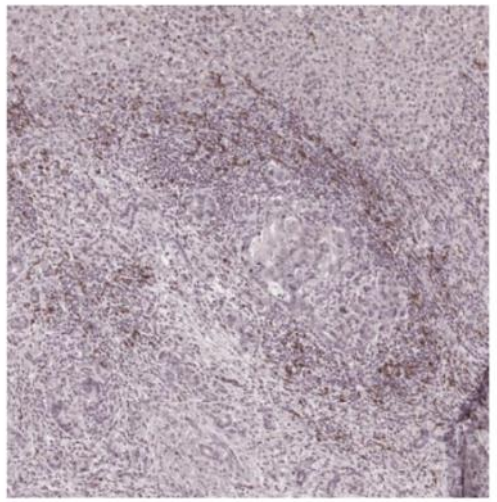
- Second surgery conducted on 17-Jun-2024, 5 weeks after initial operation): right liver was resected, including the Alpha DaRT-treated lesion
- No significant complications or unexpected events during the post-operative period
- The patient was discharged as planned
- Recovery post-discharge was uneventful, without any complications

- Histopathological observations:
  - Treated tumor was non-desmoplastic
  - Adjacent (non-treated but responding) tumor was desmoplastic
  - Minimal to no damage observed in the surrounding liver parenchyma

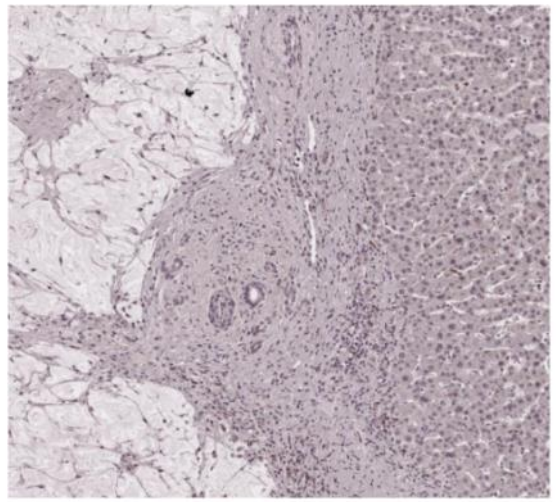
Adjacent liver parenchyma appears viable and normal

Adaptive Immune Response

- Increased infiltration of CD8+ T cells in the right liver lesions (both treated and untreated), particularly at the tumor margin of the Alpha DaRT-treated lesion
  - Despite the temporal distance from chemotherapy
- This observation may support our hypothesis that enhanced antigen exposure induced by the Alpha DaRT sources can activate cytotoxic T cells
- This heightened response was reflected in the increased abundance of cytotoxic T cells (CD8) at the Alpha DaRT-treated tumor margin, as well as higher levels of helper T cells (CD4) and B cells (CD20)
- This is not typical for non-desmoplastic tumors, which tend to have a more innate immune microenvironment, and may be explained by the presence of Alpha DaRT in this tumor



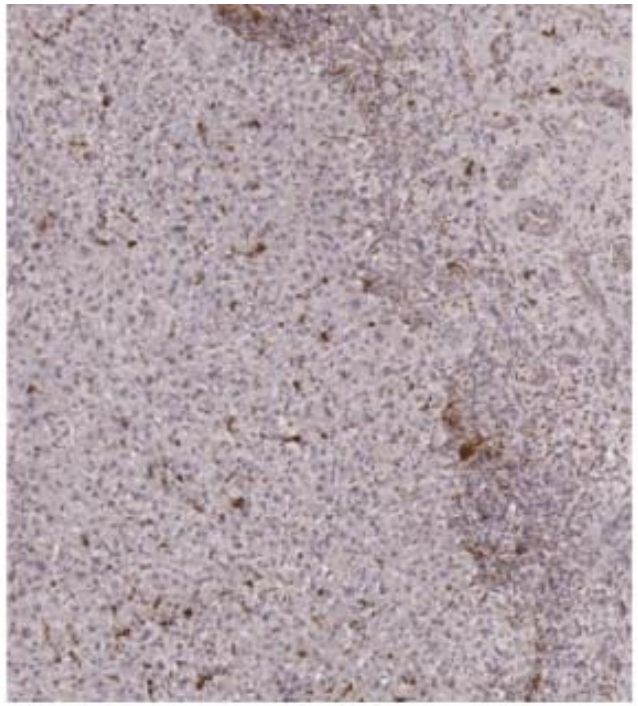
Right sided liver tumor (Alpha DaRT-treated)
CD8 cells cluster at the liver-tumor margin in a right-sided liver tumor



Right sided liver tumor, not treated with Alpha DaRT (liver/tumor margin)
Significant tumor necrosis can be visualized

Innate Immune Response

- The innate immune response displayed a mixed pattern in the Alpha DaRT-treated tumor, with a notable increase in dendritic cells and neutrophils but a lower abundance of macrophages compared to the untreated tumor
- This finding is significant, particularly in light of research in mouse models showing that macrophages can contribute to CD8 T cell apoptosis and increased resistance to immunotherapy



Alpha DaRT-treated tumor
Low levels of CD68 stain are seen in the tumor

Case Summary

- The implantation of (Alpha DaRT) was performed without significant technical difficulties
- **No adverse events** related to Alpha DaRT treatment were observed throughout the clinical course of the patient
- **There was no evidence of source migration**, and complete removal of all Alpha DaRT sources from the liver was confirmed during the second hepatectomy
- No safety concerns were observed regarding the insertion of Alpha DaRT source for either the medical staff, nursing staff, or the patient
- No instances of excessive hemorrhage
- The patient's **recovery followed a normal trajectory**, and the postoperative course was consistent with expectations for liver resection
- The **adaptive immune response appeared more pronounced** in the Alpha DaRT-treated tumor
- Reduced macrophages **may indicate reduced immune suppression** and corresponds to the preclinical findings
- **Decrease in the tumor size was observed in the untreated adjacent lesion** despite long period without chemotherapy

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Disclosures:
Consultant for Alpha Tau Medical

Outline of Checkpoint Inhibitor Combination Trial – CTP-HNCPI-00

Key Eligibility Criteria

Recurrent unresectable or metastatic head and neck squamous cell carcinoma (like KEYNOTE-048)

No **previous treatment for metastatic disease**

Trial Objectives

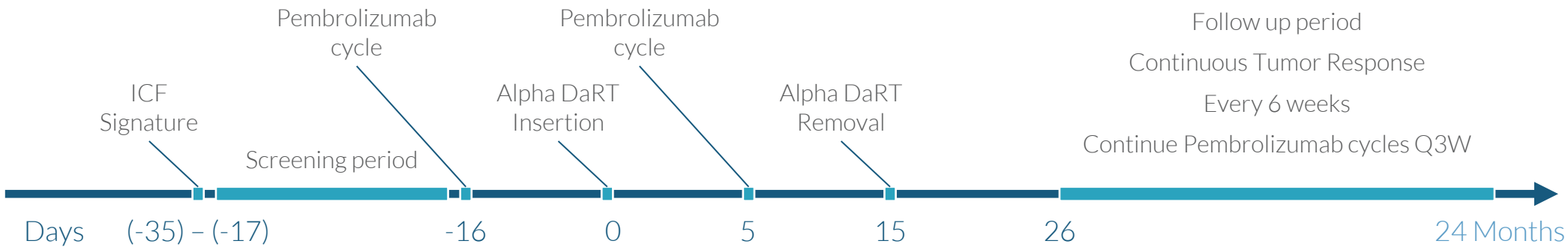
- **Primary objective:** Evaluate confirmed Best Overall Response (BOR) per RECIST version 1.1
- **Secondary objectives:** Evaluate Safety, Progression Free Survival (PFS), Overall Survival (OS) and Duration of Response (DOR)

Two-Stage Adaptive Design

- Using the H_1 optimal EF design, **in the first stage 18 patients are evaluated: if no more than 2 patients respond, then terminate the trial for futility, if more than 6 patients respond then stop the trial for success**
  - Otherwise, accrual continues to a total of 43 patients
  - Allowing for a 10% loss to follow-up, we may recruit up to 48 patients to the study
- **We would conclude that the treatment is effective if more than 12 of the 43 patients have a BOR of CR, PR, or SD**

Note: Sample size calculated for this trial design assuming $p_1 = 35\%$ and $p_0 = 20\%$ for power $(1 - \beta)$ of 80%, and α of 10%

Treatment Regimen and KEYNOTE-048 Benchmark

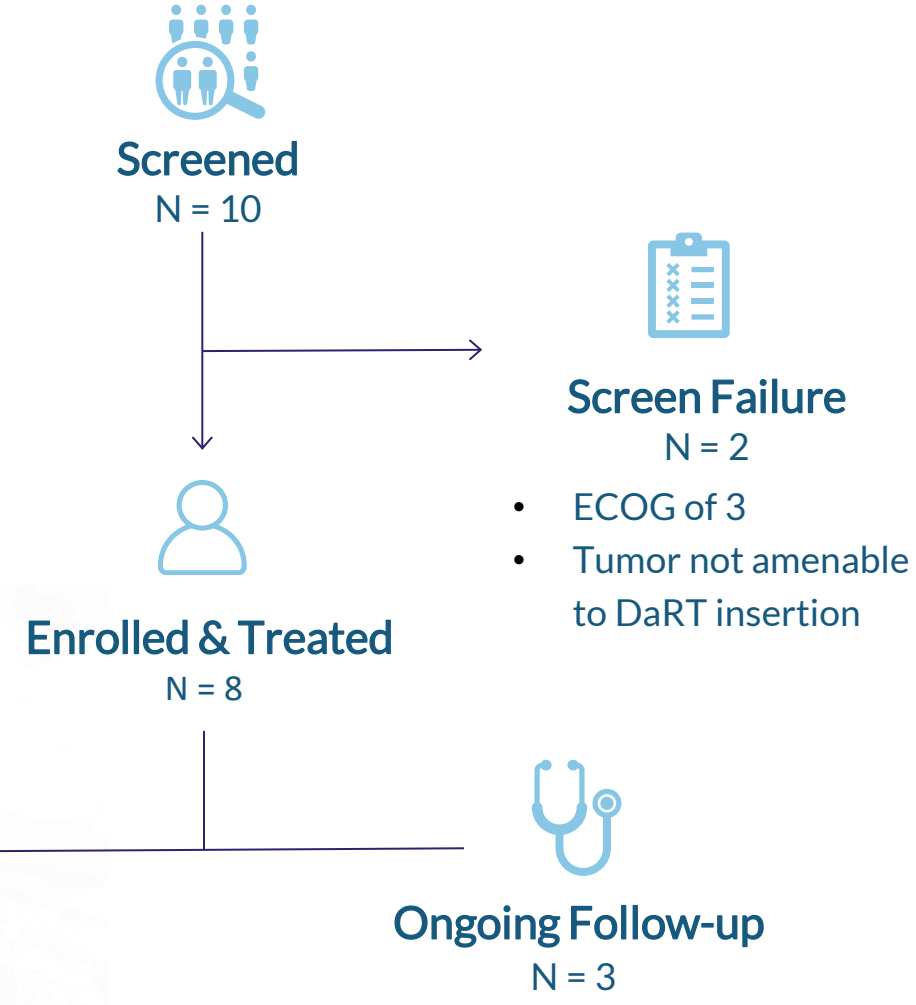


KEYNOTE-048: Benchmark comparator data for 1L Pembrolizumab in patients with recurrent or metastatic HNSCC

Population	Benchmark Regimen	Systemic ORR	Systemic CR %
PD-L1 CPS ≥ 20	Pembrolizumab Alone	23%	8%
PD-L1 CPS ≥ 1	Pembrolizumab Alone	19%	5%
Total population	Pembrolizumab Alone	17%	5%

Source: Burtness, B. et al (2019). Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. The Lancet. doi:10.1016/s0140-6736(19)32591-7
Note: Benchmark data provided for illustrative purposes only. Not a head-to trial.

Subject Disposition



Demographics and Tumor Characteristics

Subject ID	Age	Sex	Stage	Alpha DaRT Target Tumor Location	Tumor Volume (cm^3)
HNCPI-00-01-001	74	Male	Stage IV	Neck	2.6
HNCPI-00-01-002	90	Male	Stage IV	Tongue	4.7
HNCPI-00-01-003	96	Female	Stage IV	Mandibular alveolus	7.6
HNCPI-00-01-004	63	Female	Stage II	Neck	79.8
HNCPI-00-01-007	69	Female	Stage IV	Jaw	6.1
HNCPI-00-01-008	92	Male	Stage IV	Left mandible	13.0
HNCPI-00-01-009	71	Male	Stage III	Neck	210.2
HNCPI-00-01-010	61	Male	Stage IV	Neck	13.0

Adverse Events

Subject ID	AE #	Adverse Event Description	SAE	Relationship to Device	Severity
HNCPI-00-01-002	1	Cardiac arrest	Yes	Not related	5 - Death
	2	Weight loss	No	Not related	1 - Mild
	3	Fall	No	Not related	2 - Moderate
HNCPI-00-01-003	1	Skin infection	No	Not related	2 - Moderate
HNCPI-00-01-004	1	General deterioration	Yes	Not related	5 - Death
	2	Hypothyroidism	No	Not related	1 - Mild
	3	Tracheostomy	No	Not related	
HNCPI-00-01-007	1	Lymphadenopathy	No	Not related	1 - Mild
	2	Hyperthyroidism	No	Not related	2 - Moderate
	3	Inflamation	No	Not related	2 - Moderate
	4	Tachycardia	No	Not related	1 - Mild
HNCPI-00-01-009	1	Pulmonary embolism	No	Not related	3 - Severe
	2	Thyroiditis autoimmune	No	Possibly related	1 - Mild
	3	Intestinal perforation	Yes	Not related	3 - Severe
HNCPI-00-01-010	1	Fever	No	Not related	1 - Mild
	2	Rash	No	Probably related	1 - Mild

Early Interim Data as of Jan 9, 2025 Show Strong Systemic Responses

- Patients received an average of 4 cycles of pembrolizumab (range 2-9)
- Systemic responses observed:
  - Three complete responses
  - Three partial responses
  - Two patients died prior to evaluation
- Only two Alpha DaRT-related adverse events, both were Grade 1 (mild)

37.5%
Systemic Complete Responses

75%
Systemic Objective Response Rate (CR + PR)

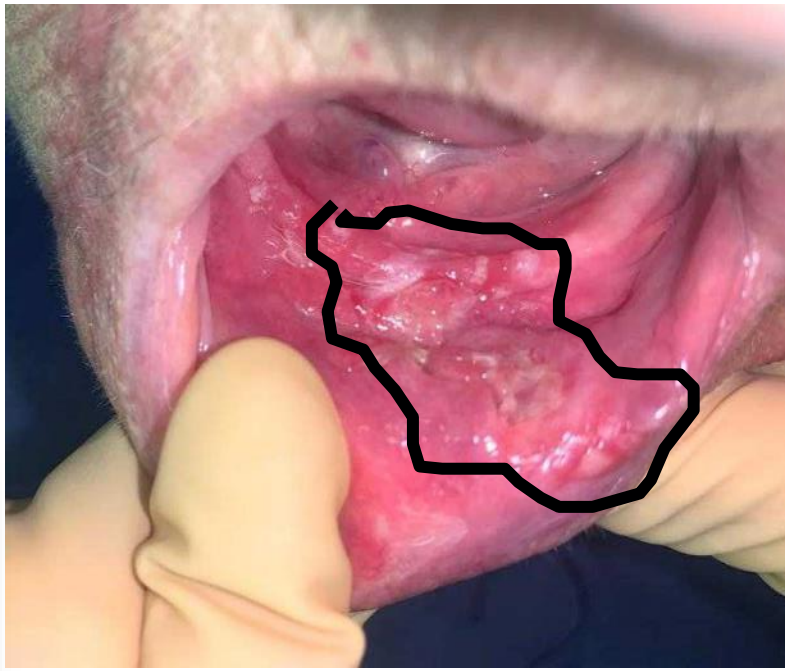
No Related SAEs

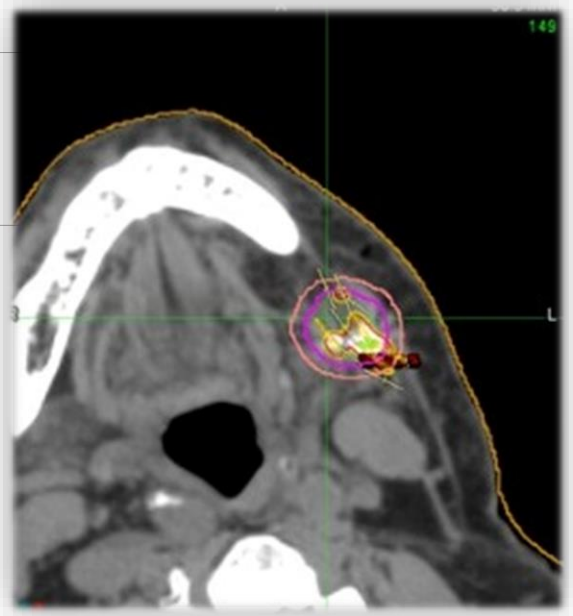
HNCPI-00-01-003

Pembrolizumab Combination Case Study

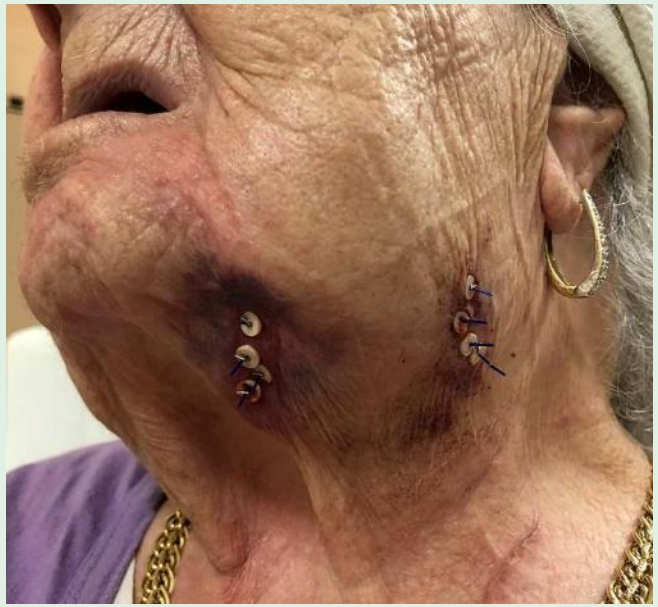
Case Background – HNCPI-00-01-003

Age	96
Sex	Female
Tumor Type	SCC
Date of First Diagnosis	Jul-2022
Location	Alveolar ridge & lip plus dermal involvement
Prior Treatments	None
Medical Background	• Cardio • Dementia • ECOG3
Cancer Stage	• Stage IV • T2N1M1

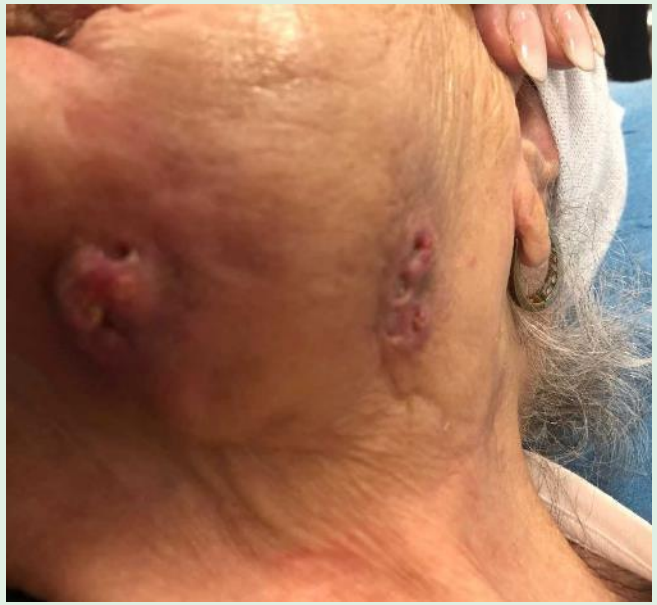




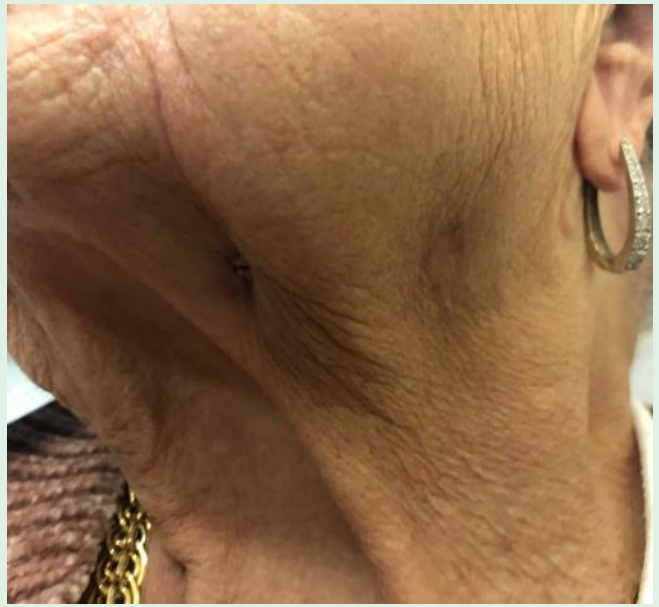
Alpha DaRT Treatment



Alpha DaRT Insertion
Sept-2022



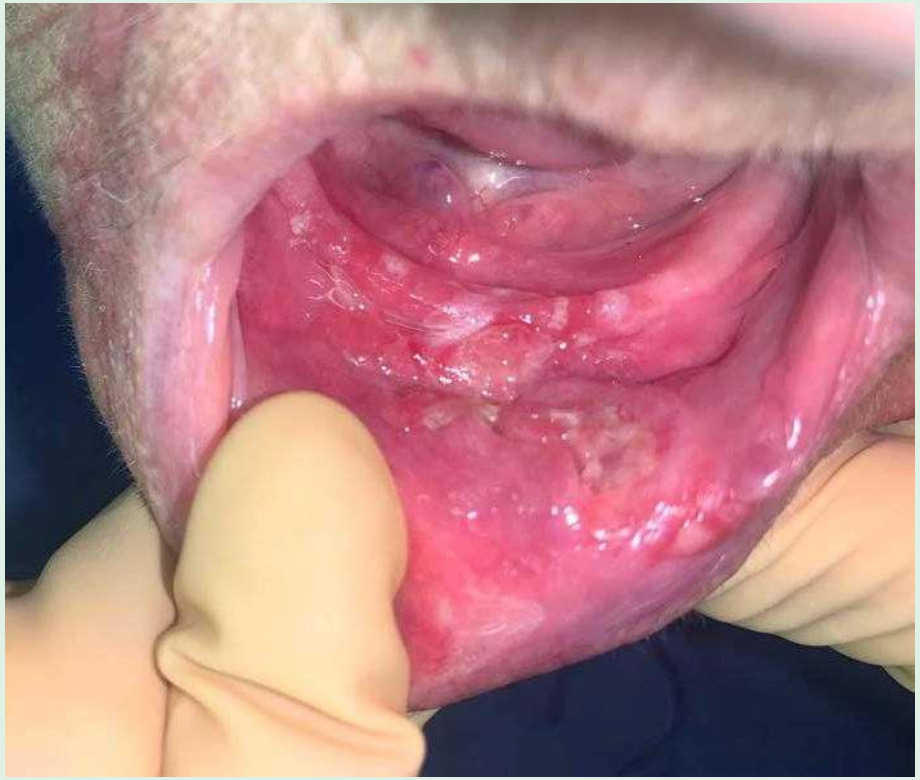
After Alpha DaRT Removal
Oct-2022



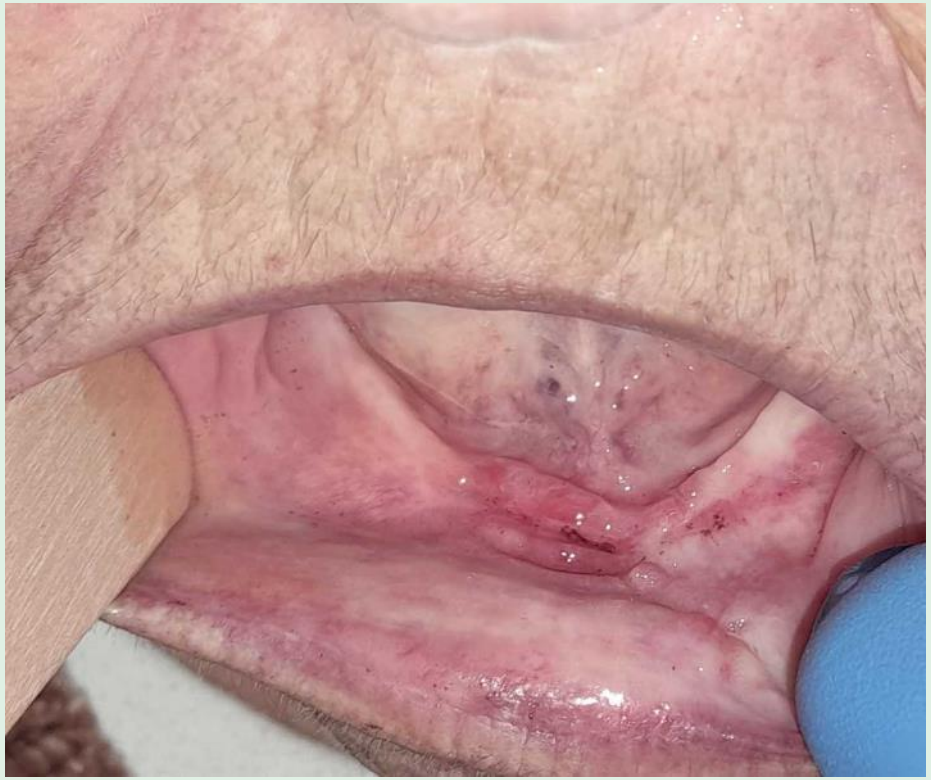
Follow-Up

Jan-2023

Clinical Follow-Up

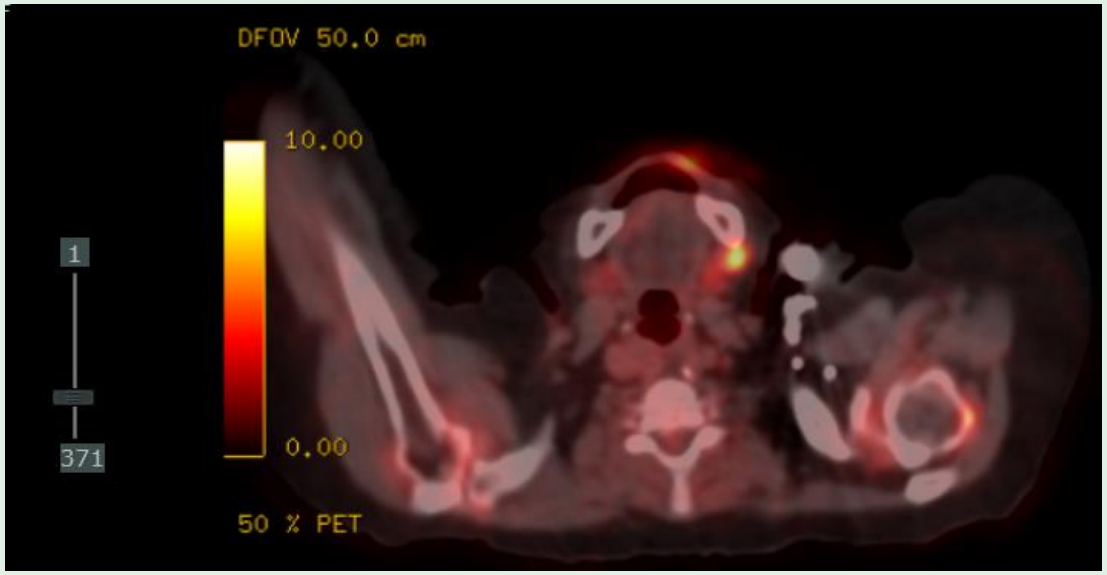


Pre-Treatment

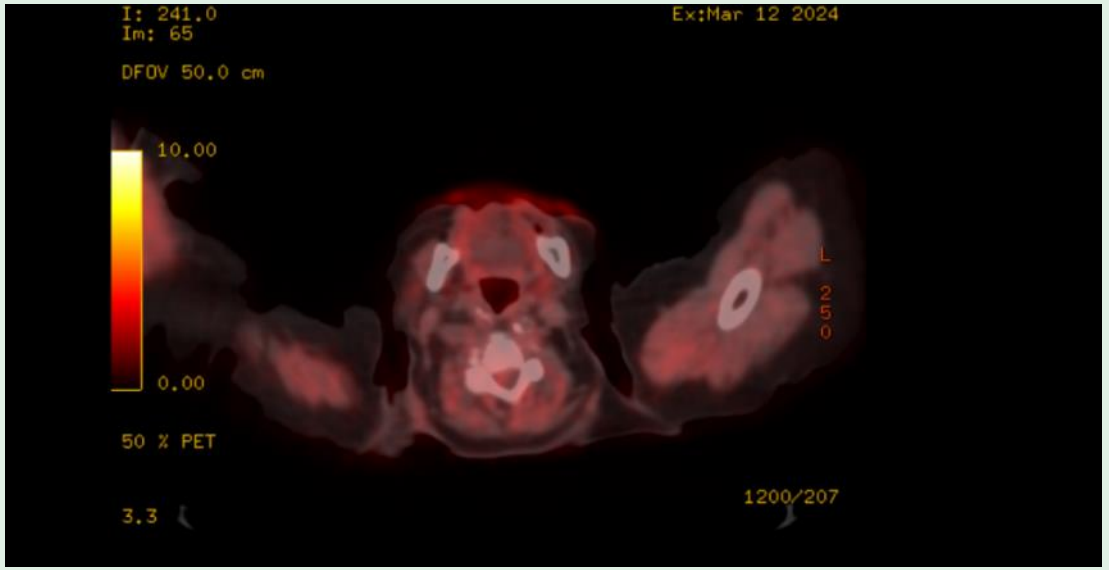


Nine Weeks Post Treatment

PET Follow-Up



Pre-Treatment
Aug-2022



Post-Treatment
Mar-2024

Patient Status

- Patient stopped Pembrolizumab after 12 months
- Patient still alive with no evidence of disease at October 2024 followup

Agenda

1. **Introduction**
   Raphi Levy, CFO | Alpha Tau
2. **Updated Interim Pancreatic Cancer Data as of Jan 8, 2025**
   Robert Den, MD, CMO | Alpha Tau
3. **Pancreatic Cancer Case Study**
   Philip Blumenfeld, MD, MPH | Hadassah Medical Center
4. **Treatment Experience – Endoscopic Delivery to the Pancreas**
   Corey Miller, MD, MSc | McGill University
5. **Clinical Challenges in Reirradiation: Lung & Rectal Case Studies**
   Philip Blumenfeld, MD, MPH | Hadassah Medical Center
6. **First Treatment of Liver Metastases**
   Robert Den, MD, CMO | Alpha Tau
7. **Combination Treatment of Alpha DaRT and Checkpoint Inhibitor**
   Prof. Aron Popovtzer, MD | Hadassah Medical Center
8. **Next Steps, Milestones and Q&A**
   Raphi Levy, CFO | Alpha Tau

Therapeutic Focus

We are focused on delivering solutions to three markets that we believe would be best served by the unique characteristics of the Alpha DaRT

Localized & Unresectable

- Localized tumors that are not surgical candidates and tumors that recur after surgery and are resistant to other therapies, specifically radiotherapy
- Alpha DaRT to be evaluated as a later line therapy
- Tumor types we are targeting include SCC, H&N SCC and prostate

High Unmet Need

- Solid tumors that have limited treatment options with limited standard of care offering
- Alpha DaRT could potentially target broad patient populations
- Tumor types we are targeting include GBM and pancreatic cancer

Metastatic

- Alpha DaRT being evaluated for its potential to induce an immune response in metastatic tumors
- Alpha DaRT being evaluated in combination with checkpoint inhibitors as an adjuvant therapy
- Tumor types we are targeting include liver, breast and H&N (which includes lip, oral cavity, salivary glands, oropharynx & pharynx) cancers

USA - Proposed Trials For Initiation In 2025

Pancreas – Pilot – **Approved**

Recurrent GBM – Early Feasibility Study

- Under Breakthrough Device Designation + TAP Program

Head & Neck – Combination with Pembrolizumab

Anticipated Milestones

Geography	Target Indication	H1 2025	H2 2025	H1 2026
United States	Recurrent Cutaneous SCC		Completion of multi-center pivotal trial recruitment	Data Readout + Potential FDA submission
	Pancreatic Cancer	First Patient in Pilot Study	Complete Recruitment in Pilot Study	Readout from Pilot Study
	Recurrent GBM	Early Feasibility Study IDE		Readout from Early Feasibility Study
Israel	Brain Cancer (GBM or Metastases)	Targeted first patient treated		
Europe	Pancreatic Cancer (French Multicenter)		Targeted first patient treated	
Japan	Head & Neck Cancer	PMDA Response		

Clinical | Regulatory

Development Pipeline

- FDA Breakthrough Device Designation received for certain uses in skin cancer and GBM

Geography	Target Indication	Pre-Clinical Research	Feasibility Trial	Pivotal Trial	Marketing Authorization	Anticipated Milestones
North America	Rec. Cutaneous SCC		U.S.			• Complete patient recruitment in Q3 2025
	Pancreatic Cancer		U.S.			• IDE received, targeting first patient Q2 2025
	Recurrent GBM		U.S.			• Targeting IDE for early feasibility study in Q2 2025
	Pancreatic Cancer		Canada			
	Liver Metastases		Canada			
Israel	Skin & Oral SCC					
	All Skin & Oral Cancers					
	Ia/mHNSCC (combo with pembrolizumab)					• Exploring U.S. IDE submission for similar study
	Pancreatic Cancer					
	Lung Cancer					
	Brain (GBM + mets)					• Targeting first patient in H1 2025
	Prostate Cancer					
Europe	Skin Cancers					
	Vulvar SCC					
	Pancreatic Cancer					• Targeting first patient in H2 2025 in French trial
Japan	Head & Neck Cancer					• Targeting PMDA response in Q2 2025

Questions?