AlphaTAU

(NASDAQ:DRTS)

Company Overview

August 2024

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The Alpha Tau Mission

AlphaDaRT

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

- Platform technology may be utilized alone or synergistically with other cancer treatment modalities
- Radiation delivery can be customized to tumor type and geometry
- Milestones and data from multiple clinical trials in various stages in different indications expected in 2024 - 2025
- 1st potential U.S. marketing authorization in 2025 / 2026, with blockbuster market opportunity across multiple tumor types

Alpha Tau – Key Investment Highlights

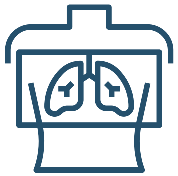
1. Proprietary Alpha DaRT designed to safely deliver alpha radiation with localized precision in solid tumors, sparing surrounding healthy tissue
2. Broad potential and preclinical evidence supporting evaluation across various solid tumors (skin, pancreas, breast, GBM, etc.) with 23 peer-reviewed pre-clinical papers
3. Compelling potential immuno-stimulatory effect and synergetic combination with other therapies
4. Over 150 superficial tumors treated to date, with great results. 100% CR seen at 12 weeks in 1st US study. Strong interim safety and feasibility results and initial signs of efficacy in pancreatic cancer trial.
5. Favorable safety profile observed, no systemic toxicities, no serious late-onset toxicity.
6. Robust clinical-trial strategy with leading global centers, with U.S. pivotal study underway in recurrent cutaneous SCC. Two FDA Breakthrough Device Designations (skin & GBM)
7. Solid logistics based on purpose-built manufacturing facilities, built or in planning, in the US, Israel and Asia, with a highly scalable and optimized proprietary production process
8. Strong intellectual property (method and device) with over 100 issued and over 200 pending patents worldwide
9. Experienced management team, including Alpha DaRT's co-inventors, with expertise in oncology development, manufacturing scale up and commercialization

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 include **SCC, H&N SCC and prostate**



High Unmet Need

- Solid tumors that have **limited treatment options** with limited SOC offering
- Alpha DaRT could potentially target **broad patient populations**
- Tumor types include **GBM and pancreatic cancer**

Metastatic

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

Development Pipeline

- Our clinical trial strategy involves progressing our lead program (superficial tumors), particularly in the US, and conducting feasibility studies in other tumors to evaluate the Alpha DaRT in tumors of high unmet need or metastatic disease
- FDA Breakthrough Device Designation received for certain uses in skin cancer and GBM

Geography	Indication	Pre-Clinical Research	Feasibility Trial	Pivotal Trial	Marketing Authorization	Anticipated Milestones
North America	Rec. Cutaneous SCC	U.S. (bar through Pivotal Trial)				Complete patient recruitment around YE 2024
	Pancreatic Cancer	Canada (bar through Feasibility Trial)				Interim safety readout in Q4 2023; targeting announcement of further data in Q1 2025
	Liver Metastases	Canada (bar through Feasibility Trial)				First patient treated in Q2 2024
Israel	Skin & Oral SCC	(bar through Marketing Authorization)				
	All Skin & Oral Cancers	(bar through Pivotal Trial)				Trial completion and submission
	la/mHNSCC (combo with pembrolizumab)	(bar through Feasibility Trial)				Feasibility combination trial with Keytruda initiated Q4 2021; awaiting interim results
	Pancreatic Cancer	(bar through Feasibility Trial)				Feasibility trial underway
	Breast Cancer	(bar through Feasibility Trial)				Feasibility trial opened
	Lung Cancer	(bar through Feasibility Trial)				First patient in feasibility trial targeted H2 2024
	Brain (GBM + mets)	(bar through Feasibility Trial)				Targeting first patient in H2 2024
	Prostate Cancer	(bar through Feasibility Trial)				First patient treated in feasibility trial for focal treatment of recurrent prostate cancer in Q2 2024
Europe	Skin Cancers	(bar through Pivotal Trial)				Trials underway
	Vulvar SCC	(bar through Feasibility Trial)				Trial initiated in Q2 2023
	Pancreatic Cancer	(bar through Pre-Clinical Research)				Trial in planning
Japan	Head & Neck Cancer	(bar into Pivotal Trial)				PMDA application sent Q4 2023, awaiting reply
	Pancreatic Cancer	(bar through Pre-Clinical Research)				Trial in planning (TBD)

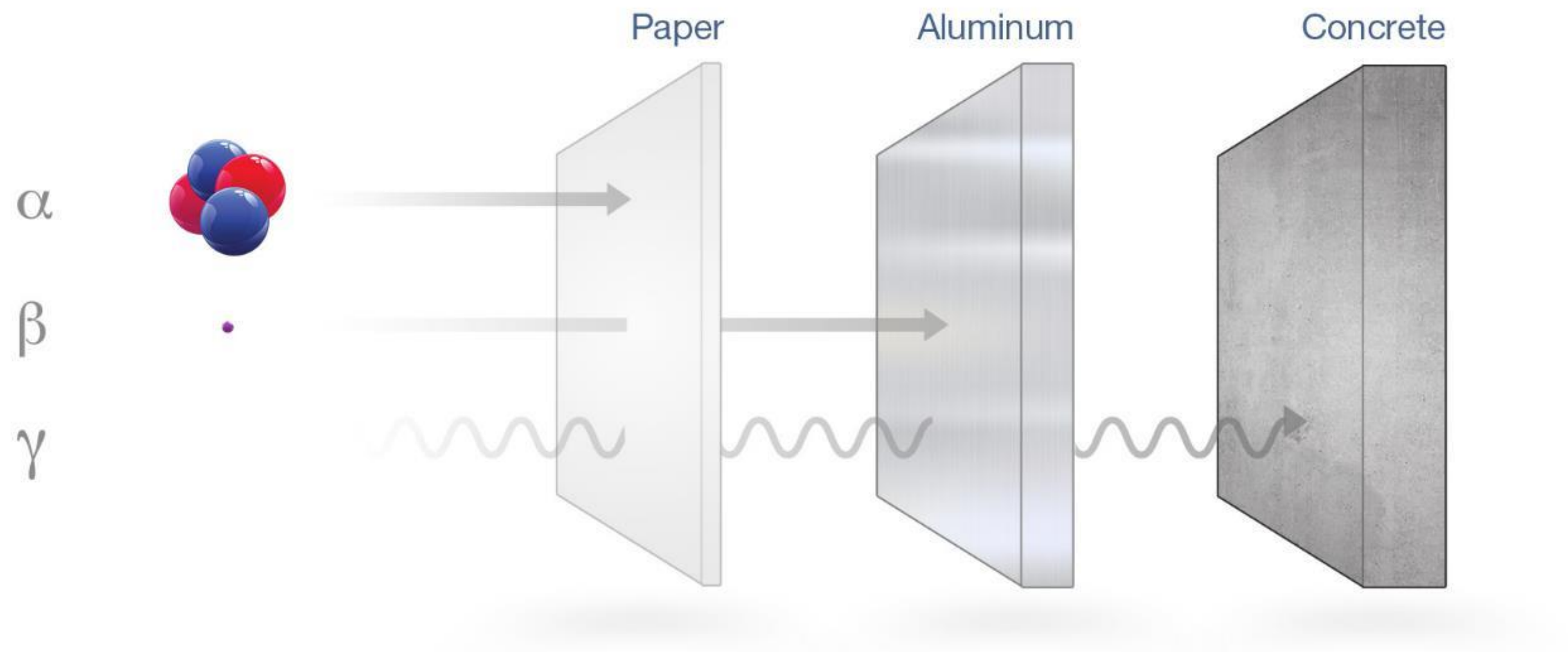
Trials may be conducted across multiple geographies, or there may be interaction between multiple studies (e.g. pooling of long-term response data)

Platform Technology

Alpha DaRT Mechanism of Action and Novel Delivery Techniques Make the Treatment Broadly Applicable

Types of Radioactive Decay

Due to the mass of the alpha particle, in comparison to beta particle, alpha has a low penetration power. This means that the outside layer of the human skin, for example, can block these particles.

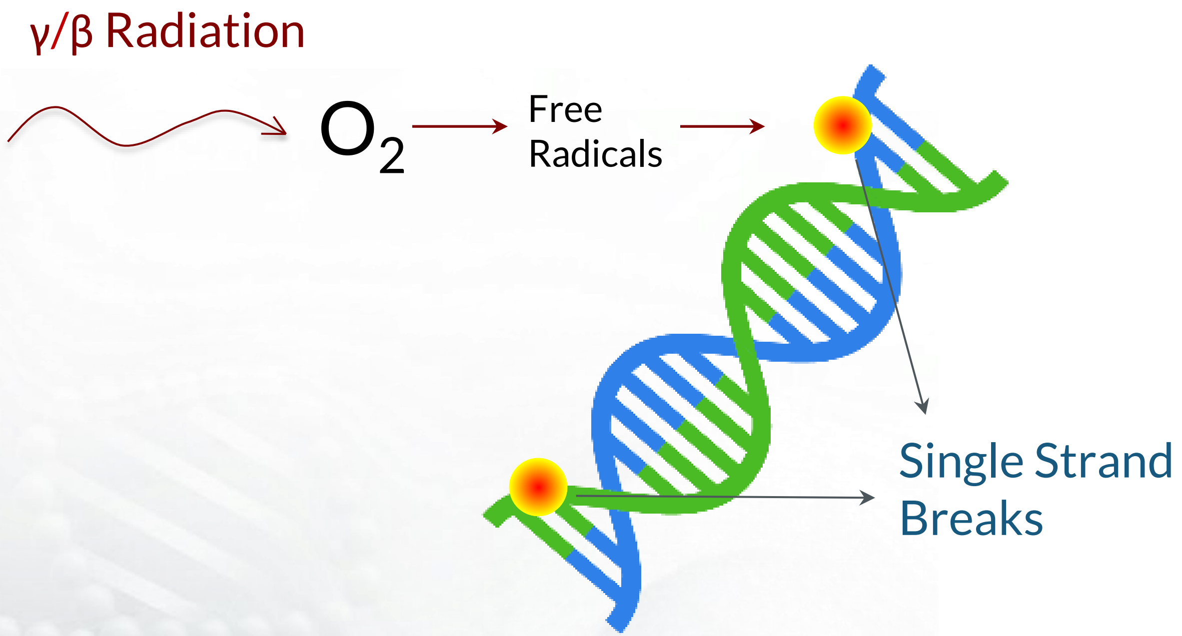


Potent Alpha Radiation: Extensively Damages the DNA

Local radiation therapy with gamma or beta radiation is a mainstay of cancer treatment, but requires high local dose to be effective, as it primarily relies on single-strand breaks in a process relying on oxygen. Alpha radiation can be significantly more efficient given its ability to destroy both strands of the DNA directly, requiring lower levels of radiation

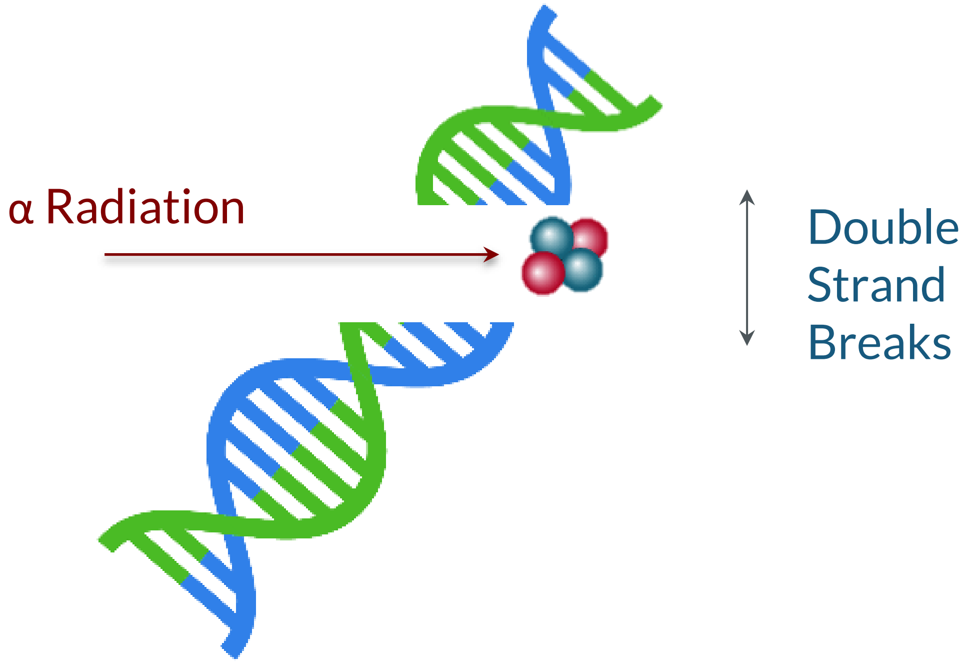
Conventional Gamma/Beta Radiation

- Indirectly damaging the DNA
- Dependent on oxygen presence
- **Repairable single strand breaks**



Alpha Radiation

- Directly damaging the DNA
- Independent of oxygen presence
- **Irreparable double strand breaks**

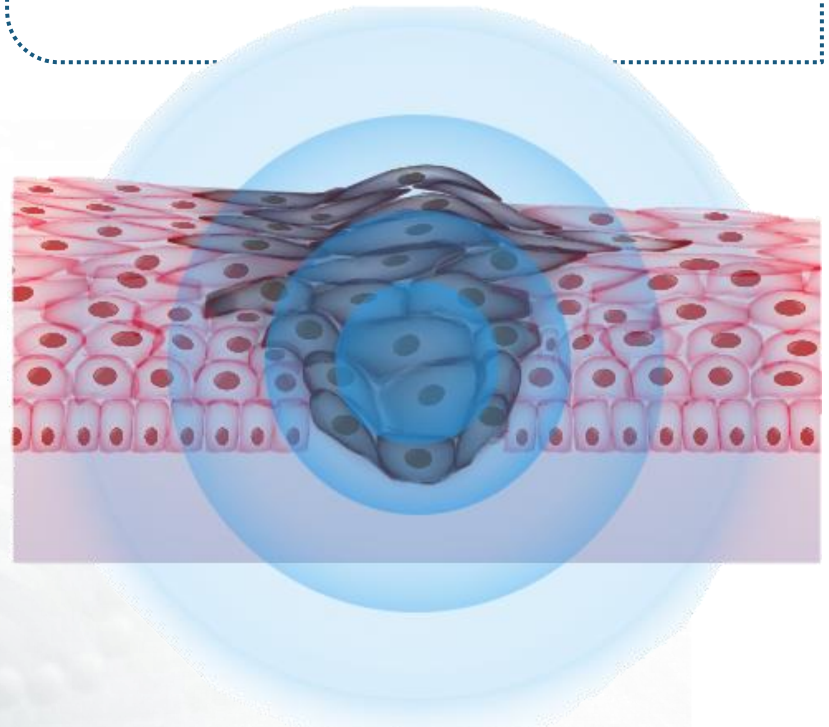


Alpha Radiation is Focal - Short Range Limits Clinical Use

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

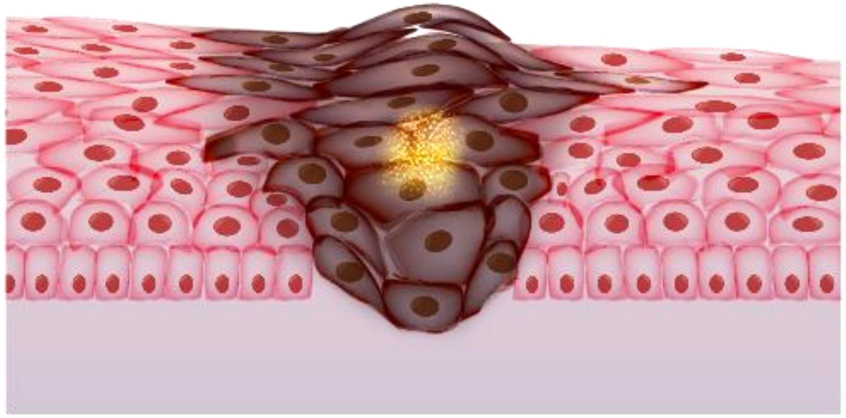
Beta/Gamma Radiation

Long therapeutic range with risk to surrounding organs



Alpha Radiation

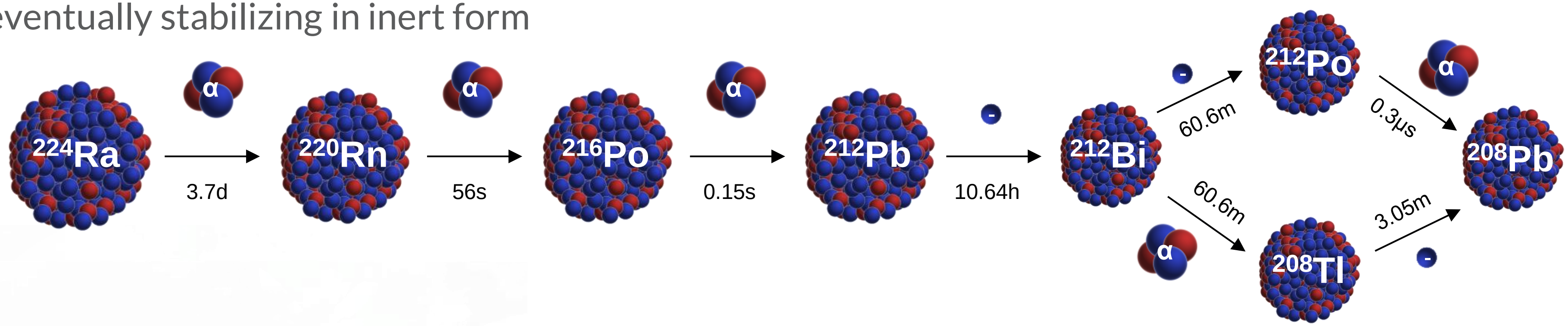
Short range in tissue limits damage to surrounding organs but also limits coverage



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

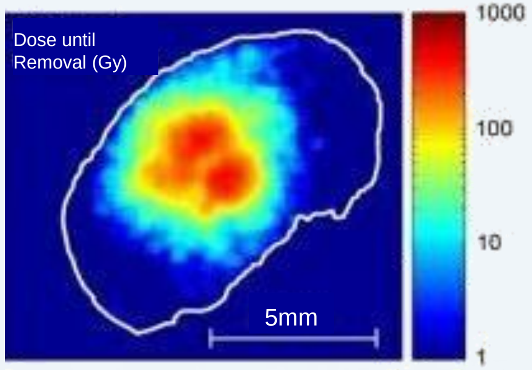
Alpha DaRT is designed to overcome the range limitations of alpha particles through precise release of alpha emitters into the tumor, generating a potent and tight distribution of alpha radiation

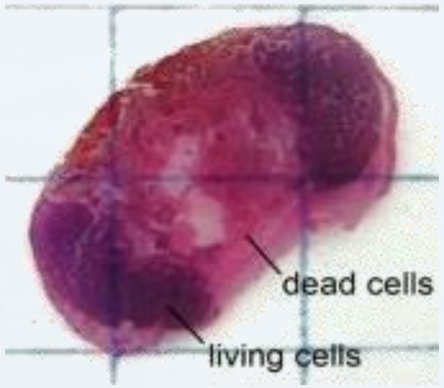
Alpha DaRT - Diffusing Alpha-emitters Radiation Therapy

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

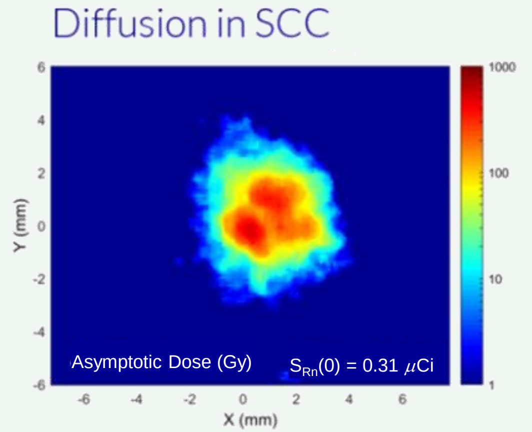
Alpha DaRT Has a Unique Potential to Preserve Healthy Tissues

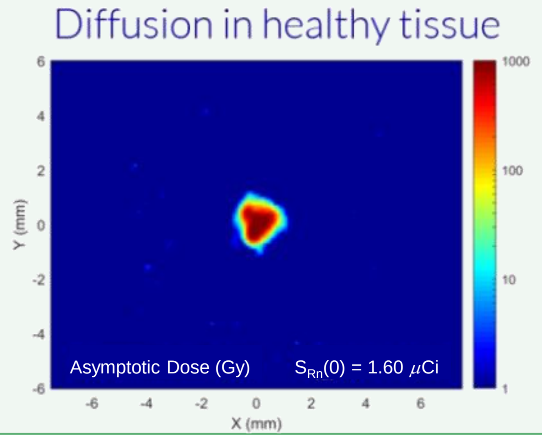
Alpha DaRT is unique in its potential to deliver a high dose of radiation in a very conformal form, with sharp dose drop-off outside of a 5mm range





The range of the Alpha DaRT was observed to be meaningfully more extensive in tumor tissue than in healthy tissue in animal studies





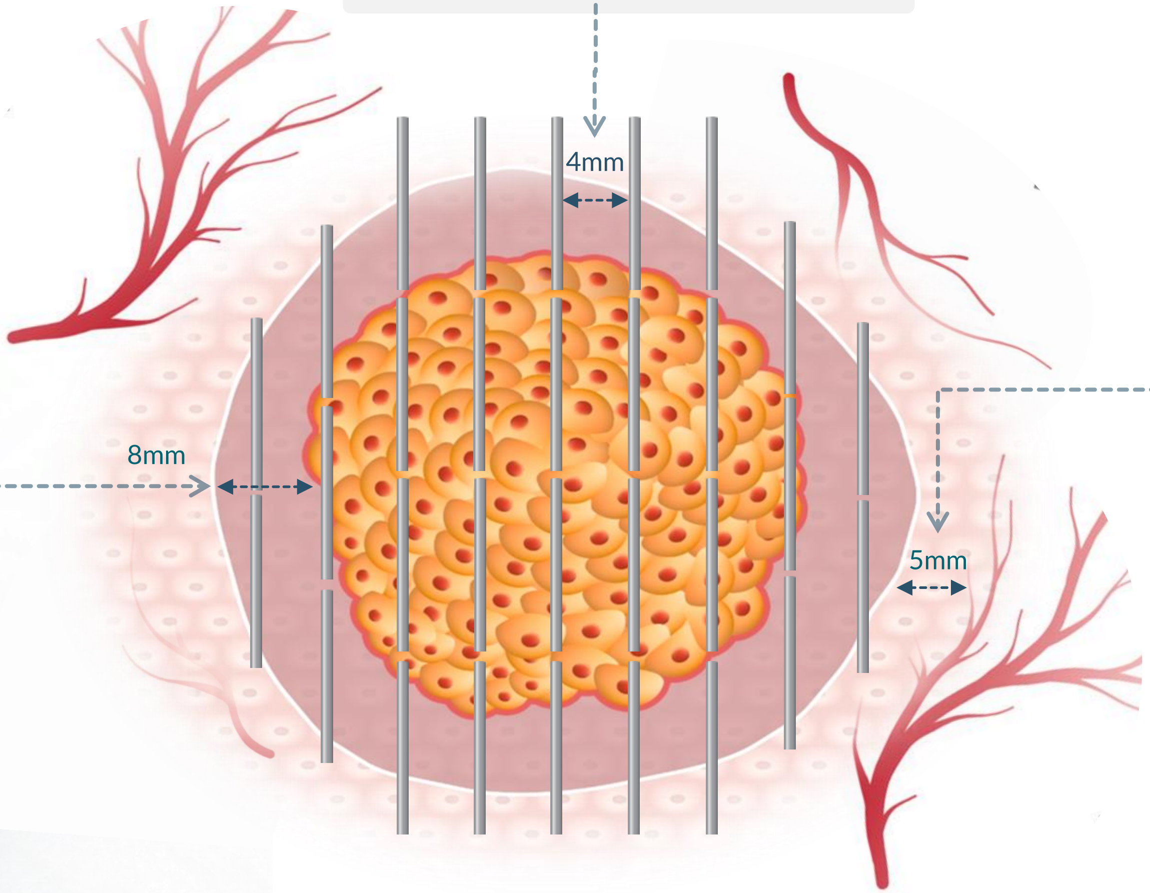
Alpha DaRT Source Placement

Through a series of Alpha DaRT injections to the tumor, spread a few millimeters apart, a clinician can potentially deliver alpha radiation to the full geometry of the tumor while taking care to avoid sensitive healthy tissue around the tumor

< **5 mm** between sources

Coverage of margins of **8 mm** (last source to be placed **5 mm** outside of the tumor)

5 mm safety distance from critical organs



Our Applicators Allow Delivery Into Both Superficial & Internal Tumors

We Have a Total of Seven Applicators Which Have Been Developed for a Range of Potential Uses to Accommodate for:

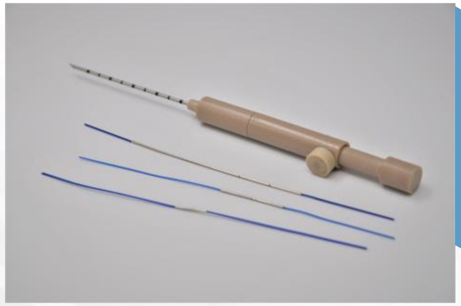
- Treatment delivery method
- Duration of implantation
- Tumor Location

Temporary Implants (Superficial Tumors)

Applicators are supplied preloaded, sealed and designed for immediate use

Sources are hollow and strung onto a surgical suture, allowing the clinician to insert the sources into the tumor and leave the suture in place

Alpha DaRT Needle Applicator



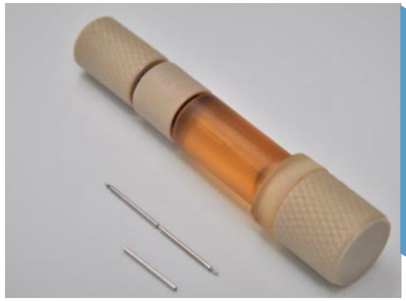
Needle Applicator in Action

Example Indication: Superficial Tumors.
sources are affixed to a biocompatible suture and loaded inside the needle

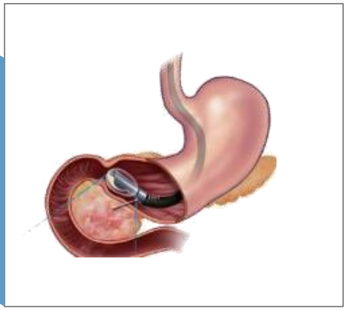
Permanent Implants (Internal Tumors)

Applicators are designed to allow clinicians flexibility to receive the sources preloaded, or load the sources in the course of treatment, and to select how many sources to deliver

Loading Device



Procedure: FNA in Conjunction with Endoscopic Ultrasound

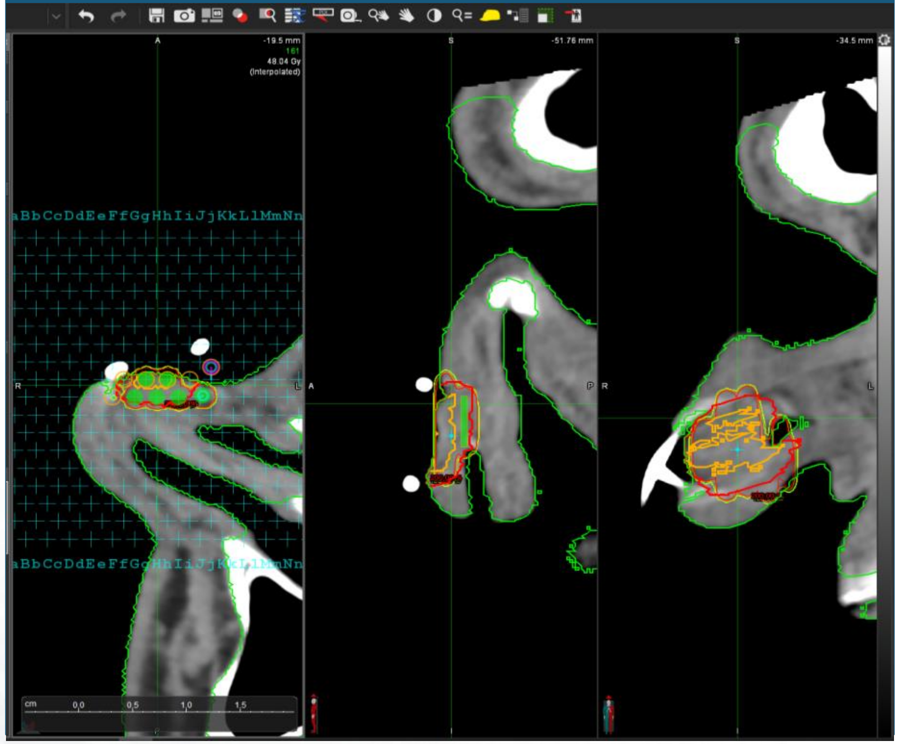


Example Indication: Pancreatic Tumors.
Device is designed to be fitted to existing needles such as standard Fine Needle Aspirator (FNA) to ultimately deliver sources into the tumor

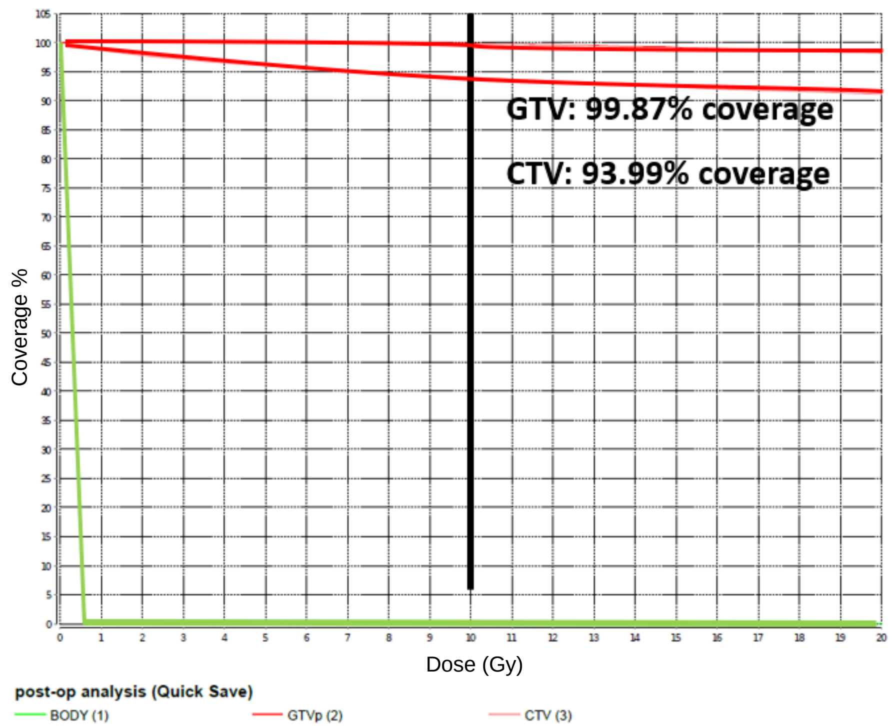
Treatment Planning in Partnership with MIM Software

Treatment planning software may serve to increase the precision and robustness of Alpha DaRT use, by allowing the clinician to calculate the alpha-specific dosimetry for the desired plan before treatment, and then check the tumor coverage post treatment

Pre-Treatment Planning



Post-Treatment Dosimetry Confirmation



Alpha Tau has announced an agreement with MIM Software for continued collaboration on Alpha DaRT treatment planning, including development of new features and support for the Alpha DaRT across multiple potential indications, integration into all clinical trials involving the Alpha DaRT, and bundling the MIM software with the Alpha DaRT for future commercial sales.

Preclinical Data

Demonstrated Local and Immune Responses Across a Variety of Tumor Types in Animal Models

Response Observed in All Tested Solid Tumors in Preclinical Studies

23 Published Preclinical Studies in Peer-Reviewed Journals

Across a variety of tumor types, we have not observed resistance to the radiation delivered by the Alpha DaRT

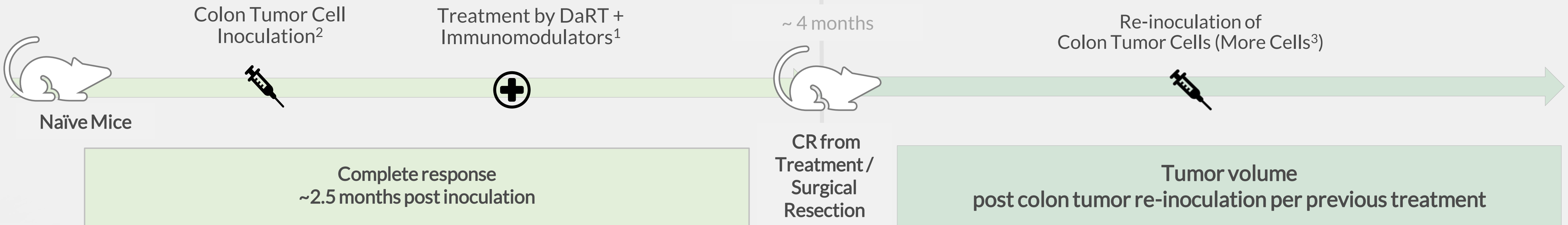
- Squamous Cell Carcinoma
- Colon Carcinoma
- Lung Adenocarcinoma
- Glioblastoma Multiforme
- Lung Squamous Cell Carcinoma
- Sarcoma
- Pancreas Adenocarcinoma
- Melanoma
- Prostate Adenocarcinoma
- Breast Carcinoma

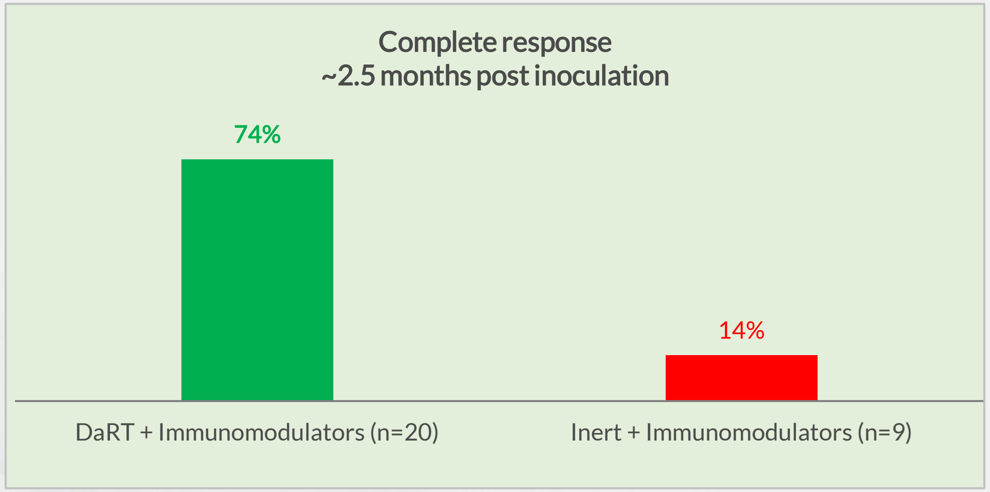
Observed Cancer-Specific Immune Protection (1/2)

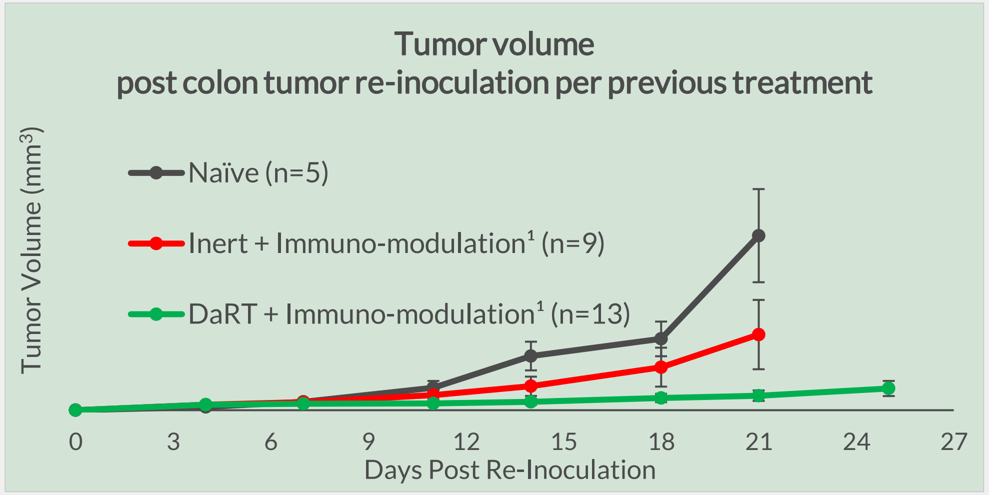
In challenging mice 4 months after treatment, those previously treated by the Alpha DaRT displayed a meaningful retained protection against regrowth of the same tumor type, as compared to the two control groups

Tumor Treatment by DaRT + Immunomodulators[1]

Tumor Re-Inoculation after Treatment by DaRT + Immunomodulators vs. Inert[1]







(1) Three groups of mice were inoculated with 5×10^5 CT26 tumor cells and then treated with (1) DaRT + CP, Sildenafil and 2xCpG, N=10 (2) DaRT + CP, Sildenafil and CpG, N=10 or (3) inert + CP, Sildenafil and 2xCpG, N=9. Complete responders or tumor-resected mice were re-challenged ~4 months after DaRT with 5×10^6 CT26 tumor cells.

(2) CT26 5×10^5.

(3) CT26 5×10^6.

Observed Cancer-Specific Immune Protection (2/2)


Combining alpha radiation-based brachytherapy with immunomodulators promotes complete tumor regression in mice via tumor-specific long-term immune response

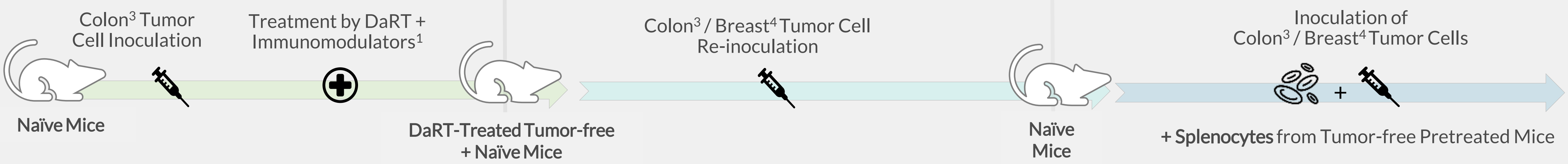
Vered Domankevich, Adi Cohen, Margalit Efrati, Michael Schmidt, Hans-Georg Rammensee, Sujit S. Nair, Ashutosh Tewari, Itzhak Kelson & Yona Keisari

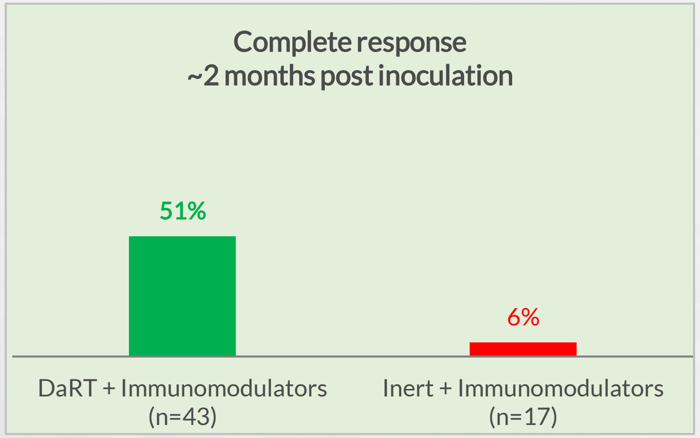
This activity was then shown to be tumor-specific – the challenge only resisted regrowth of the same tumor line. It was also shown to be transferrable via the transfer of splenocytes

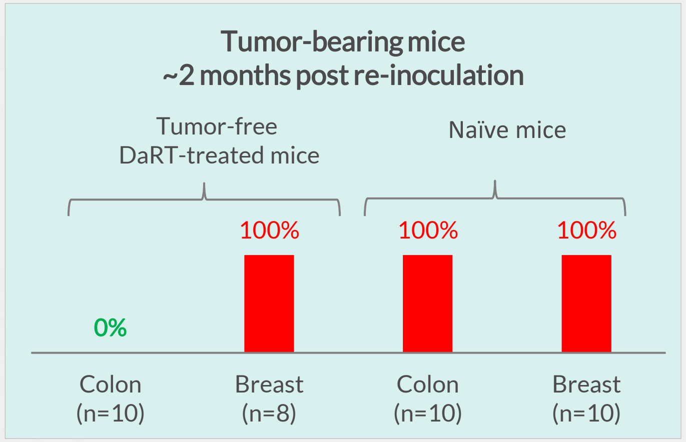
Tumor Treatment by DaRT + Immunomodulators

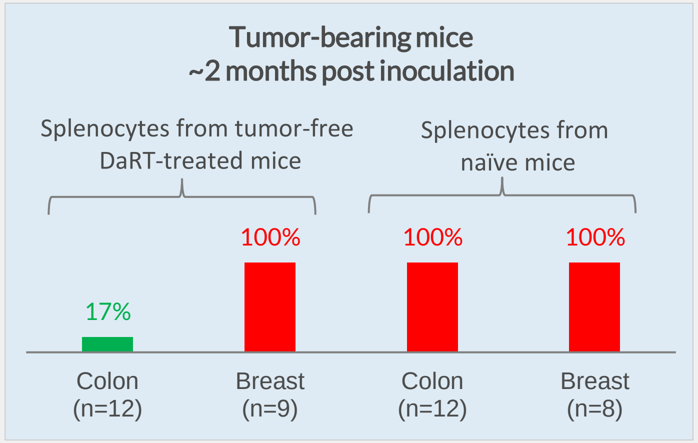
Tumor Re-Inoculation[2] (Challenge Assay)

Immune-Memory Transfer[2] (Winn Assay)





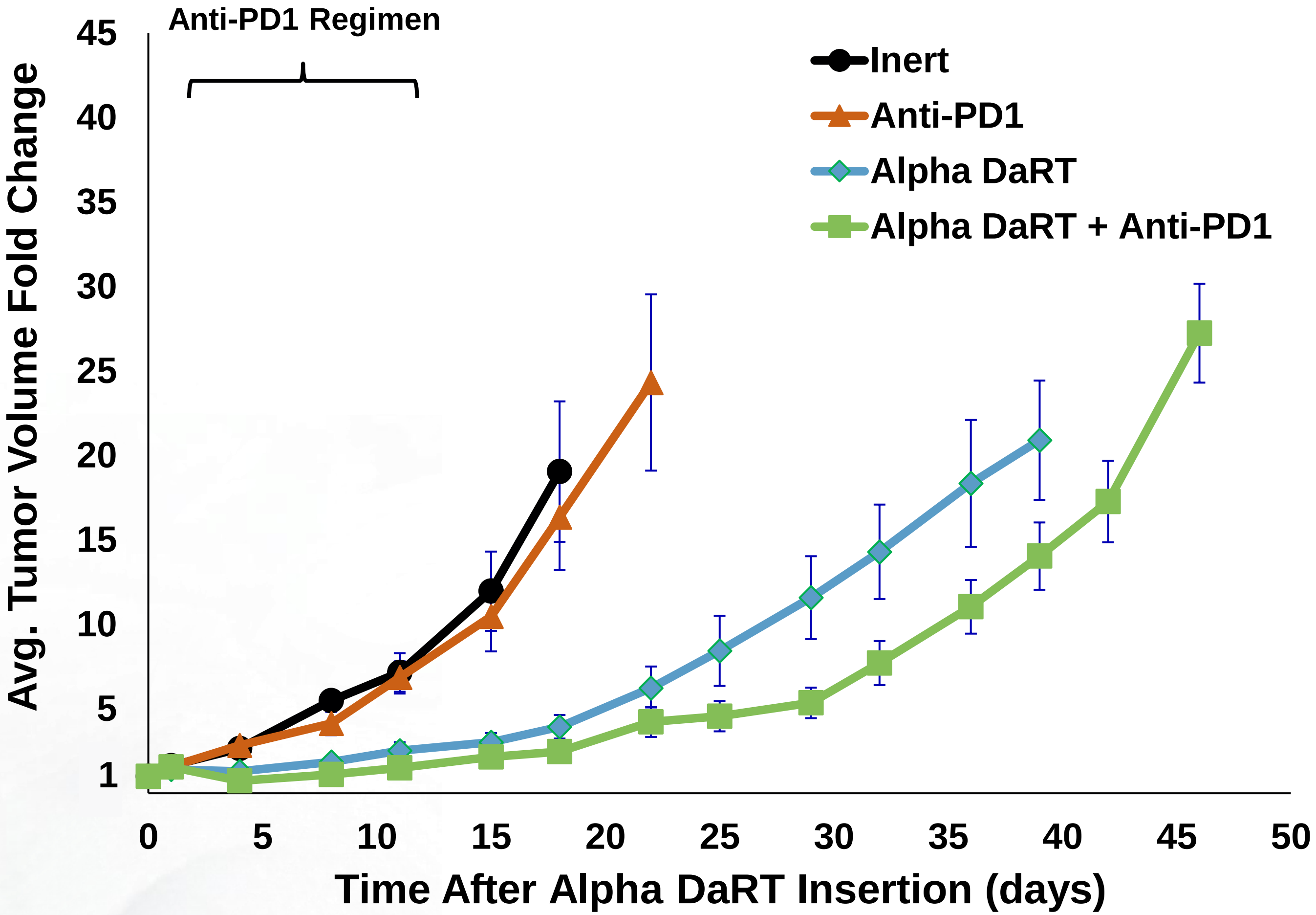




(1) Immuno-modulation refers to a combination of low dose CP, Sildenafil and CpG.
(2) Mice with CR from DaRT + immuno-modulators (n = 18) and naïve mice (n = 20) were inoculated with 5 x 10^5 CT26 or DA3 cells 52 days post inoculation (Challenge Assay). Naïve mice were injected intradermally with splenocytes from either naïve or CT26-bearing mice treated by DaRT and immunomodulators, coupled with CT26 or DA3 tumor cells (Winn assay). The presented results are based on cumulative data from two different experiments.
(3) CT26 5 x 10^5.
(4) DA3 5 x 10^5.

Alpha DaRT Elicits Effect from anti-PD1 in SCC Mouse Model (SQ2)

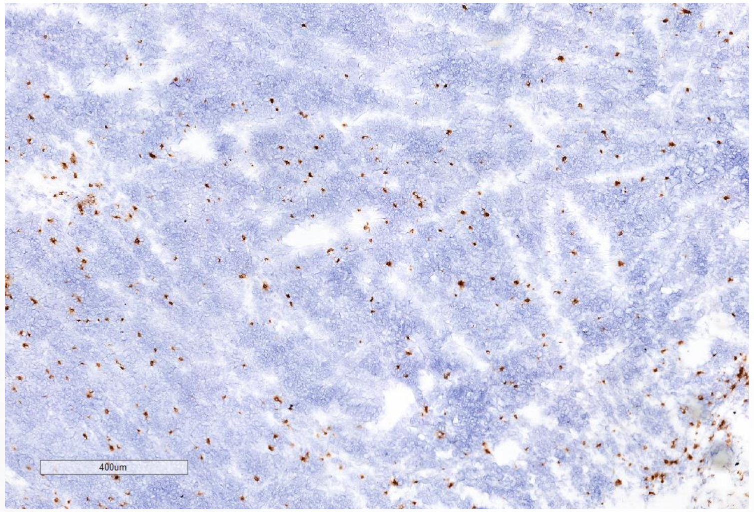
While mice with the SQ2 squamous cell carcinoma model showed little to no effect when treated with a murine anti-PD1 agent, the observed effect was larger for the combination with Alpha DaRT than for Alpha DaRT on its own



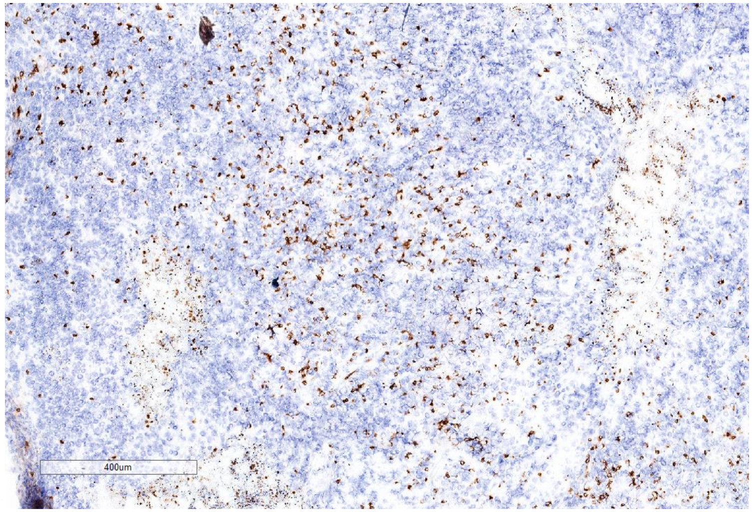
Alpha DaRT Increases Infiltration of CD3+ T-cells Into the Tumor

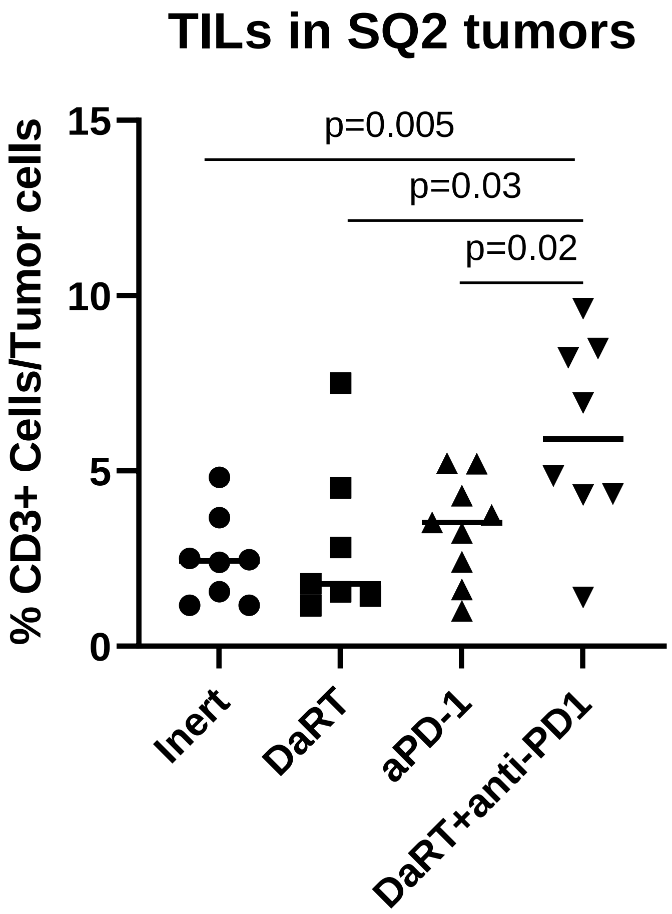
The combination of Alpha DaRT with anti-PD1 demonstrates the highest level of TILs in mice with SQ2 SCC tumors, potentially indicating an ability to potentiate the checkpoint blockade

anti PD-1



Alpha DaRT + anti PD-1

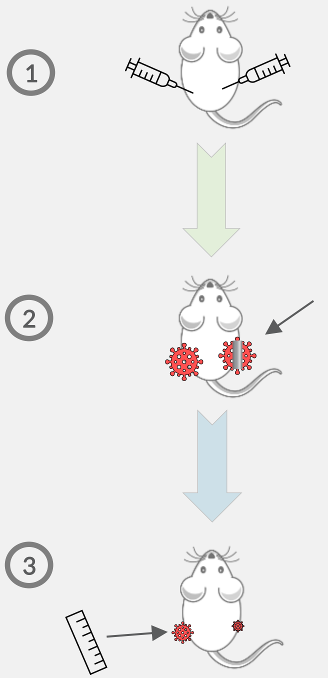




Immune Response Observed Even in "Cold" Pancreatic Tumor Model

When treating one pancreatic cancer tumor with Alpha DaRT sources instead of inert sources, a statistically significant decline in secondary tumor growth rate was seen.

Experiment Design

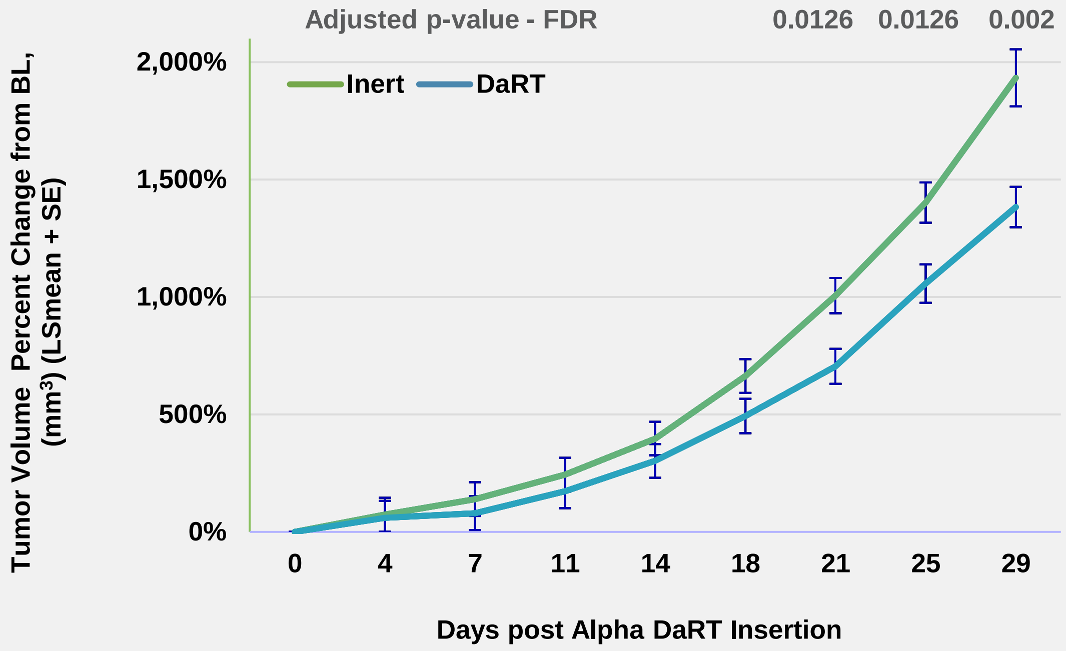


Intracutaneous inoculation of two Panc02 or KPC tumors

Insertion of Alpha DaRT sources into primary tumor after 9-10 days

Measurement of the secondary tumor volume over time

Secondary Tumor Growth (Untreated)



Similar effect also observed when examining the Panc02 and KPC tumor models individually rather than grouped into a larger analysis.

The percent change in tumor volume over time was assessed and compared between the groups with Repeated Measures ANOVA models, applying a False Detection Rate (FDR) correction for multiple comparisons.

Clinical Data

Encouraging Results Across a Variety of Solid Tumor Types

Outline of Our First Clinical Study: Skin / Head & Neck SCC

Trial Sites: Israel, Italy

Primary objective: Evaluate feasibility & safety

Secondary objective: Evaluate initial tumor response & local progression-free survival

Key Eligibility Criteria

SCC histopathologically confirmed

Lesions ≤ 5 cm*

Age ≥ 18

ECOG performance scale ≤ 2

Patients W/O immunosuppression

Generally **previously treated by radiation or surgery, recurrent**

Treatment & Procedure

Treatment plan based on CT-simulation

Sources 1cm length, 0.7mm diam.

Activity per source 2 μCi

Outpatient setting

Local anesthesia

Number of sources inserted: min 3, max 169

Timeline and Follow-Up

Alpha DaRT sources insertion

Removal after 15 days

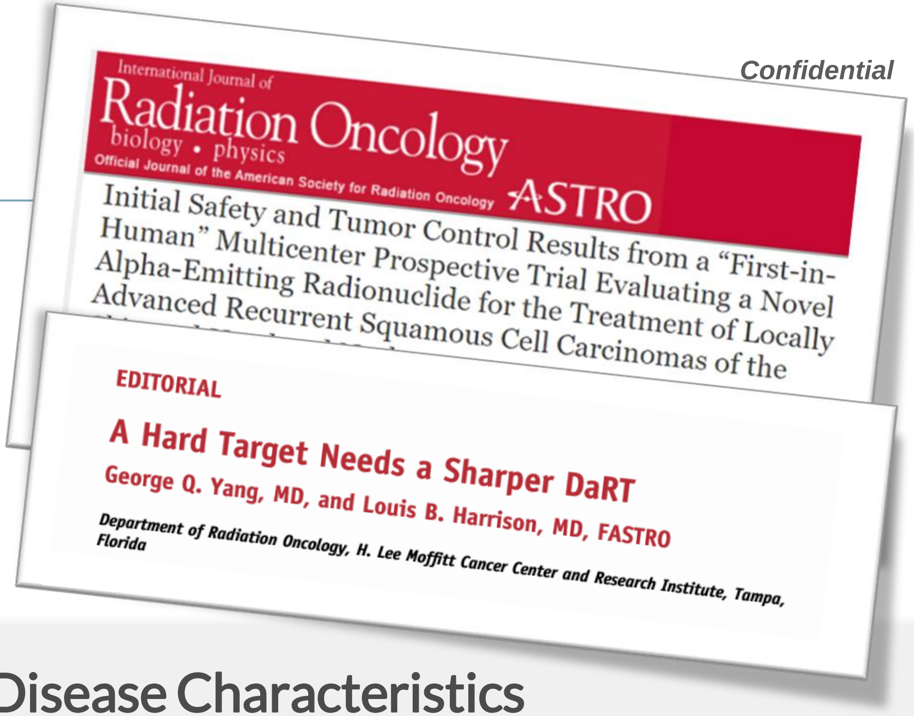
Check-up on days 4, 9 and 30 after insertion

Long term follow up based on standard of care

*in the longest diameter (without nodal spread).

Skin / Head & Neck SCC Study Results

- 100% overall response rate
- Durable responses observed
- Responses observed within days
- Well tolerated; no systemic toxicity observed


International Journal of Radiation Oncology biology • physics
Official Journal of the American Society for Radiation Oncology ASTRO

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

EDITORIAL

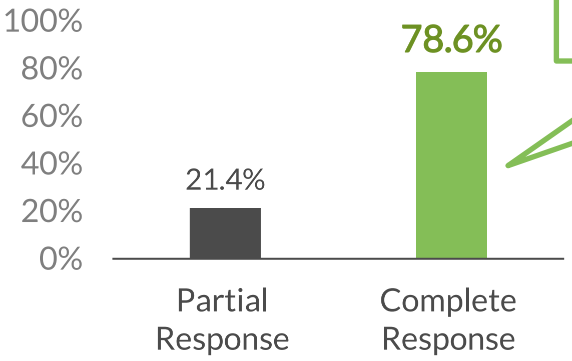
A Hard Target Needs a Sharper DaRT

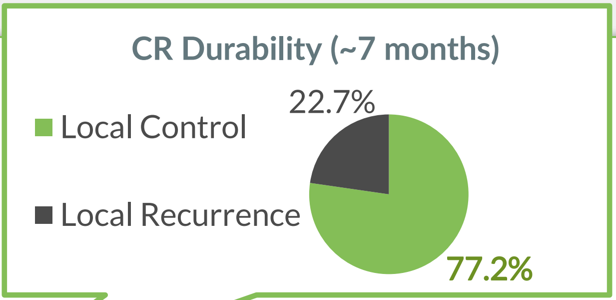
George Q. Yang, MD, and Louis B. Harrison, MD, FASTRO

Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida

Efficacy Results

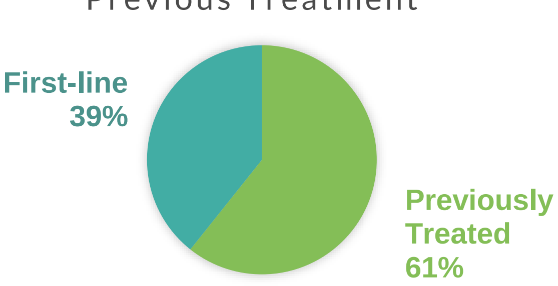
Overall Response (n=28)

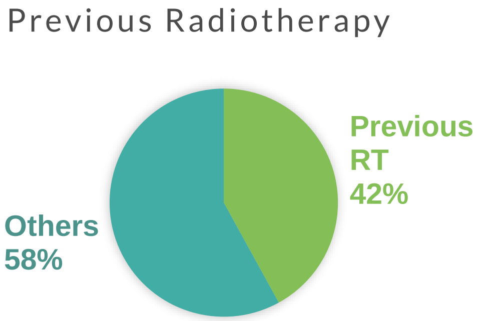




Baseline Disease Characteristics

Effective against radioresistant tumors (Patient median age = 80.5 years)

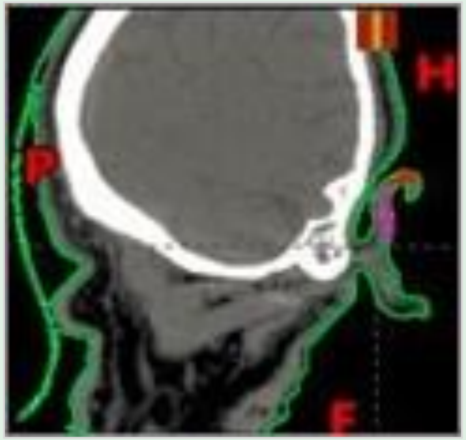




[1] Most patients (60.7%) had recurrent and previously treated disease by either surgery, prior external beam radiotherapy or both; 13 of 31 (42%) had received prior RT.

AP-02 Complete Response

Age	80	Applicators used	6
Previous treatments	Radiation, Surgery	Alpha DaRT sources inserted	10
Tumor initial volume [cm^3]	1.4	Total activity [µCi]	20



Planning

Before
21-Mar-2017

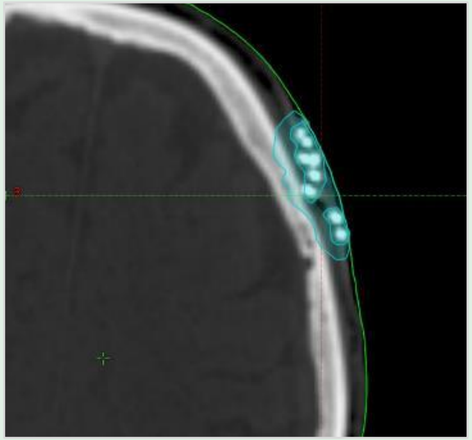
During
21-Mar-2017

After
01-Jun-2017

AP-022 Complete Response

Age	68		Applicators used	12
Previous treatments	None		Alpha DaRT sources inserted	24
Tumor initial volume [cm^3]	1		Total activity [μCi]	48

Before
27-Aug-2018



During
30-Aug-2018

During
30-Aug-2018

After
30-Sep-2018

Alpha DaRT Treatment was Well Tolerated

No systemic toxicities and minimal (< grade 2) local toxicities observed to date

Targeted treatment
Designed to spare neighboring healthy tissue

No systemic toxicity observed
Negligible and short-term radioactivity in the patient's body

Minimal local toxicity observed
Minimal local toxicity with grade ≤2 resolved within a month

Safe procedure for caregivers
No special shielding required

No suppression of immune system observed
Critical in times of pandemic

Acute Local Toxicity	Incidence (%) Severity Grade 1	2	3
Administration site erythema	11 (41%)	9 (33%)	0 (0%)
Administration site edema	9 (33%)	10 (37%)	0 (0%)
Administration site pain	8 (30%)	11 (41%)	0 (0%)
Administration site exudate	2 (7%)	8 (30%)	0 (0%)
Administration site ulcer	4 (15%)	5 (19%)	0 (0%)
Administration site numbness	1 (4%)	0 (0%)	0 (0%)
Administration site pruritus	3 (11%)	0 (0%)	0 (0%)
Administration site bleeding	1 (4%)	0 (0%)	0 (0%)
Aural myiasis (administration site)	1 (4%)	0 (0%)	0 (0%)
Decreased appetite	1 (4%)	0 (0%)	0 (0%)

Potential Systemic Immune Effect Observed in One Patient Where a Second, Untreated Lesion Manifested CR

Complete Response + Potential Systemic Immune Effect


Journal of Contemporary BRACHYTHERAPY
Official Journal of Polish Brachytherapy Society /// www.brachyterapia.com
Case report
Clinical evidence of abscopal effect in cutaneous squamous cell carcinoma treated with diffusing alpha emitters radiation therapy: a case report
Salvatore Roberto Bellia, Giacomo Feliciani, Massimo Del Duca, Manuela Monti, Valentina Turri, Anna Sarnelli, Antonino Romeo, Itzhak Kelson, Yona Keisari, Aron Popovtzer, Toni Ibrahim,

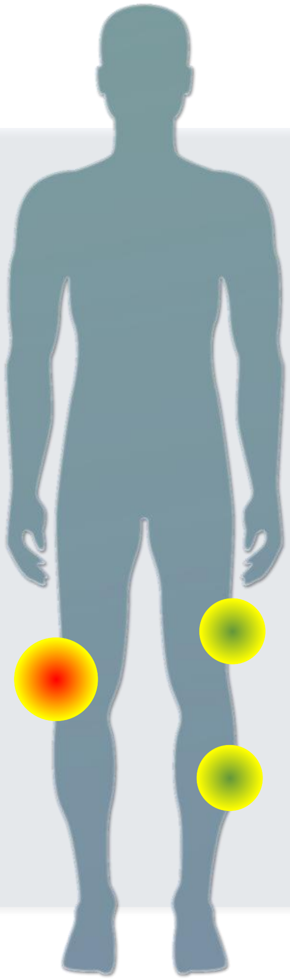
Treated Tumor

Before

30-Nov-17

After

29-Dec-17



Untreated Tumors

Before

30-Nov-17

After

29-Dec-17

U.S. Pilot Feasibility Study – Trial Design

FDA Breakthrough Device Designation received in June 2021


JAMA Network | Open

Original Investigation | Oncology

Feasibility and Safety of Diffusing Alpha-Emitter Radiation Therapy for Recurrent or Unresectable Skin Cancers

Mark A. D'Andrea, MD; Noam A. VanderWalde, MD, MS; Matthew T. Ballo, MD; Pradeep Patra, PhD; Gil'ad N. Cohen, MS; Antonio L. Damato, PhD; Christopher A. Barker, MD

Abstract

IMPORTANCE Patients with recurrent or unresectable skin cancers have limited treatment options. Diffusing alpha-emitter radiation therapy (DaRT), a novel solid tumor management strategy using alpha-particle interstitial brachytherapy, may address this challenge.

Locations	5 centers in the US, led by Memorial Sloan Kettering Cancer Center
Treatment Timeframe	H2 2021
# of Patients	10
Tumor Type	Skin Cancers
Primary Objectives	Determine feasibility of delivering radiotherapy using Alpha DaRT, with successful delivery in at least 7 patients, and assess frequency and severity of acute AEs
Secondary Objectives	Assessments of radiotherapy-related AEs, tumor response, radiation safety, stability of device placement, and QoL
Eligibility	Malignant skin or superficial soft tissue tumor 1-5 cm in size that is suitable for percutaneous interstitial brachytherapy

Case Study - 77 Y/O with Recurrent BCC on the Nose

Prior treatments:	Surgery (2005)

Tumor Size:

Longest diameter	1.59 cm
Depth	0.5 cm
Volume	0.65 ml

Alpha DaRT Treatment:

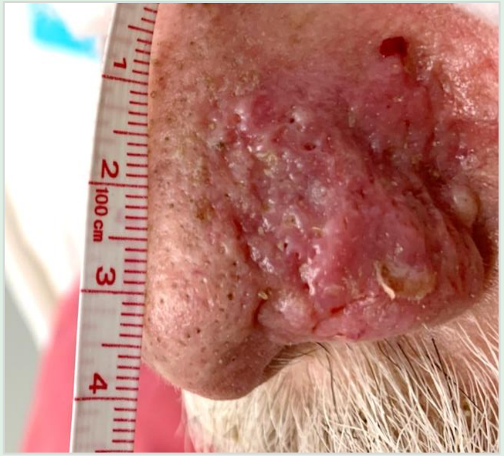
Applicators used	15
Alpha DaRT sources inserted	20
Total activity [μCi]	40

Case Study - 77 Y/O with Recurrent BCC on the Nose

Results

Simulation Day

Insertion Day



Removal Day
15 days

Complete Response
12 weeks

U.S. Pilot Feasibility Study – Safety Results

- Twenty-two (22) **total adverse events** (AEs) were reported in 7 subjects
- Most AEs were of **mild or moderate severity**
- Two (2) serious AEs (SAEs) in a single subject – **both not related to study device or procedure**

Number of Subjects with Procedure- or Device-Related* Adverse Events by Severity Grade

Adverse Event	Severity Grade 1	Severity Grade 2	Severity Grade 3
Dermatitis radiation	2	1	0
Localized edema	1	0	0
Joint range of motion decreased	0	1	0
Pain	0	1	0
Pruritis	2	0	0
Wound infection	0	1	0

Note: Adverse events are presented according to CTCAE V5 coded terms.
* Probably or possibly related

U.S. Pilot Feasibility Study – Efficacy Results

- All 10 subjects achieved a **complete response** (CR) at the 12-week follow-up visit

- There were **no reported relapses** of disease by the final study visit at 24 weeks

Impressive Efficacy & Safety Data Collected in Long-Term Follow-Up

Data Set Description

Data collected from four feasibility trials in unresectable, recurrent, or locally advanced head and neck or skin cancers

81 treated lesions in 71 patients

Median follow-up of 14 months (range: 2-51 months)

Efficacy

- ✓ 89% of treated lesions achieved complete response (CR)
- ✓ 77% two-year local recurrence-free survival (LRFS)

Safety

- ✓ ~20% of patients had acute grade 2 toxicities and no patients had acute grade 3 or higher toxicities
- ✓ No grade 2 or higher late toxicities observed 6 months post-treatment

Short-term local responses led to durable long-term control in difficult-to-treat tumors

Outline of Our 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

20 U.S. sites including UCLA, Emory University, Mayo Clinic, etc.

Timeline and Follow-Up

Alpha DaRT sources insertion

Removal after 14 to 21 days

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

Focus on Internal Organ Treatments

We continue to make progress across internal organ indications, with multiple indications in large animal testing and/or in the stage of regulatory protocol submission for upcoming clinical trials, expanding from Israel to elsewhere in the world.

Internal Organs in Focus

- Prostate – in Human Clinical Trials
- Pancreas – in Human Clinical Trials
- Liver – in Human Clinical Trial
- Brain – GBM + Brain Mets
- Breast
- Lungs
- Rectum

HADASSAH UNIVERSITY MEDICAL CENTER
Founded by Hadassah, the Women's Zionist Organization of America

MINISTRY OF HEALTH

Health Canada

RAMBAM Health Care Campus

Internal Organs

A Feasibility and Safety Study of Intratumoral Diffusing Alpha Radiation Emitters on Advanced Pancreatic Cancer

AT-PANC-101

Outline of the Pancreas Pilot Study in Canada

Primary objective: Evaluate feasibility & safety of Alpha DaRT sources inserted into pancreas in terms of incidence of device related AEs & SAEs.

Secondary objective: Evaluate efficacy (radiological ORR and change in tumor markers), OS, stent durability, and QoL

Key Eligibility Criteria

Locally **advanced (Stage II or III)** or **metastatic (Stage IV)** pancreatic adenocarcinoma

Inoperable pancreatic cancer because:

- **Unresectable**
- **Metastatic** disease
- Medically **unfit** for surgery

No **concomitant chemotherapy** or **immunotherapy**

Sample size N = 37 patients

Treatment and Procedure

Treatment plan based on CT

Sources 0.7 mm in diameter and 10 or 20 mm in length

Activity per source 3 μCi

Source insertion using **endoscopic ultrasonography** under sedation

Timeline and Follow-Up

Alpha DaRT sources insertion

Check-up on days 6, 15, 21, 35, 60 after insertion

Follow-up duration up to 2 years

Limit of 1 patient / month for first 5 patients, to confirm safety

Canada Pancreas Trial Baseline Characteristics

Subject ID	Age (years)	Sex	ECOG Score	Tumor Stage	Tumor Location	Pancreatic Cancer Inoperability	Prior Treatments	Length of Alpha DaRT Sources (cm)	GTV Coverage @ 16 Gy Alpha Radiation Dose
PANC-101-02-001	78	M	1	Stage IV	Pancreatic head/ uncinate	Metastatic disease	Chemotherapy: Gemcitabine and Paclitaxel; Gemcitabine	3	8%
PANC-101-02-002	68	F	2	Stage III	Pancreatic head	Unresectability	Chemotherapy: FOLFIRINOX (fluorouracil+leucovorin +oxaliplatin+irinotecan); Gemcitabine and Paclitaxel	11	13%
PANC-101-02-003	69	F	0	Stage II	Pancreatic head/neck	Unresectability	Chemotherapy: FOLFIRINOX; Abraxane and Gemcitabine	21	44%
PANC-101-02-004	84	F	1	Stage IV	Pancreatic head	Metastatic disease	Chemotherapy: Capecitabine	22	12.5%
PANC-101-02-005	71	F	0	Stage IV	Pancreatic neck	Metastatic disease	None	24	29.5%

Safety and Feasibility Outcomes

- **Successful delivery** to all 5 patients
- All patients were **discharged** from the hospital **on the same day** as the procedure
- All device- or procedure-associated adverse events (2) were **mild** (Grade 1)
- **No Grade 3** or higher associated events
- All SAEs were **not associated with** the Alpha DaRT or the procedure

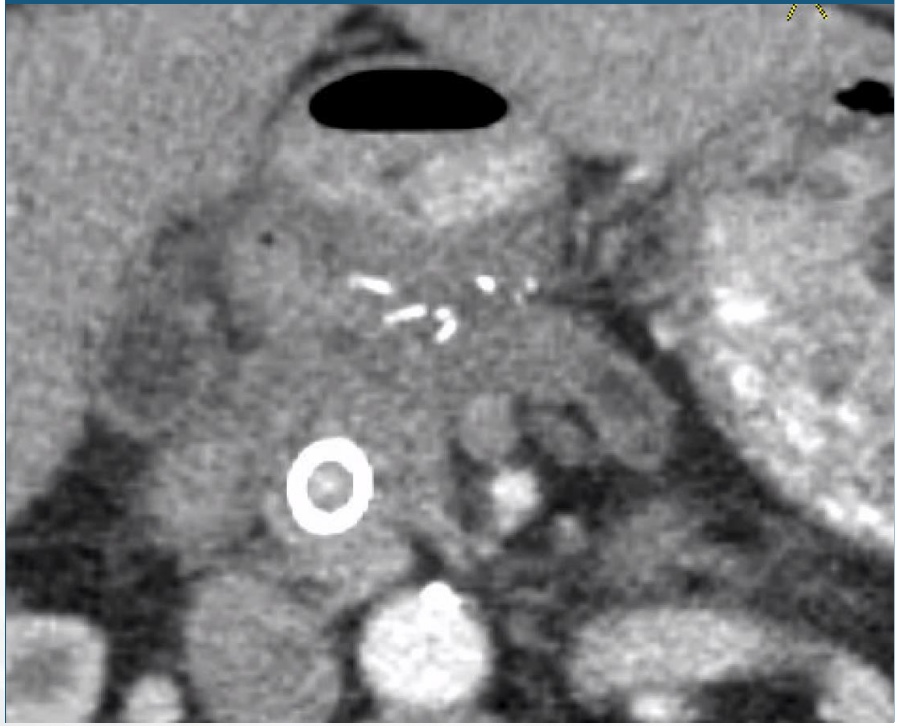
Early Response Data

Subject ID	Age (years)	Sex	ECOG Score	Tumor Stage	Tumor Location	Pancreatic Cancer Inoperability	Prior Treatments	Length of Alpha DaRT Sources (cm)	GTV Coverage @ 16 Gy Alpha Radiation Dose
Progressive Disease; Death ~3 months after treatment								3	8%
Progressive Disease; Death ~3 months after treatment								11	13%
Stable Disease at 28 days; Partial Response at 69 days								21	44%
Stable Disease at 28 and 98 days								22	12.5%
Stable Disease at 28 days								24	29.5%

PANC-101-02-003 – Partial Response

Patient #3 in the trial demonstrated a partial response at 69 days after treatment, as can be seen below, while the Alpha DaRT sources appear to stay largely in place

Imaging at ~1 Month



Imaging at ~2 Months

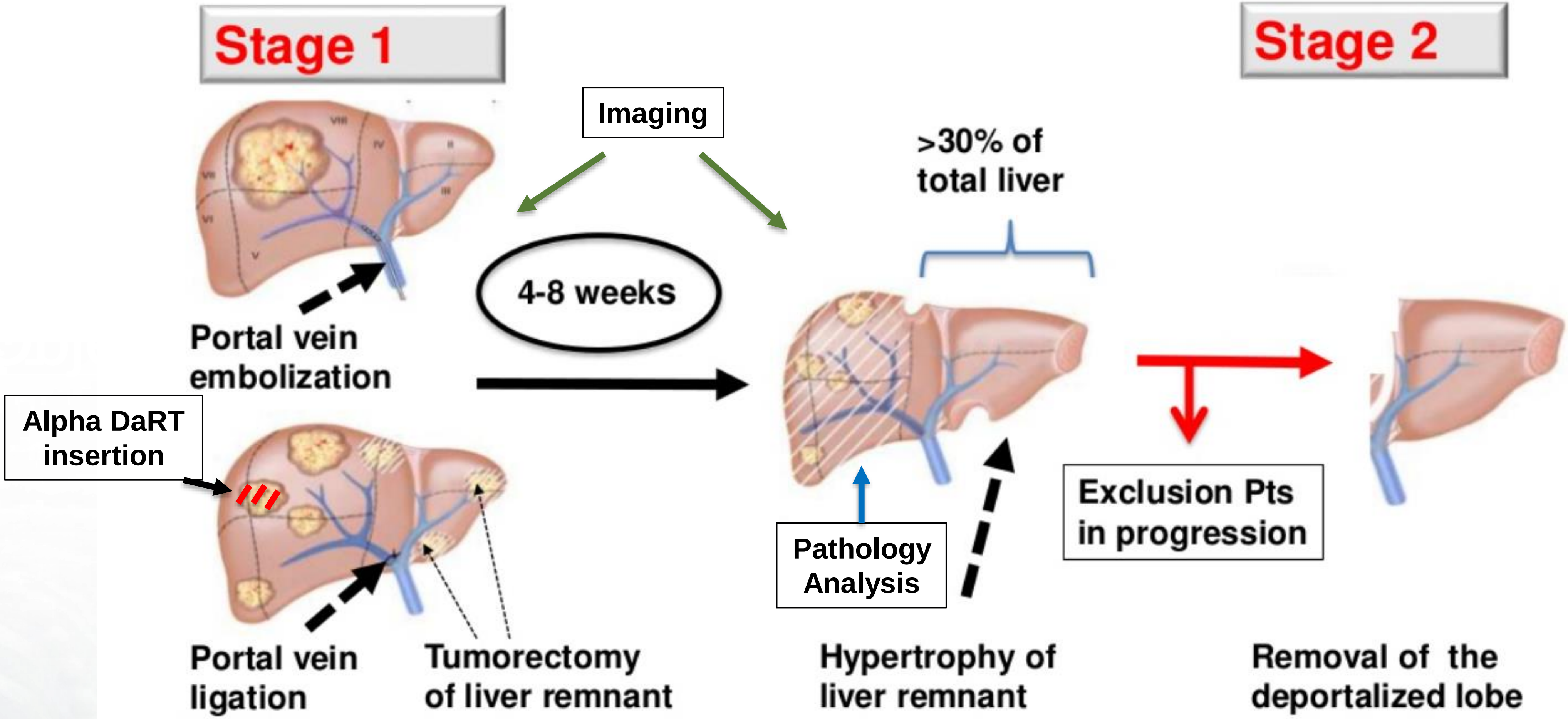
Internal Organs

A Feasibility and Safety Study of Intratumoral Diffusing Alpha Radiation Emitters for the Treatment of Liver Metastases

CTP-LIV-00

Study Schema

Liver study



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

Outline of Liver Metastases Study

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

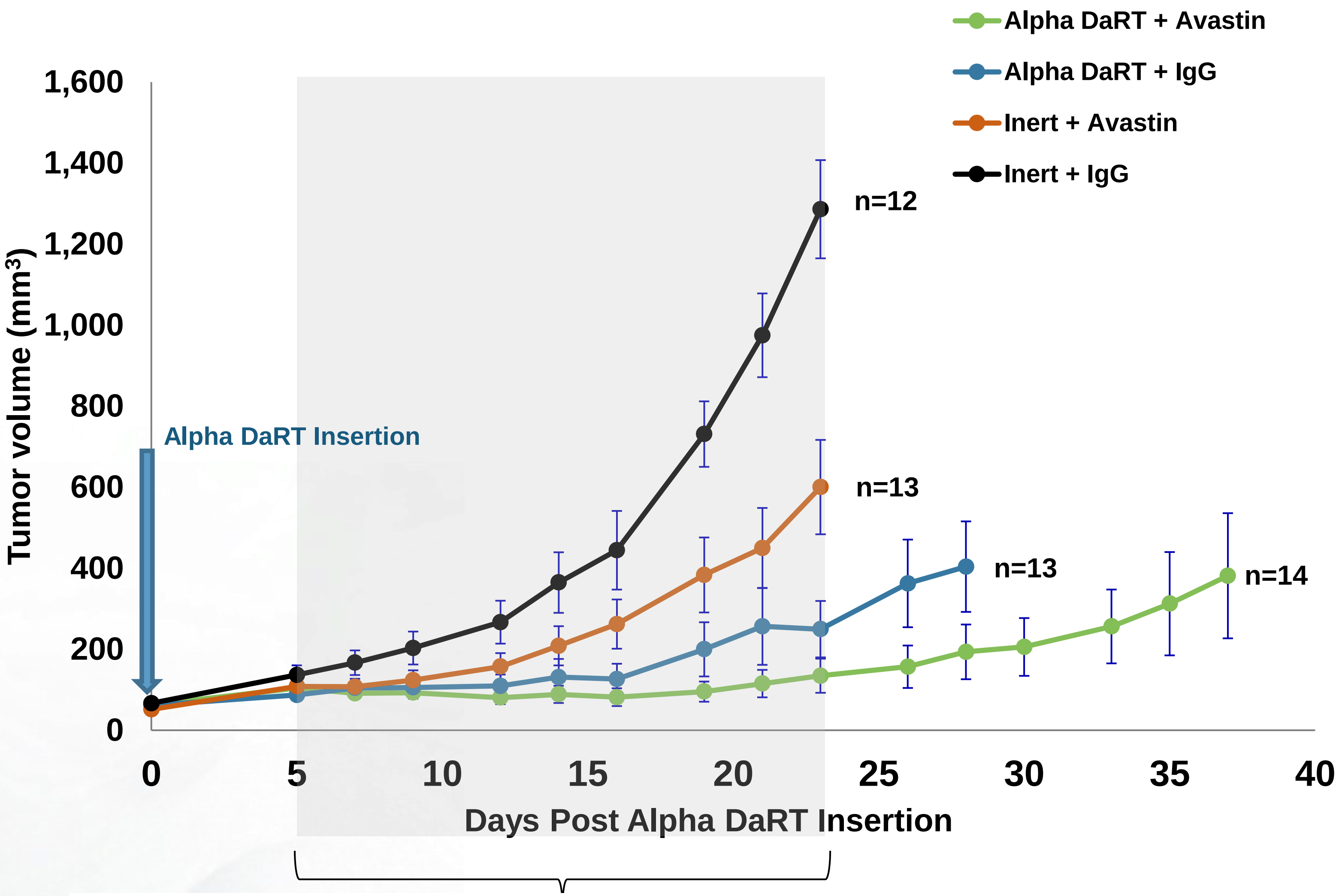
Timeline

- **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

Internal Organs

Glioblastoma Multiforme

Alpha DaRT + Avastin Combo Showed Attenuated Growth of GBM Xenografts



Avastin / IgG control injections 3 times per week for 3 weeks

Radial Applicator Overview

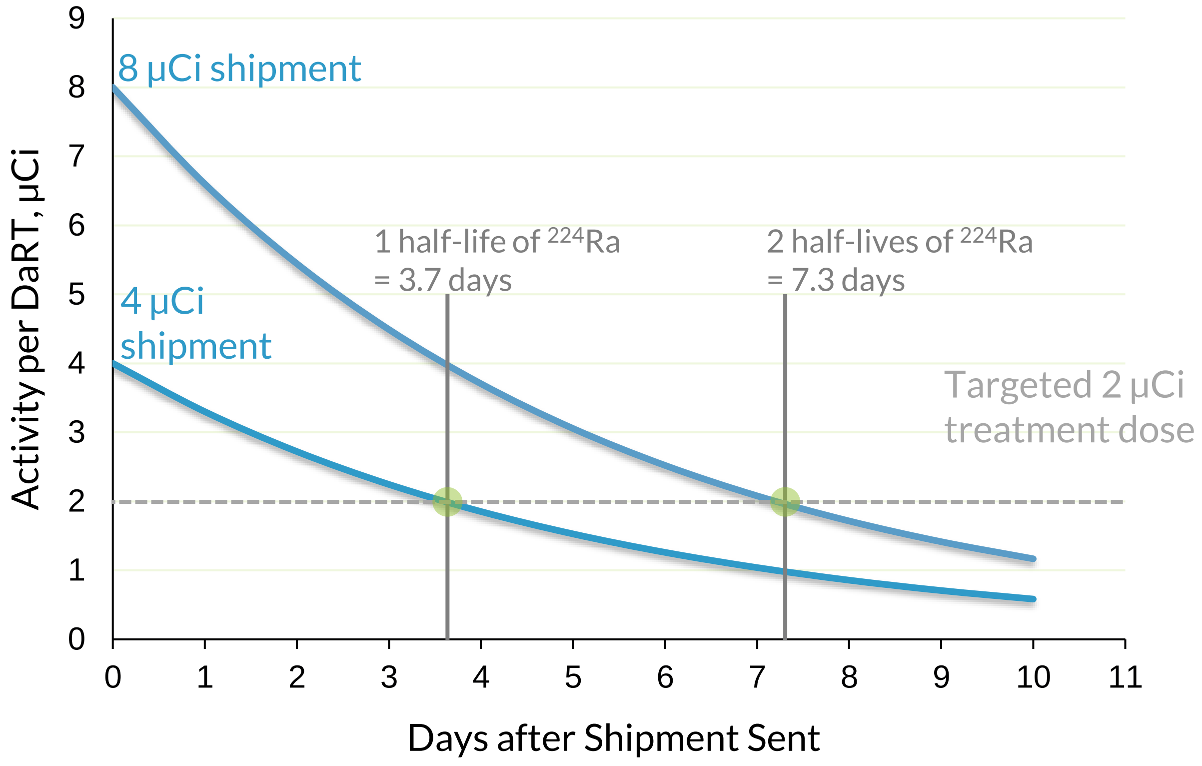
https://www.youtube.com/watch?v=IJY965J0xMk

Simple Radioactive Supply Chain

Delivery does not require any special handling and simple planning ensures on-time arrival

Alpha DaRT is shipped in Excepted Packages (low levels of radioactivity) or Type A packages, and may therefore be dispatched in suitable applicators by standard courier, requiring no special handling or protective gear in transit

Alpha DaRT Radioactive Decay



Personalized treatment, shipped out on a per-patient basis

Simple planning ensures that an Alpha DaRT arrives with the required amount of ^{224}Ra available, even when allowing for radioactive decay, based on the known half-life of the ^{224}Ra

Global Manufacturing Facilities

For efficient commercial operations, we look to establish manufacturing operations in multiple regions of the world, to enable relatively short shipping times to our core markets

Hudson, New Hampshire
(In Design)

Lawrence, Massachusetts
(~125,000 sources per year - *Ramping Up)*

Jerusalem
(~400,000 sources per year – Ramping Up)

Jerusalem
(Land Granted – Facility in Planning)

Togane, Japan
(In Design)

The Alpha Tau Executive Team

Strong management team with years of experience across the scientific and medical device space

Uzi Sofer
CEO & Chairman

- Co-Founder and CEO of BrainsWay (NASDAQ: BWAY)
- Medical device development, regulation, financing

Raphi Levy
Chief Financial Officer

- Former executive director in charge of healthcare investment banking in Goldman Sachs Israel

Prof. Itzhak Kelson
Chief Physics Officer

- Co-inventor of DaRT technology
- Emeritus professor of physics (taught at Tel Aviv University, Yale University, Weizmann Institute etc.)

Prof. Yona Keisari
Chief Scientific Officer

- Co-inventor of DaRT technology
- Professor of Immunology and Microbiology at Tel Aviv University, former NCI Post Doc Fellow

Peter Melnyk
Chief Commercial Officer

- Former CEO of Fortovia Therapeutics
- Former Chief Commercial Officer at Novocure
- Former Neuroscience marketing director at Bristol-Myers Squibb

Robert Den, MD
Chief Medical Officer

- Radiation oncologist and Associate Professor at Thomas Jefferson University Hospital
- Medical degree from Harvard Medical School

Amnon Gat
Chief Operations Officer

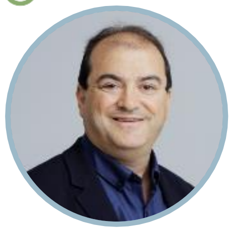
- >20 years experience in medical devices and healthcare
- Marketing strategy specialist

Ronen Segal
Chief Technology Officer

- >20 years of top leadership roles, including medical device industry
- Chairman of the BSMT Consortium

Board of Directors

Diverse mix of cancer therapeutic, medical device and financial expertise providing value-added oversight and guidance to corporate leadership



Uzi Sofer
CEO & Chairman

- Co-Founder and CEO of BrainsWay (NASDAQ: BWAY)
- Medical device development, regulation, financing

Michael Avruch
Director

- Expert in financing and restructuring
- CEO & CFO experience

Morry Blumenfeld
Director

- Former managing director at GE Healthcare, CEO of Quescon Consultants, Founding partner of Meditech Advisors Management, director at Mako

Meir Jakobsohn
Director

- Founder of Medison Ltd.
- Represents Amgen, Biogen, etc. for the marketing and distribution of their products in international markets

Alan Adler
Director

- 14 Years at McKinsey
- Senior Partner Evergreen Venture Capital
- Chairman and CEO of Oridion until its sale to Covidien

Ruth Alon
Director

- Former founder/chair, Israel Life Science Industry
- Former/current board/chair of multiple companies, e.g., Brainsgate, Vascular Biotech
- Former GP, Pitango VC

Dr. David M. Milch
Director

- Former HCCC Chairman
- Active medical investor
- MD from Harvard Medical School

Significant Industry Experience:

BrainsWay, nanox X-RAY REIMAGINED, MAKO SURGICAL CORP., McKinsey&Company, MEDISON Delivering Innovative Healthcare, INSIGHTEC, evergreen VENTURE PARTNERS, GE Healthcare, Allium Urological Solutions, VBL therapeutics, Oridion, AlphaTAU, pitango VENTURE CAPITAL

Anticipated Milestones

Geography	Indication	H2 2024	H1 2025	H2 2025
North America	Recurrent Cutaneous SCC (United States)	Completion of multi-center pivotal trial recruitment	Potential FDA submission	
	Pancreatic Cancer (Canada)		Targeted data readout	
Israel	Brain Cancer (GBM or Metastases)	First patient treated		
	Lung Cancer	First patient in feasibility trial		
Japan	Head & Neck Cancer	Potential PMDA approval		

Clinical / Enrollment | Regulatory

Financial Position

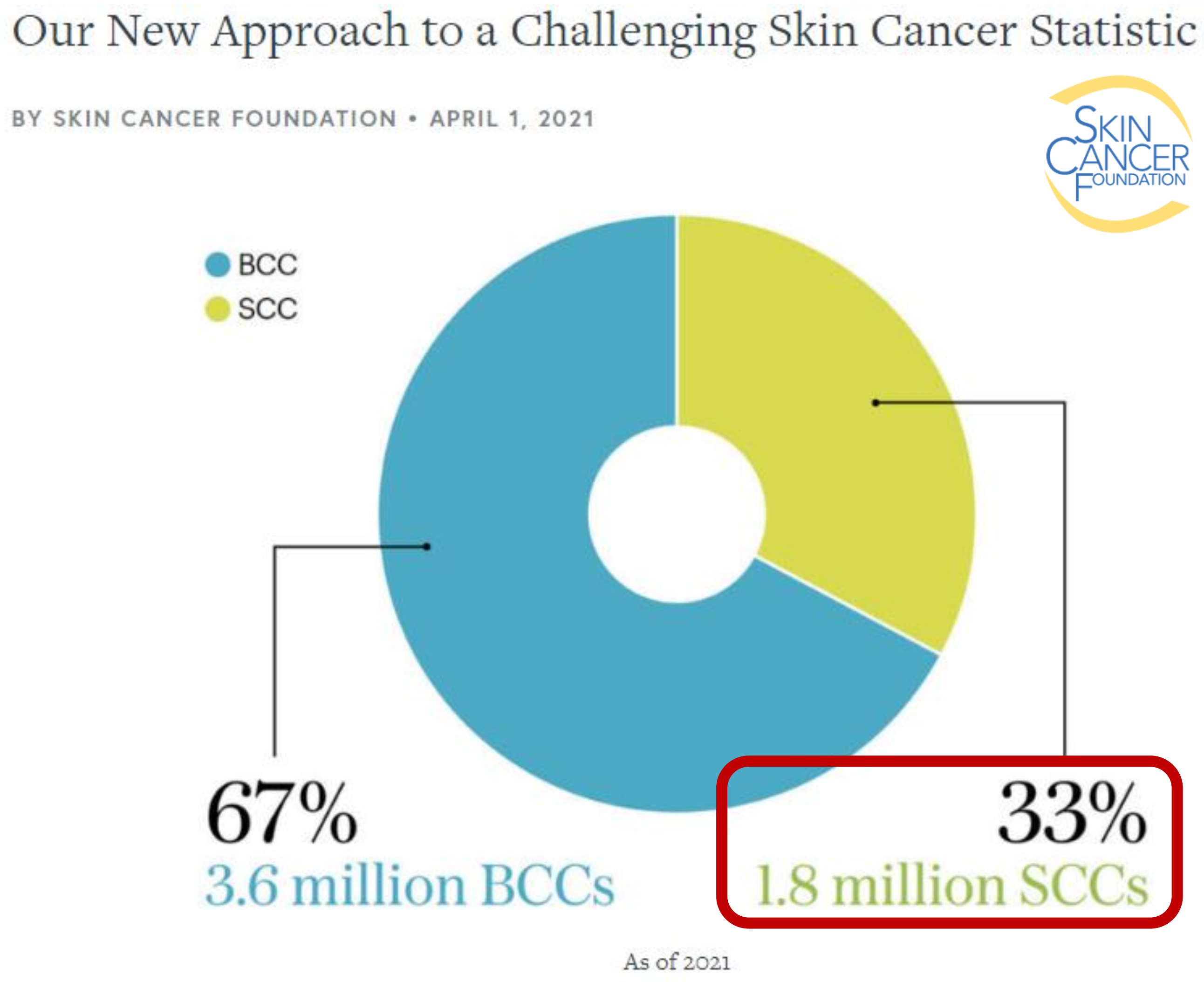
- Public Since Mar-2022 (NASDAQ:DRTS)
- $74.1mm in Cash & Deposits at Q2 2024
- 2+ Years of Cash Runway

Saving Lives Globally

Appendix

Analysis of U.S. Market Opportunity in Cutaneous Squamous Cell Carcinoma

U.S. Annual Cutaneous Squamous Cell Carcinoma Incidence



Source: https://www.skincancer.org/blog/our-new-approach-to-a-challenging-skin-cancer-statistic/

Risk Stratification Per NCCN Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

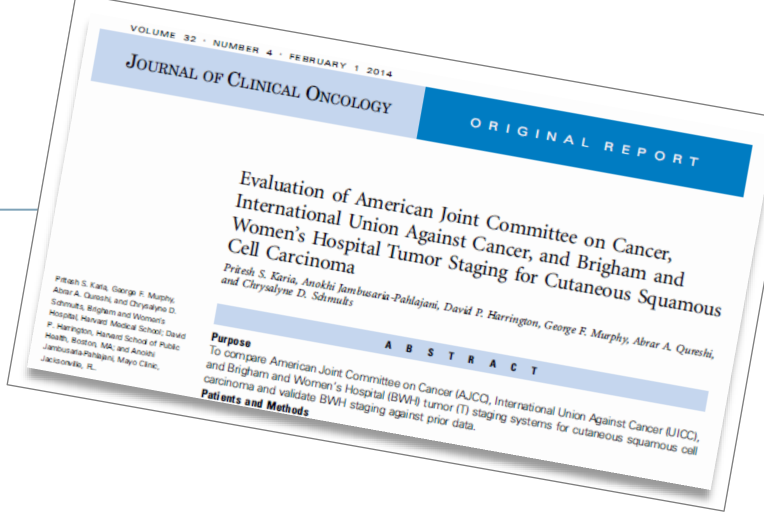
STRATIFICATION TO DETERMINE TREATMENT OPTIONS AND FOLLOW-UP FOR LOCAL CSCC BASED ON RISK FACTORS FOR LOCAL RECURRENCE, METASTASES, OR DEATH FROM DISEASE

Risk Group[a]	Low Risk	High Risk	Very High Risk
Treatment options	SCC-2	SCC-3	SCC-3
H&P			
Location/size[b]	Trunk, extremities ≤2 cm	Trunk, extremities >2 cm – ≤4 cm	>4 cm (any location)
		Head, neck, hands, feet, pretibia, and anogenital (any size)[e]	
Clinical extent	Well-defined	Poorly defined	
Primary vs. recurrent	Primary	Recurrent	
Immunosuppression	(-)	(+)	
Site of prior RT or chronic inflammatory process	(-)	(+)	
Rapidly growing tumor	(-)	(+)	
Neurologic symptoms	(-)	(+)	
Pathology (SCC-A)			
Degree of differentiation	Well or moderately differentiated		Poor differentiation
Histologic features: Acantholytic (adenoid), adenosquamous (showing mucin production), or metaplastic (carcinosarcomatous) subtypes	(-)	(+)	Desmoplastic SCC
Depth[c,d]: Thickness or level of invasion	<2 mm thick and no invasion beyond subcutaneous fat	2–6 mm depth	>6 mm or invasion beyond subcutaneous fat
Perineural involvement	(-)	(+)	Tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm
Lymphatic or vascular involvement	(-)	(-)	(+)

Focus Patients

Source: NCCN Guidelines for Cutaneous SCC: https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf

How Many Are "High/Very-High Risk"?
Staging from Brigham & Women's Hospital (BWH) Researchers


VOLUME 32 · NUMBER 4 · FEBRUARY 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital Tumor Staging for Cutaneous Squamous Cell Carcinoma

Pritesh S. Karia, Anokhi Jambusaria-Pahlajani, David P. Harrington, George F. Murphy, Abrar A. Qureshi, and Chrysalyne D. Schmults

ABSTRACT

Purpose

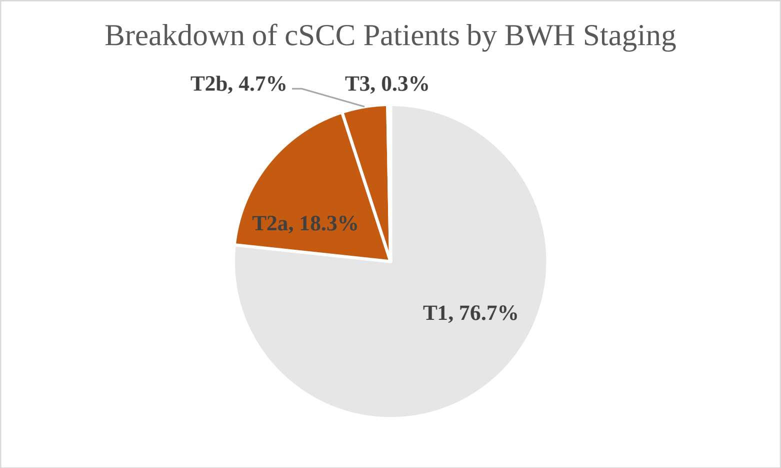
To compare American Joint Committee on Cancer (AJCC), International Union Against Cancer (UICC), and Brigham and Women's Hospital (BWH) tumor (T) staging systems for cutaneous squamous cell carcinoma and validate BWH staging against prior data.

Patients and Methods

BWH Tumor Stage	Description
T1	0 high-risk factors*
T2a	1 high-risk factor
T2b	2-3 high-risk factors
T3	≥ 4 high-risk factors

*Note: High-risk factors include tumor diameter ≥ 2 cm, poorly differentiated histology, perineural invasion ≥ 0.1 mm, or tumor invasion beyond fat (excluding bone invasion which automatically upgrades tumor to BWH stage T3).

Compare to high-risk factors from NCCN Guidelines on previous page!



23.3% of cSCC are stages T2a – T3 (high-risk, i.e., at least 1 risk factor)

At 1.8 million cSCC incidences per year, that translates into **~419k high-risk cases per year**!

Source: *Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital Tumor Staging for Cutaneous Squamous Cell Carcinoma*
Pritesh S. Karia, Anokhi Jambusaria-Pahlajani, David P. Harrington, George F. Murphy, Abrar A. Qureshi, and Chrysalyne D. Schmults. Journal of Clinical Oncology 2014 32:4, 327-334

What Are cSCC Outcomes Like?

Data from Brigham & Women's Hospital (BWH) Researchers

STUDY

Factors Predictive of Recurrence and Death From Cutaneous Squamous Cell Carcinoma

A 10-Year, Single-Institution Cohort Study

Chrysalyne D. Schmults, MD, MSCE; Pritesh S. Karia, MPH; Joi B. Carter, MD; Jiali Han, PhD; Abrar A. Qureshi, MD, MPH

NCCN Risk Factors Correspond to Recurrence and Metastatic Outcomes

Table 3. Results of Univariate Analysis for Outcomes of Interest

	LR		NM		DSD		ACD	
	SHR (95% CI)	*P* Value	SHR (95% CI)	*P* Value	SHR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y								
<70	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
70-80	2.1 (1.1-3.9)	.02	1.2 (0.6-2.5)	.66	1.1 (0.4-2.7)	.89	1.7 (1.4-2.0)	<.001
>80	1.7 (0.8-3.8)	.17	1.0 (0.4-2.8)	.99	0.9 (0.2-3.3)	.88	2.5 (2.0-3.1)	<.001
Sex								
Female	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Male	1.6 (0.9-3.0)	.11	2.4 (1.0-5.5)	.04	2.8 (1.9-8.3)	.06	1.9 (1.6-2.3)	<.001
Tumor diameter, cm								
<2	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
≥2	8.9 (5.1-15.7)	<.001	15.2 (6.6-35.2)	<.001	28.5 (9.4-86.3)	<.001	1.0 (0.8-1.3)	.75
Tumor differentiation								
Well	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Moderate	2.7 (1.3-5.9)	.01	5.6 (1.6-19.1)	.006	2.5 (0.6-11.2)	.23	1.3 (1.1-1.6)	.02
Poor	10.4 (5.4-19.0)	<.001	29.8 (10.2-87.0)	<.001	19.4 (6.4-58.5)	<.001	1.7 (1.3-2.1)	<.001
Tumor depth								
Dermis	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Subcutaneous fat	5.9 (3.0-11.7)	<.001	7.2 (2.8-18.1)	<.001	8.8 (2.8-27.8)	<.001	1.5 (1.1-2.0)	.006
Beyond fat	24.4 (12.9-46.1)	<.001	43.0 (19.6-93.2)	<.001	51.4 (19.1-137.8)	<.001	1.7 (1.2-2.6)	.008
Perineural invasion								
No	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Yes	8.8 (4.8-16.4)	<.001	14.5 (7.1-29.8)	<.001	11.3 (4.5-28.1)	<.001	1.7 (1.2-2.3)	.003
Lymphovascular invasion								
No	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Yes	5.7 (2.4-13.4)	<.001	2.7 (0.6-11.3)	.17	2.1 (0.3-15.3)	.47	1.3 (0.8-2.1)	.33
Tumor location								
Other	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Head or neck (excluding ear and temple)	2.5 (1.5-4.4)	.001	2.4 (1.3-5.0)	.009	1.8 (0.8-4.3)	.18	1.1 (0.9-1.3)	.34
Ear	3.8 (1.4-10.4)	.01	3.1 (0.9-11.0)	.03	2.6 (0.8-9.0)	.12	1.4 (1.0-1.9)	.03
Temple	3.2 (1.1-9.0)	.03	3.8 (1.2-12.5)	.03	1.8 (0.2-13.5)	.56	1.5 (1.0-2.3)	.07
Perianal	17.4 (4.1-72.4)	<.001	64.3 (12.4-321.1)	<.001	39.0 (10.7-142.4)	<.001	1.0 (0.3-4.0)	.79
Genitalia	15.0 (2.6-88.2)	.003	69.4 (14.6-329.8)	<.001	47.6 (8.0-282.4)	<.001	0.9 (0.2-5.4)	.78

Abbreviations: ACD, all-cause death; DSD, disease-specific death; HR, hazard ratio; LR, local recurrence; NM, nodal metastasis; SHR, subhazard ratio.

Estimate of Patient Pool with Local Recurrence or Nodal Metastasis

*We conducted the **largest study of CSCC outcomes since 1968**...The median follow-up was 50 (range, 2-142) months. **Local recurrence occurred in 45 patients (4.6%) during the study period; 36 (3.7%) developed nodal metastases**; and 21 (2.1%) died of CSCC.*

1.8 million incidences per year, with 4.6% local recurrence and another 3.7% nodal metastasis, translates into ~**148 thousand recurrent / metastatic cases per year**

Source: *Factors Predictive of Recurrence and Death From Cutaneous Squamous Cell Carcinoma: A 10-Year, Single-Institution Cohort Study*
Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. JAMA Dermatol. 2013;149(5):541–547. doi:10.1001/jamadermatol.2013.2139

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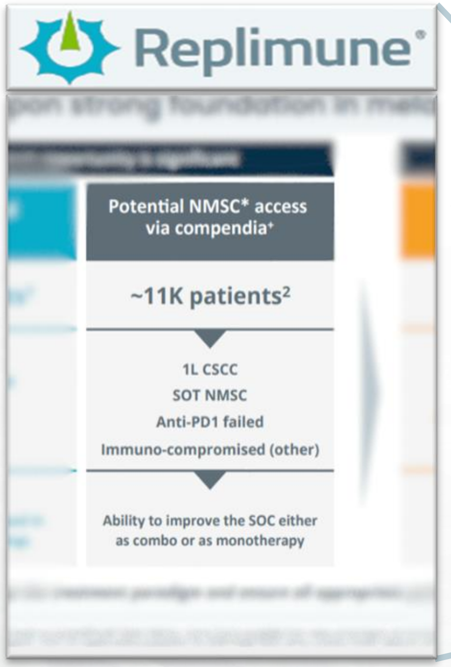
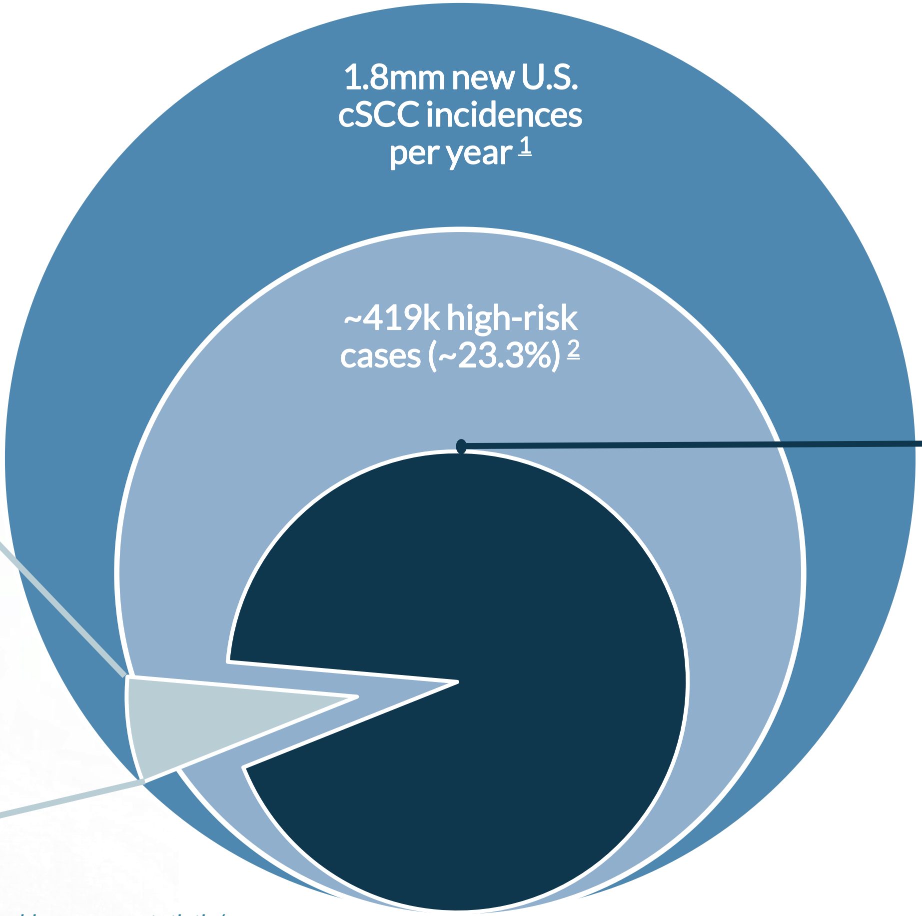
Potential cSCC Patient Breakdown - Estimated U.S. Incidence

~ 11k patients
Excluded Population
Replimune's Assumed
Target Population for
Systemic cSCC Therapy[4]





Targeted population
~137k cases per year

Estimated new U.S. cases per year of cSCC with local recurrence and/or nodal metastasis (8.2%)[3], excluding 11k who are so metastatic as to require systemic therapy[4]

[1] https://www.skincancer.org/blog/our-new-approach-to-a-challenging-skin-cancer-statistic/
[2] Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital Tumor Staging for Cutaneous Squamous Cell Carcinoma
Pritesh S. Karia, Anokhi Jambusaria-Pahlajani, David P. Harrington, George F. Murphy, Abrar A. Qureshi, and Chrysalyne D. Schmults. Journal of Clinical Oncology 2014 32:4, 327-334
[3] Factors Predictive of Recurrence and Death From Cutaneous Squamous Cell Carcinoma: A 10-Year, Single-Institution Cohort Study
Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. JAMA Dermatol. 2013;149(5):541–547. doi:10.1001/jamadermatol.2013.2139
[4] https://ir.replimune.com/static-files/41e9e141-6ff8-44c9-9b5e-e25c9acb5a8e

Alpha DaRT – Analyst Views on Potential Treatment Selling Price

Wall street analysts' views – not company view

>$20K — H.C.WAINWRIGHT&CO.

"We estimate that Alpha DaRT may be priced at over $20,000 per treatment course per patient"

April 2023

$60K — PIPER | SANDLER

"We've conservatively assumed an ASP per procedure of $60K, although payment rates for therapies such as NVCR's Optune ($100K+) represents upside opportunity to our estimates if DRTS could secure a commensurate therapy payment rate."

April 2022

$65K — CANTOR Fitzgerald

Alpha DaRT Gross Price	$65,000
% Price Growth	2%

Source: Cantor Fitzgerald Estimates

April 2022

$125K — citi

"We model per-patient pricing at $125,000 at launch, consistent with the annualized cost of cancer immunotherapies (i.e., cemiplimab)."

December 2023

Benchmarking of U.S. Treatment Prices

- Local radiotherapy medical device (competing liver radioembolization products)
- Local radiation therapy for adjuvant cSCC
- Locally injected drug product candidate for cSCC
- FDA comparator systemic therapies for pivotal trial statistics

~$17k — SIRT (Boston Scientific, SIRTeX)

~$32k — External Beam Radiation Therapy

~$61k — Image-Guided Radiation Therapy

~$93k — LIBTAYO
Average 30.8 weeks
Max 24 months
3 weeks per cycle
$9,100 per cycle

~$95k — Intensity-Modulated Radiation Therapy (IMRT)

~$113k — KEYTRUDA
Average 6.9 months
3 weeks per cycle
$11.3k per cycle

~$145k — Proton Therapy

~$200k — Replimune RP1
10 Months
$20k per month

LIBTAYO
Max 24 Months
~$315k

KEYTRUDA
Max 24 Months
~$393k

Note: ReSTART trial inclusion criteria envisions usage when standard radiation therapy is not indicated, and uses systemic therapies as historical control arms

Source for SIRT pricing: https://www.sirtex.com/Media/womp5u2s/Sirtex%20Coding%20Guide_Hosp%20%28HEPRA-US-001-02-24%293.pdf
Source for cSCC radiation therapy pricing: https://ncbi.nlm.nih.gov/pmc/articles/PMC10826833/#:~:text=Based%20on%20four%20radiation%20treatment,patient%2C%20detailed%20in%20Table%201B-
Source for Libtayo price and cycle length: https://investor.regeneron.com/news-releases/news-release-details/fda-approves-libtayor-cemiplimab-rwlc-first-and-only-treatment
Source for Libtayo average treatment length https://www.pharmaline.co.il/wp-content/uploads/2021/12/LIBTAYO-9.12D.pdf
Source for Libtayo max treatment length: https://www.medicalnewstoday.com/articles/drugs-libtayo-dosage#dosage
Source for Keytruda price and cycle length: https://www.keytruda.com/financial-support/#:~:text=The%20list%20price%20for%20each,out%2Dof%2Dpocket%20costs .
Source for Keytruda average treatment length: https://www.merck.com/news/fda-approves-expanded-indication-for-mercks-keytruda-pembrolizumab-in-locally-advanced-cutaneous-squamous-cell-carcinoma-cscc/
Source for Keytruda max price: https://www.keytrudahcp.com/dosing/options/
Source for RP1 Replimune: Barclays research model as of 24-Feb-2024 for Replimune Group Inc

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