

**Advances and Innovations in Endoscopic Oncology and  
Multidisciplinary Gastrointestinal Cancer Care**

# Pancreaticobiliary Cancer

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# Disclosures

- Consultant/Advisor for Boston Scientific Corp, Pentax America, and Ambu USA
- On the Speaker's Bureau for Abbvie

*This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.*

*This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.*

*This presentation has been peer-reviewed and no conflicts were noted.*

# Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

## STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

*The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.*

## EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

***This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.***

# Ablation for Pancreaticobiliary Cancers

## **Fine Needle Injection**

- Alcohol
- Paclitaxel
- Dendritic cell vaccine

## **Probe Based Ablation**

- Photodynamic Therapy (PDT)
- Radiofrequency Ablation (RFA)
- Microwave ablation\*
- Irreversible electroporation (IRE)\*

# 1<sup>st</sup> Case of EUS RFA

66-year-old man

Diarrhea

Dehydration

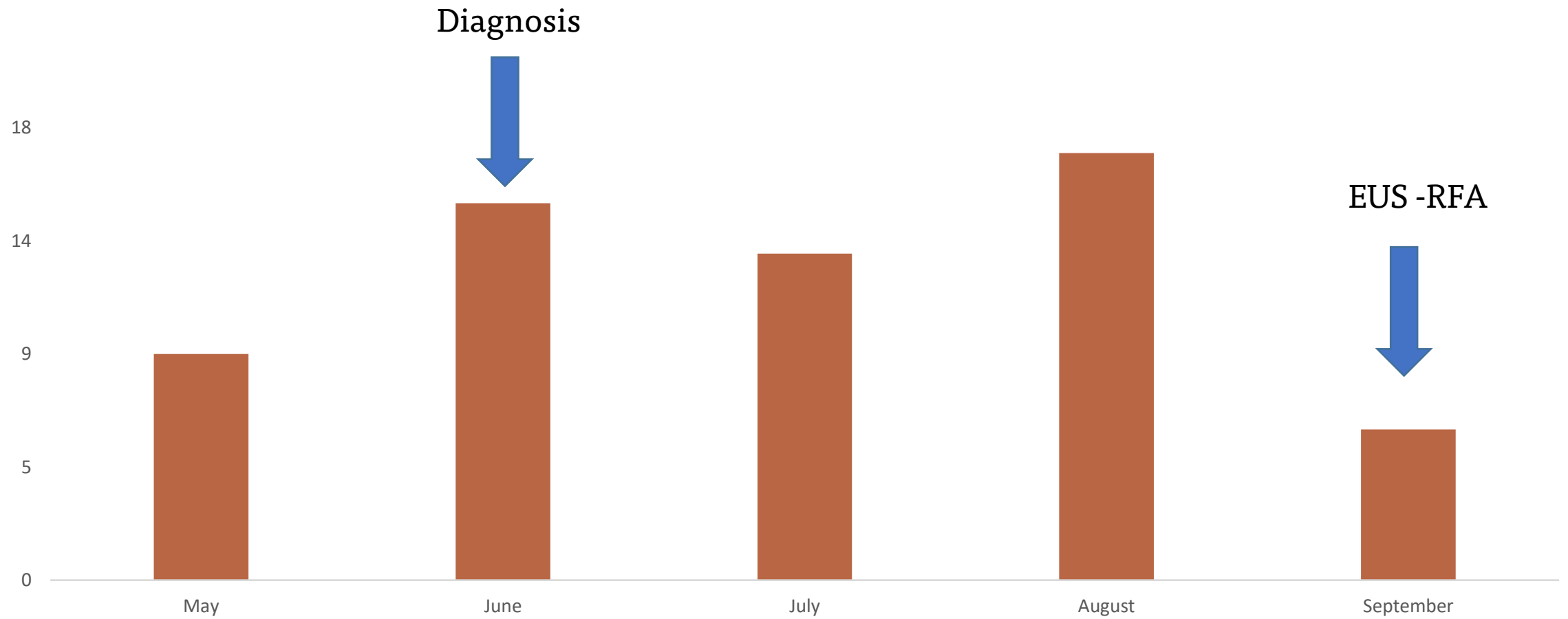
Hypokalemia

Achlorhydria

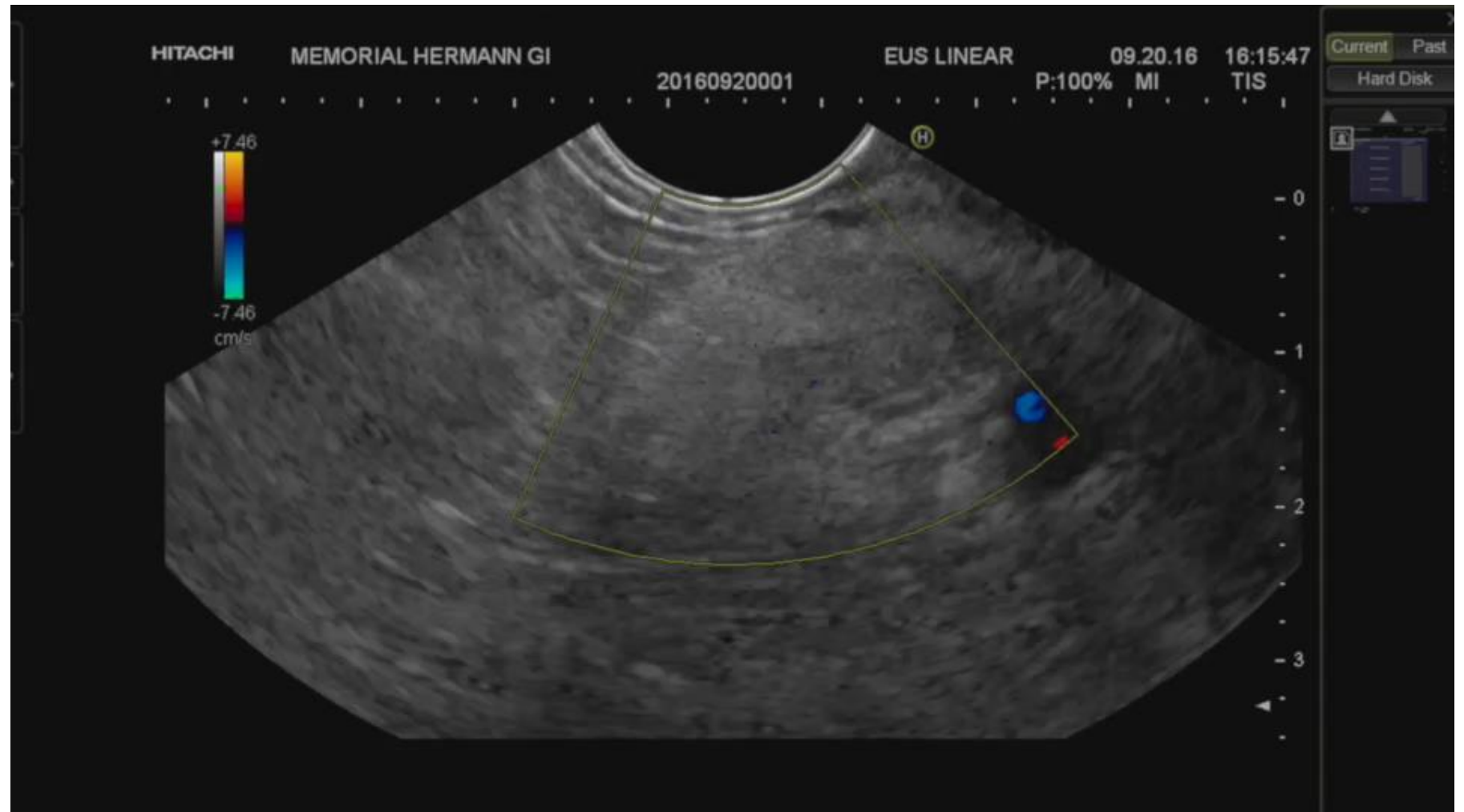
Mass at body of pancreas



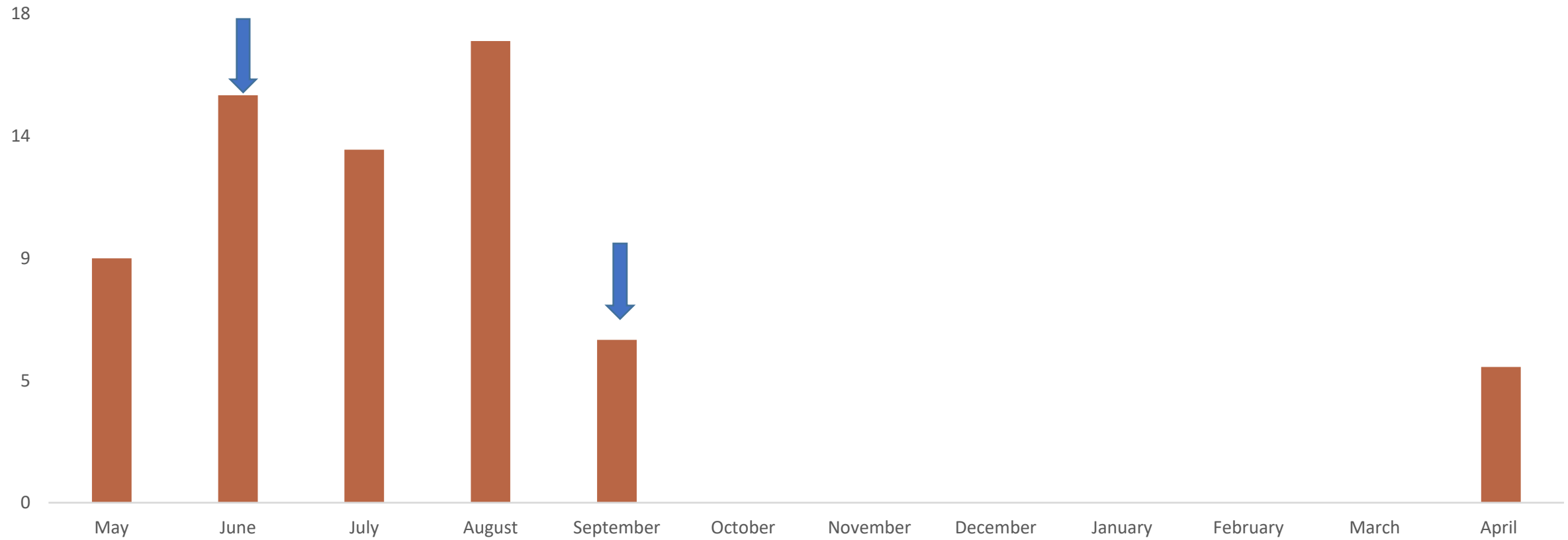
# VIPoma



# EUS RFA - VIPoma



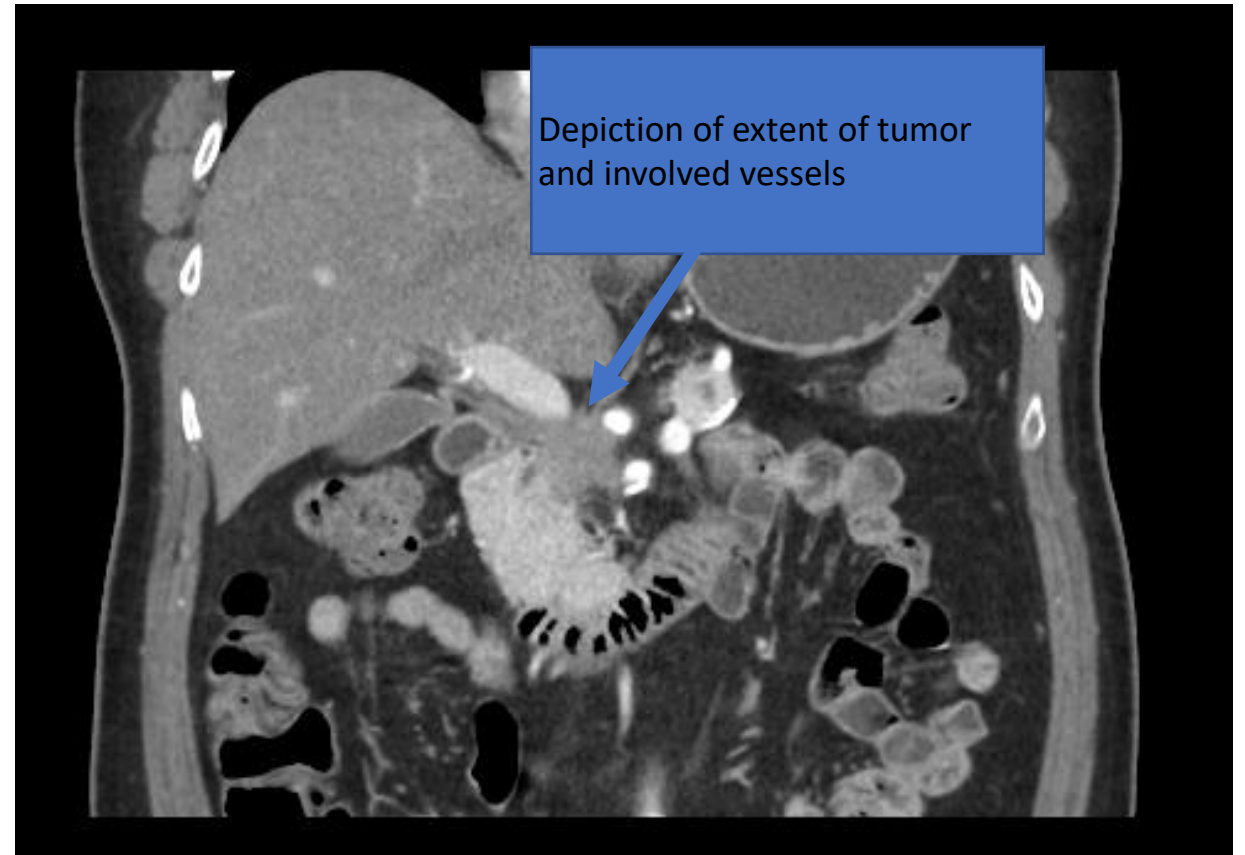
# VIPoma



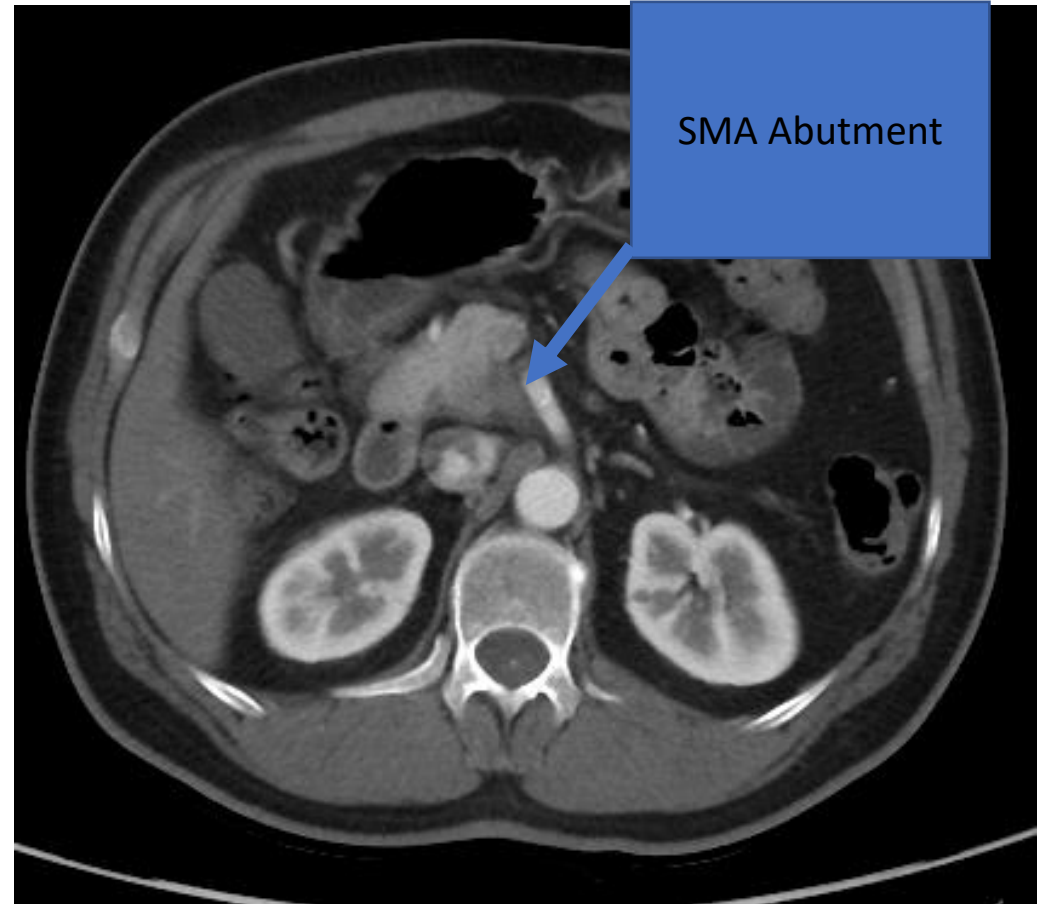
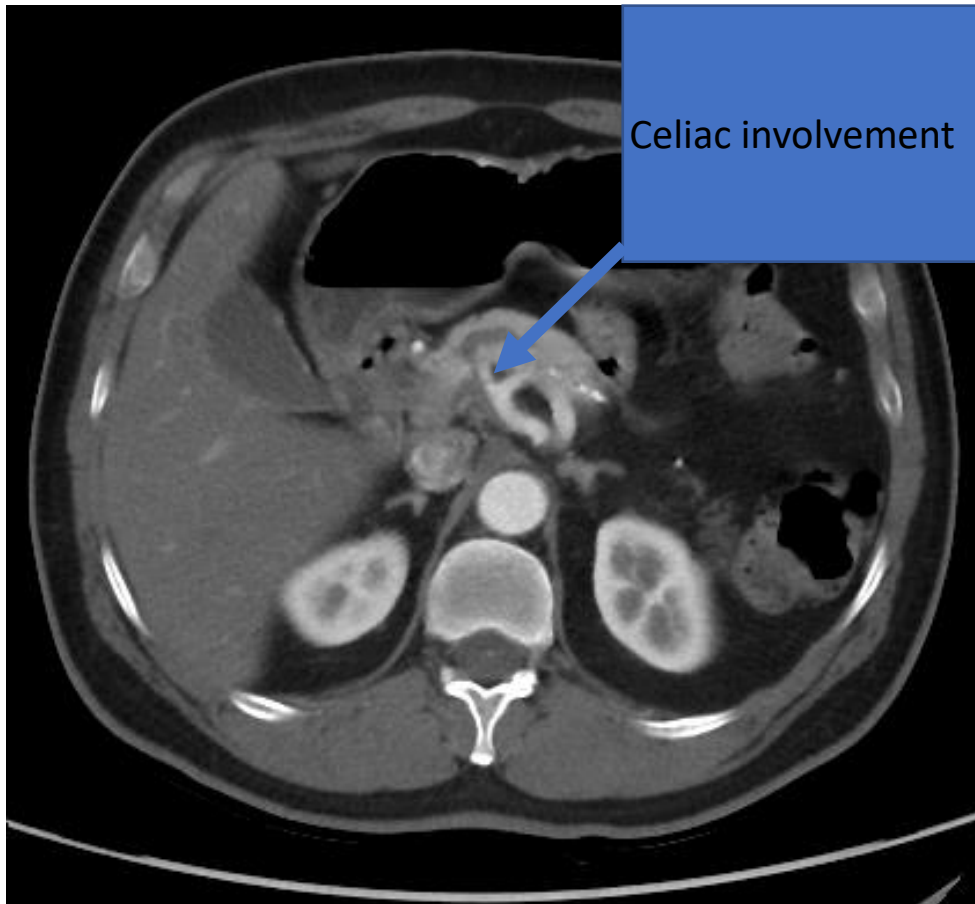


## Clinical case 2

- 65-Year-old man
- Unresectable pancreatic cancer
- Involvement of
  - Celiac axis
  - SMA
  - Portal confluence
- Chemotherapy + Radiation therapy



# Case 2: Pancreatic Cancer



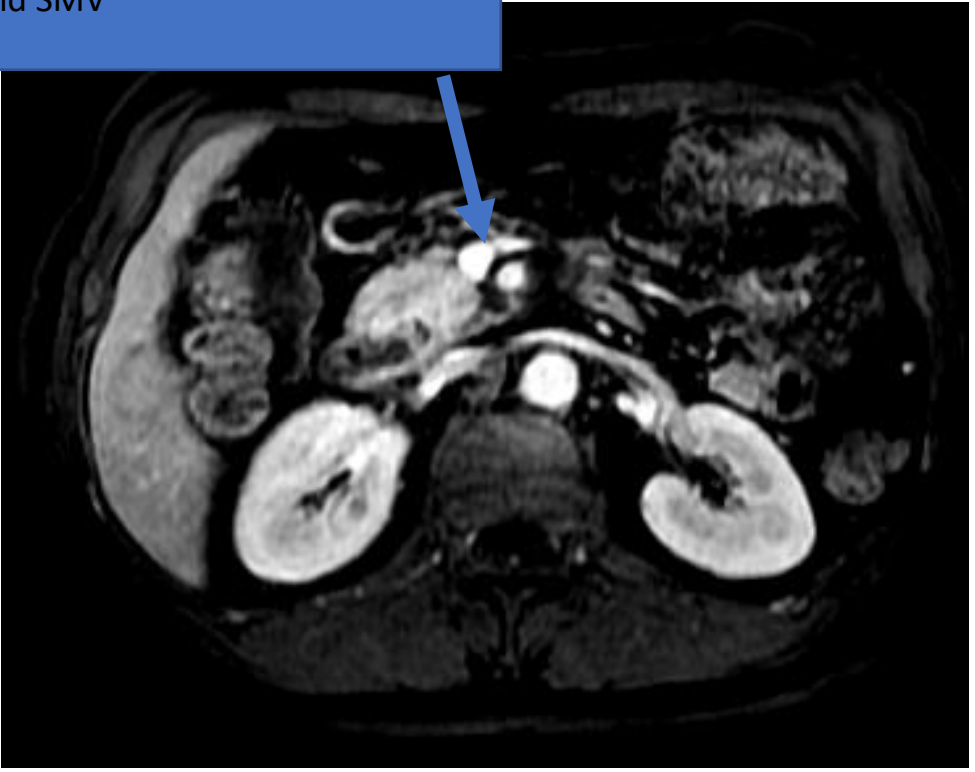
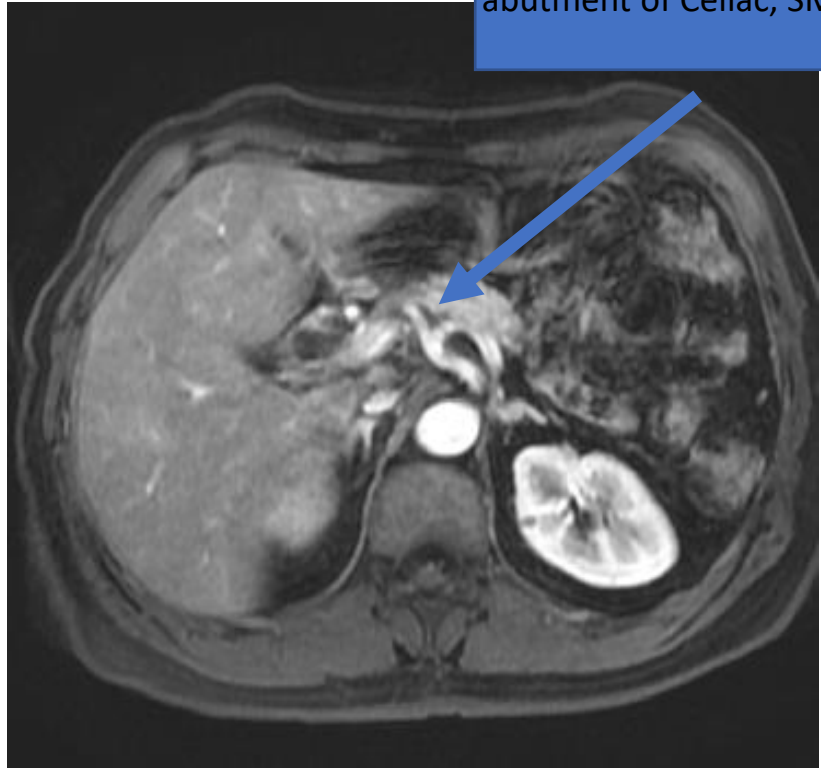
# Case 2: Pancreatic Cancer s/p EUS RFA # 2



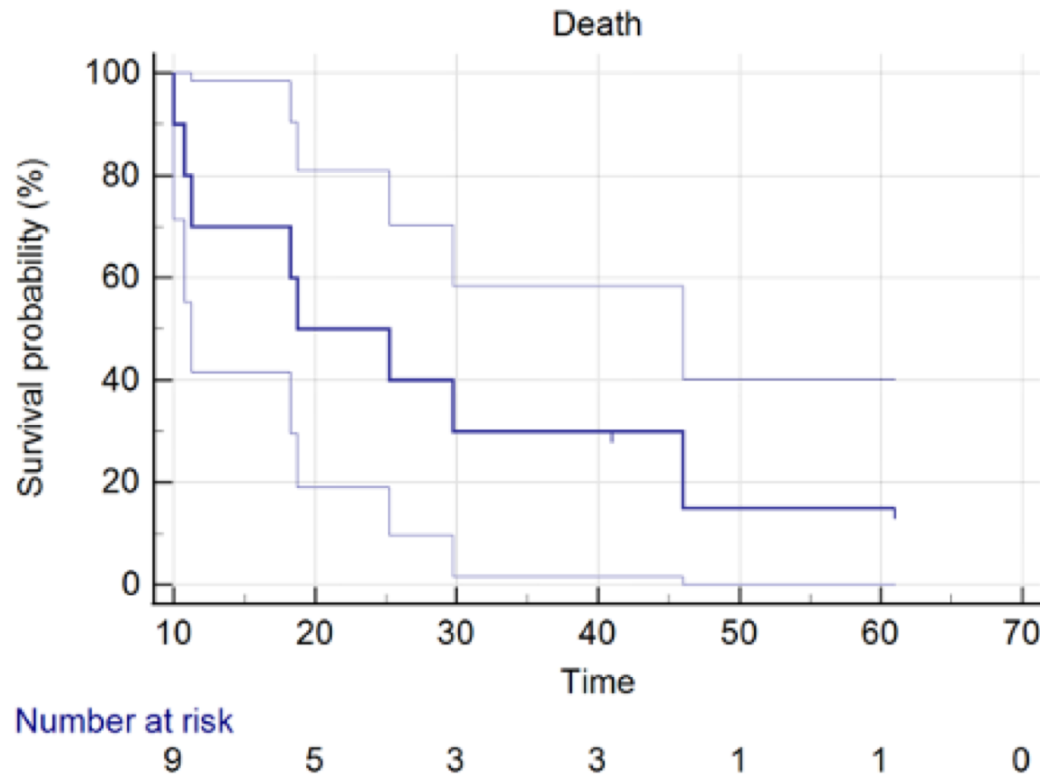
Following EUS guided RFA  
Complete opening of portal vein and SMV  
with pre-treatment tear drop appearance no  
longer seen

# Case 2: Pancreatic Cancer s/p EUS RFA # 3

2-months after EUS guided RFA  
MRI shows further improvement with no tumoral abutment of Celiac, SMA and SMV



# EUS-RFA for Unresectable Pancreatic Cancer



18.75 months survival  
(95% CI, 10 to 46 Months)

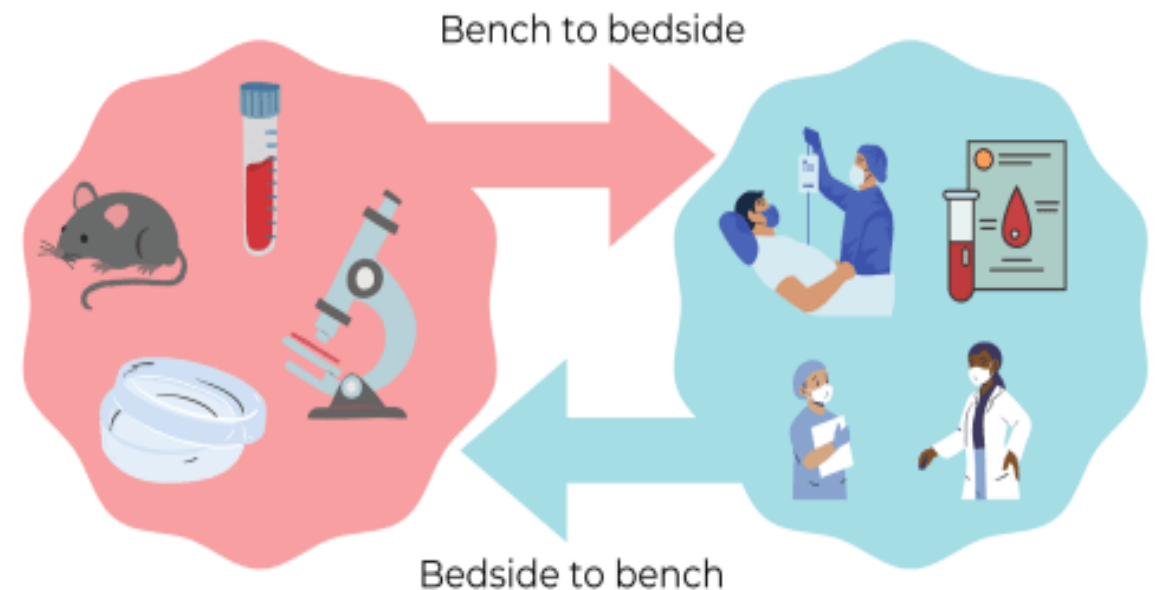
Expected Survival  
(SEER Data)  
9-12 months

Limitations:  
No control group  
Safety is primary endpoint,  
not survival

Kaplan Meier Survival Analysis

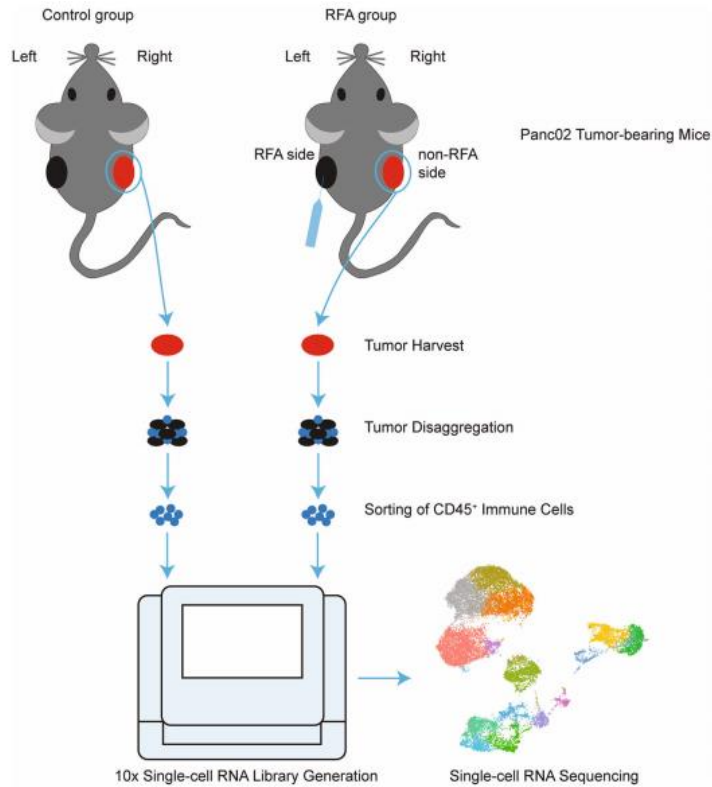
# Comprehensive EUS RFA Program

- Prospective EUS RFA registry including tissue banking
- PANCARDINAL 1 Trial: Endoscopic Ultrasound PANcreatic CAncer RAdiofrequeNCy ABlation Trial
- Mice model for pancreatic cancer RFA treatment



# RFA in Pancreatic cancer

## - Animal model -syngeneic-



### Analysis in non-RFA side:

- ✓ Isolated CD45+
- ✓ Single cell sequencing
- ✓ T cell receptor (TCR) sequencing

Fei et al. *Cell Death and Disease* (2020)11:589  
<https://doi.org/10.1038/s41419-020-02787-1>

Cell Death & Disease

ARTICLE

Open Access

## High-dimensional single-cell analysis delineates radiofrequency ablation induced immune microenvironmental remodeling in pancreatic cancer

Qinglin Fei<sup>1</sup>, Yu Pan<sup>1</sup>, Wenji Lin<sup>2</sup>, Yuanyuan Zhou<sup>3</sup>, Xingxing Yu<sup>1</sup>, Zelin Hou<sup>1</sup>, Xunbin Yu<sup>4</sup>, Xianchao Lin<sup>1</sup>, Ronggui Lin<sup>1</sup>, Fengchun Lu<sup>1</sup>, Hongdan Guan<sup>5</sup> and Heguang Huang<sup>1</sup>

“RFA modified T Cell Receptors (TCR), reduced the proportions of immunosuppressive cells and increased the percentages of functional T cells in distant non-RFA tumors.

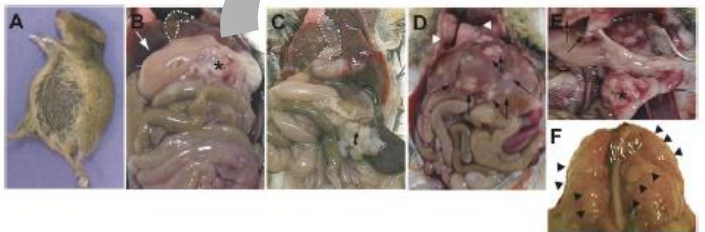
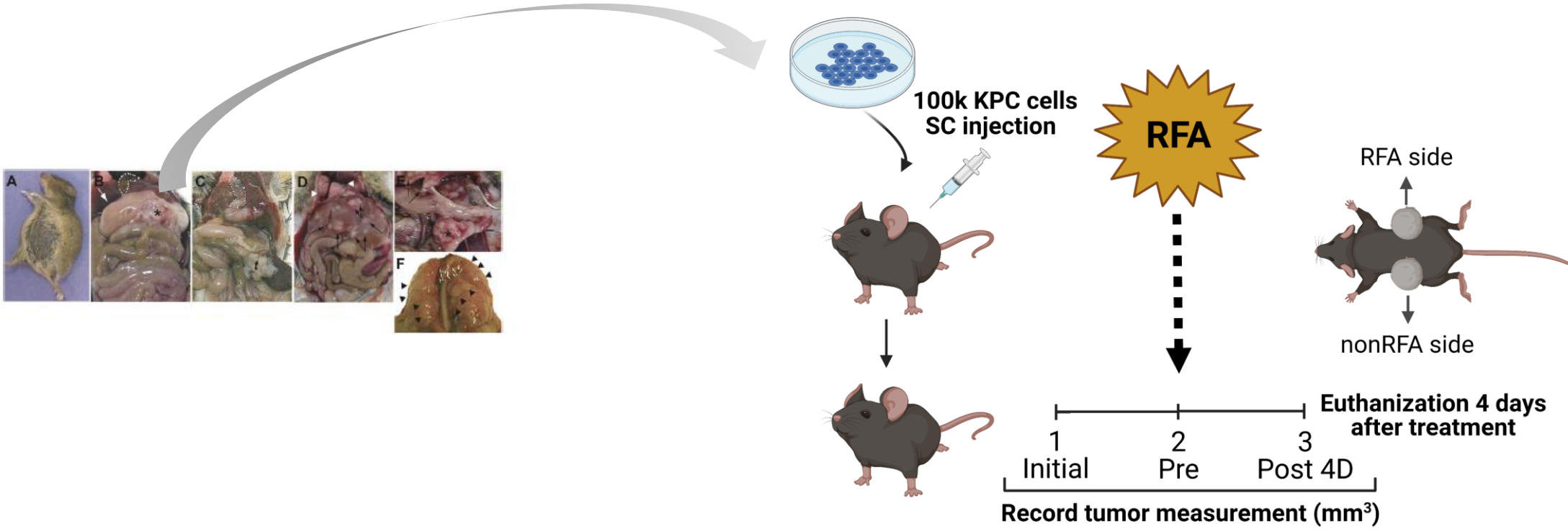
Immune checkpoints including PD-1 and LAG3 were upregulated in the T cells in distant non-RFA tumors after RFA, suggesting that combining RFA with immune checkpoint inhibitors may be an effective treatment approach.”

# Experimental design – KPC (PDAC syngeneic mouse model)

ARTICLE

## *Trp53<sup>R172H</sup>* and *Kras<sup>G12D</sup>* cooperate to promote chromosomal instability and widely metastatic pancreatic ductal adenocarcinoma in mice

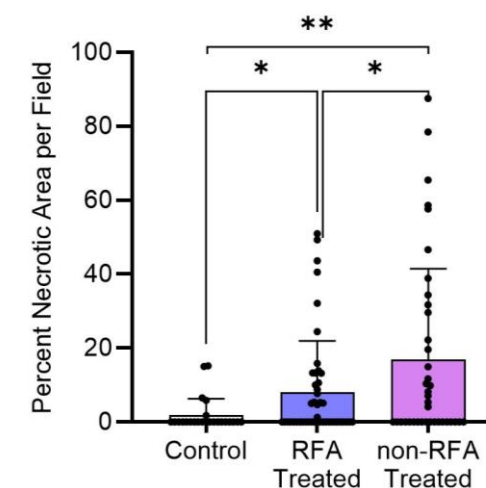
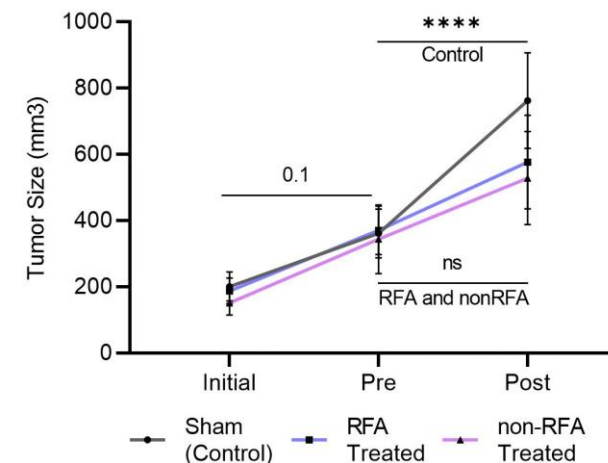
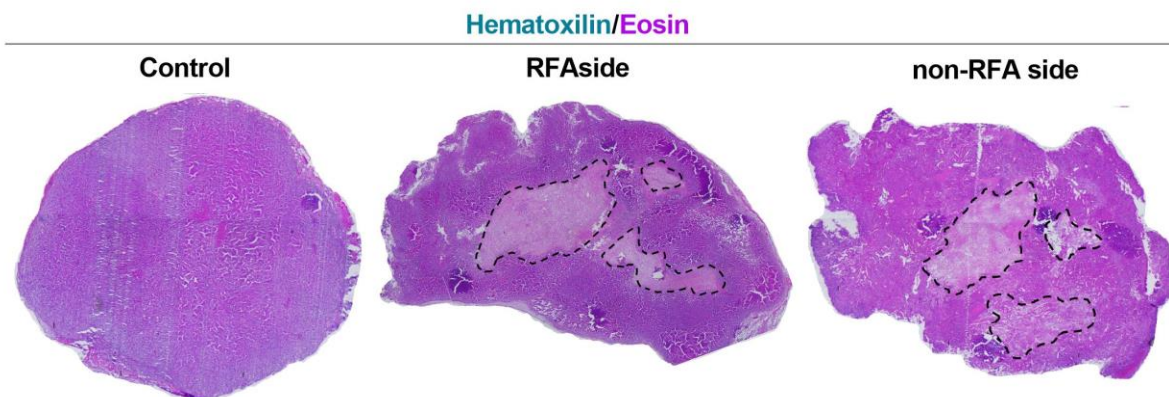
Sunil R. Hingorani,<sup>1,2,\*</sup> Lifu Wang,<sup>2</sup> Asha S. Multani,<sup>4</sup> Chelsea Combs,<sup>2</sup> Therese B. Deramaudt,<sup>1,3</sup> Ralph H. Hruban,<sup>5</sup> Anil K. Rustgi,<sup>1,3</sup> Sandy Chang,<sup>4</sup> and David A. Tuveson<sup>1,2,\*</sup>





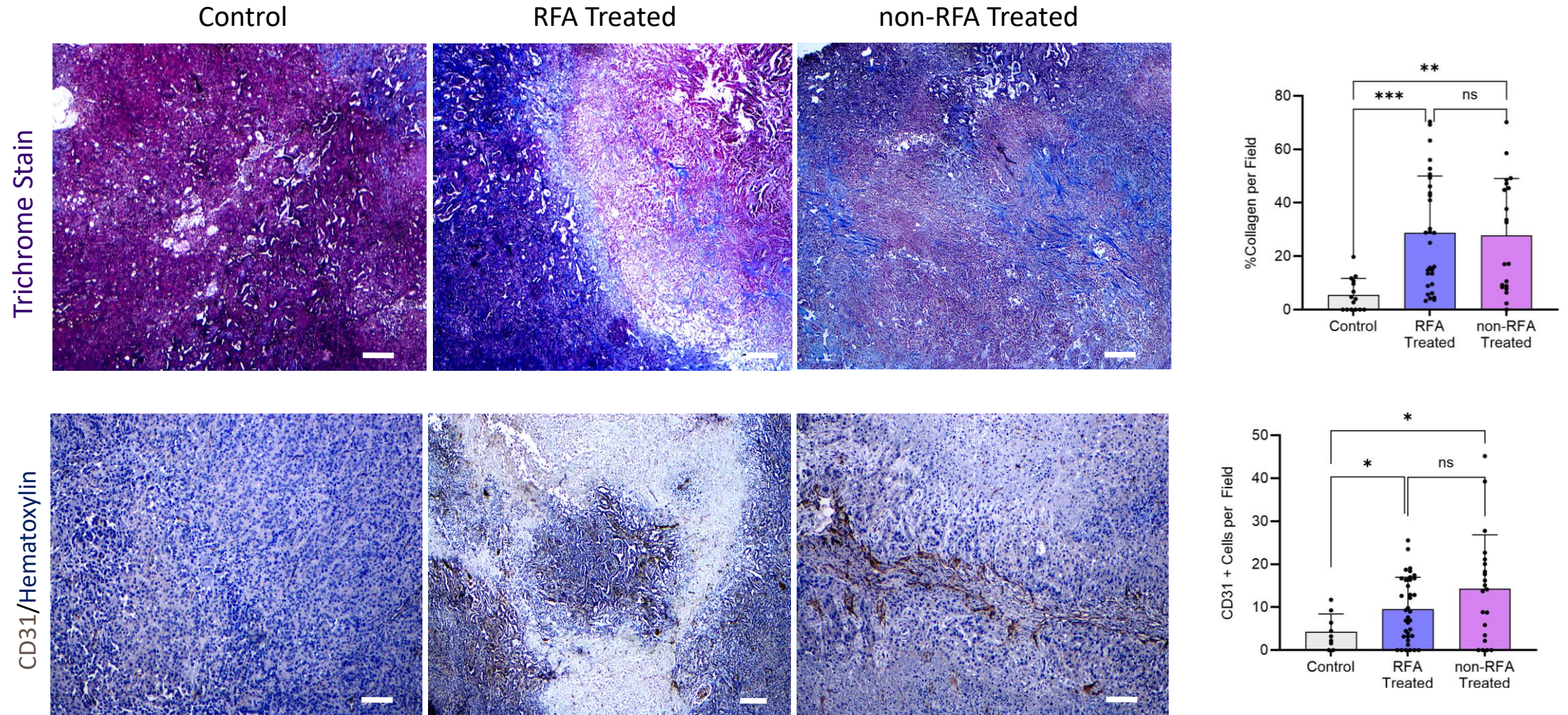
## Radiofrequency Ablation Remodels the Tumor Microenvironment and Promotes Neutrophil-Mediated Abscopal Immunomodulation in Pancreatic Cancer

Erika Y. Faraoni<sup>1</sup>, Baylee J. O'Brien<sup>1</sup>, Lincoln N. Strickland<sup>1</sup>, Baron K. Osborn<sup>2</sup>, Victoria Mota<sup>1</sup>, Jarod Chaney<sup>1</sup>, Constance Lynn Atkins<sup>1</sup>, Putao Cen<sup>3</sup>, Julie Rowe<sup>3</sup>, Jessica Cardenas<sup>2</sup>, Kyle L. Poulsen<sup>1,4</sup>, Curtis J. Wray<sup>2</sup>, Nirav C. Thosani<sup>5</sup>, and Jennifer M. Bailey-Lundberg<sup>1,4,5</sup>



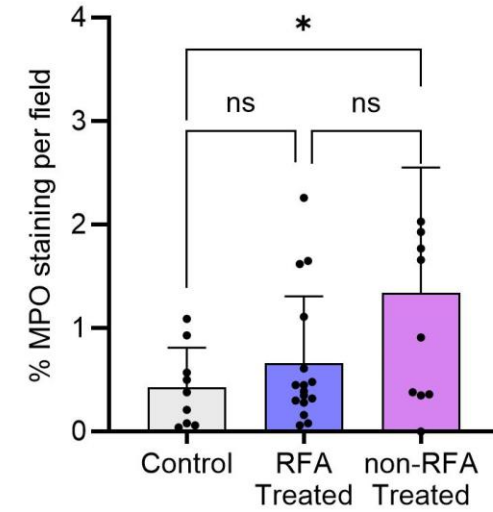
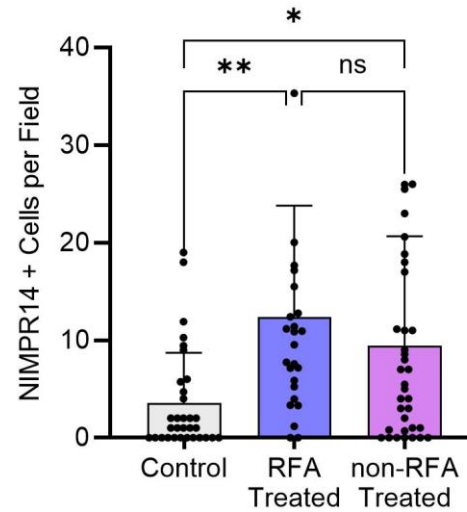
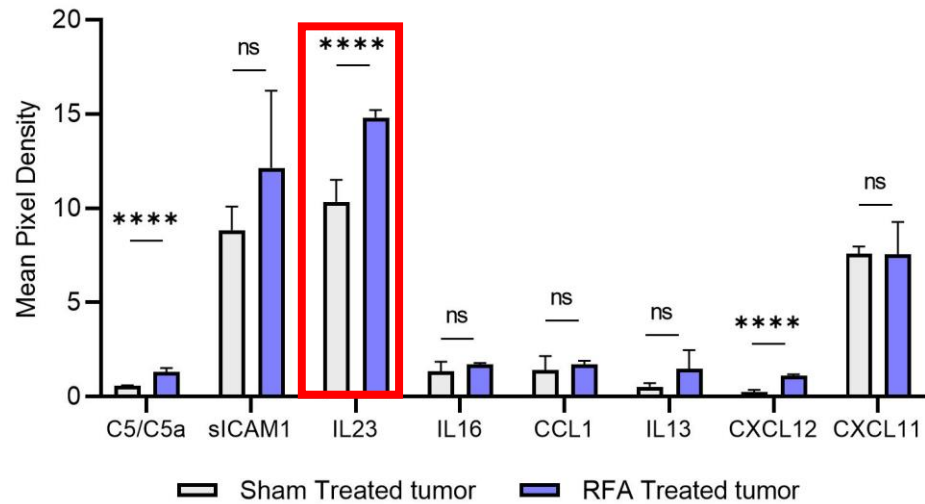
- Inhibition of tumor growth
- Does RFA induce stromal changes?

# RFA induces local and systemic remodeling of the tumor microenvironment



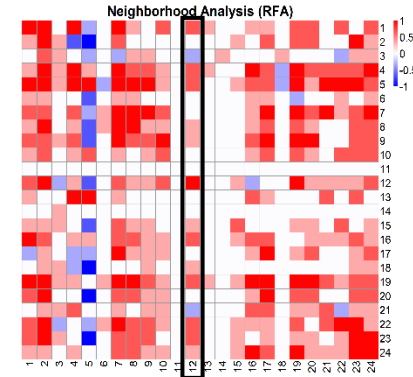
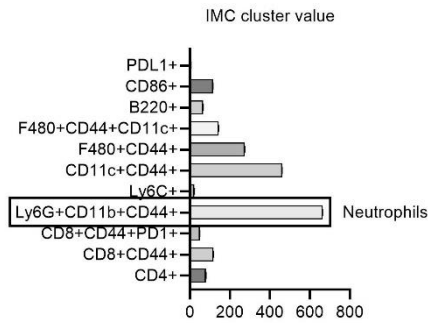
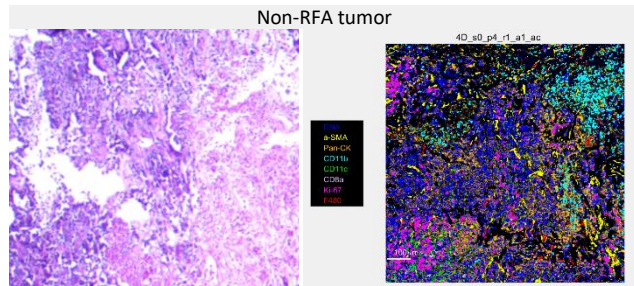
Cardenas Lab, McGovern Medical School

## RFA increases neutrophil infiltration

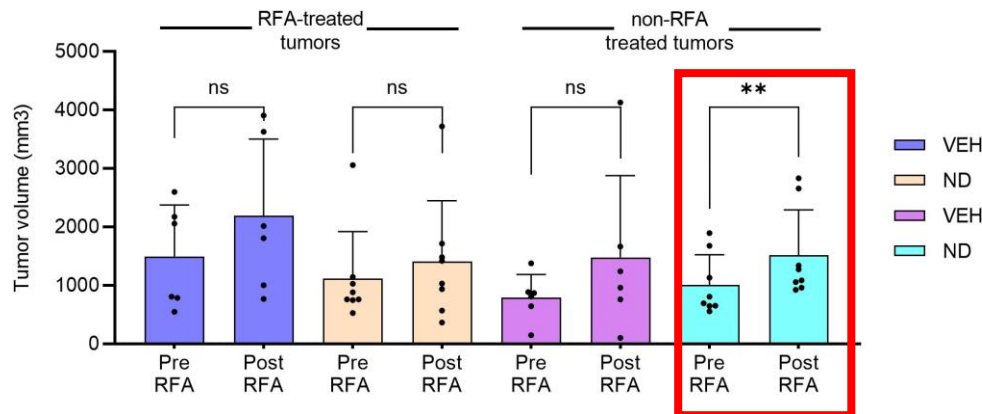
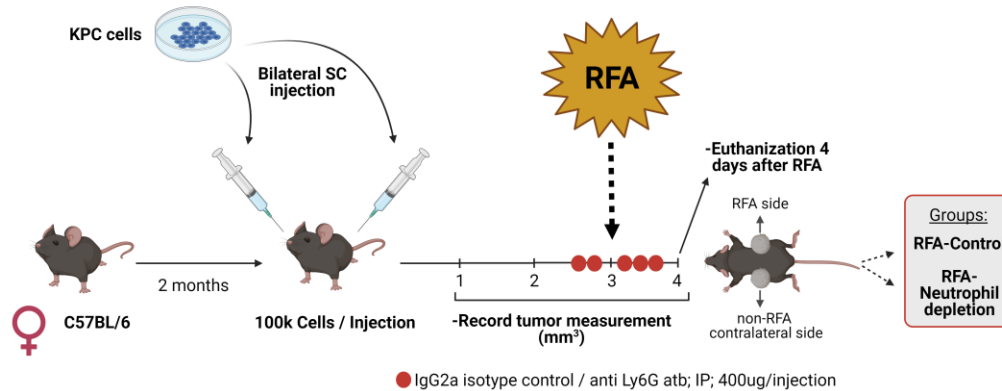


## Neutrophil role in RFA response?

# Neutrophils are critical for the anti-tumor response on the abscopal tumor

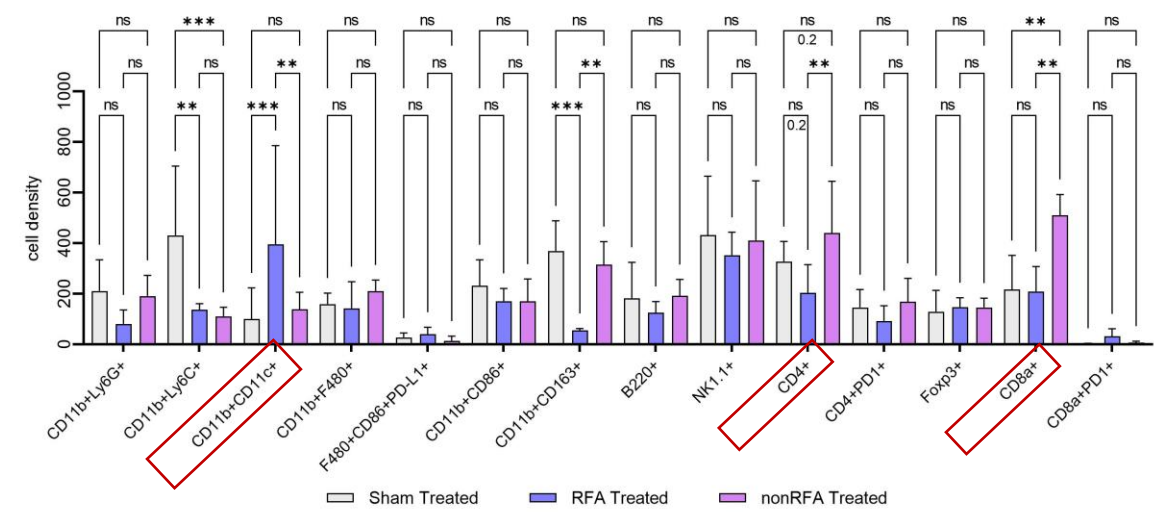
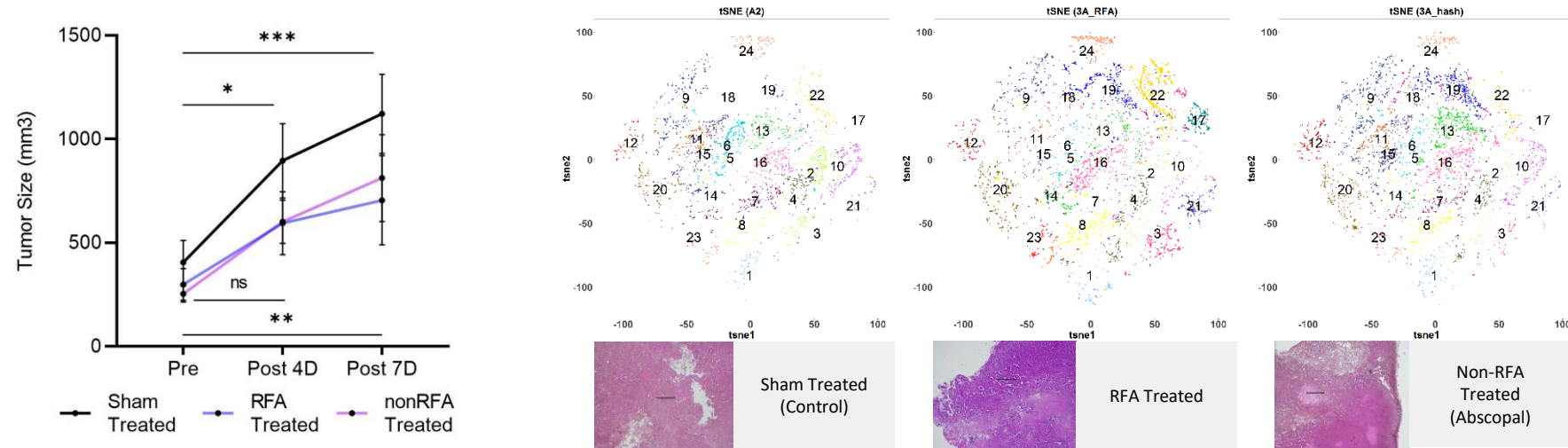


- Colocalization with:
- αSMA
  - PanCK+ tumor cells
  - Tumor stem cells
  - Dendritic cells
  - Macrophages

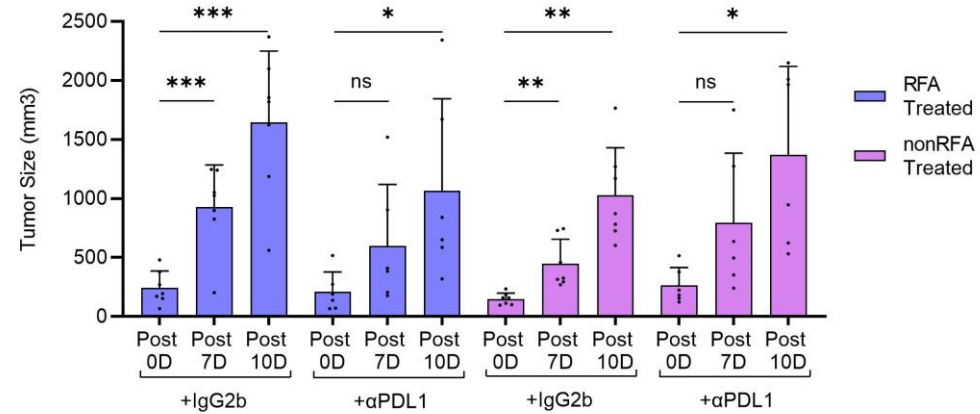
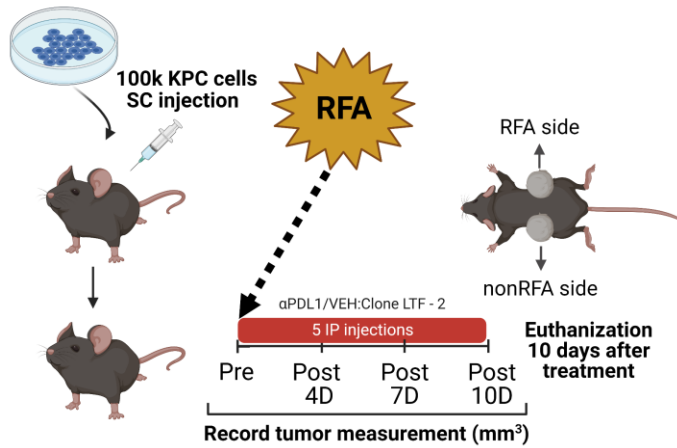
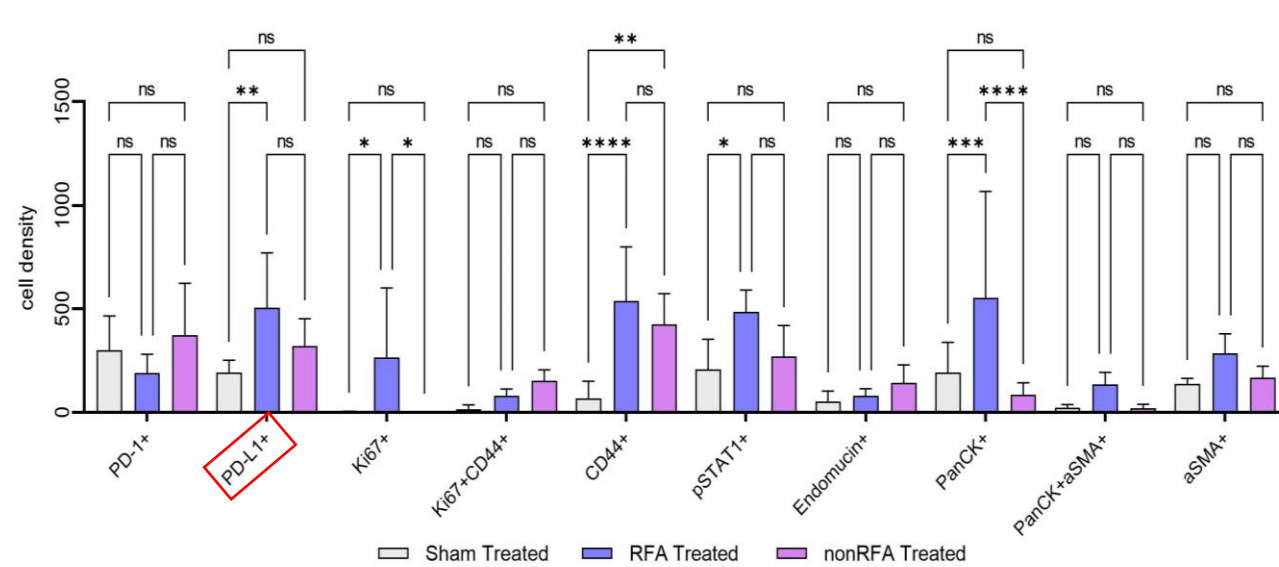


- Neutrophils mediate acute RFA induced responses.
- Long-term outcomes for RFA local and abscopal responses?

# RFA promotes CD4+ and CD8+ T cell infiltration into distant tumors



# In vivo ICB therapy targeting RFA-induced PD-L1 in combination with RFA sustains tumor progression inhibition in both local and abscopal sites



## In vivo RFA + αPDL1 combination therapy

> Front Oncol. 2022 Sep 6;12:995027. doi: 10.3389/fonc.2022.995027. eCollection 2022.

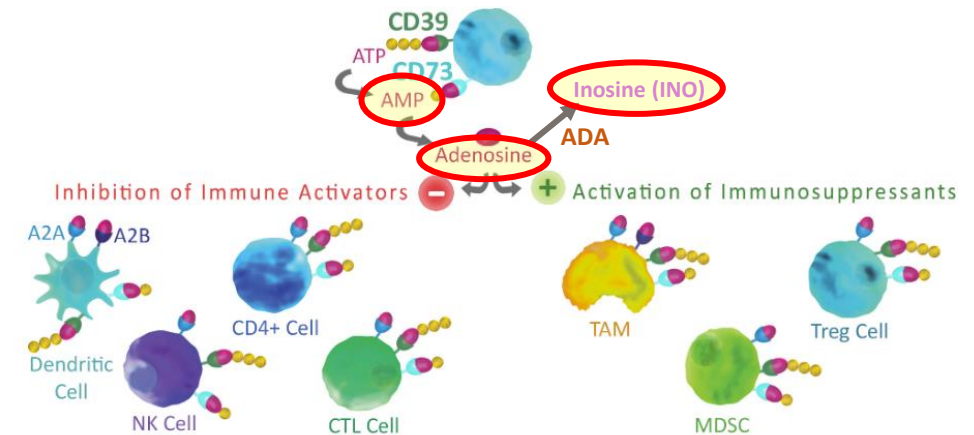
# Radiofrequency ablation in combination with CD73 inhibitor AB680 reduces tumor growth and enhances anti-tumor immunity in a syngeneic model of pancreatic ductal adenocarcinoma

Erika Y Faraoni<sup>1</sup>, Lincoln N Strickland<sup>1</sup>, Baylee J O'Brien<sup>1</sup>, Joseph F Barraza<sup>1</sup>, Nirav C Thosani<sup>2</sup>, Curtis J Wray<sup>3</sup>, Tingting W Mills<sup>4</sup>, Jennifer M Bailey-Lundberg<sup>1 2 5</sup>

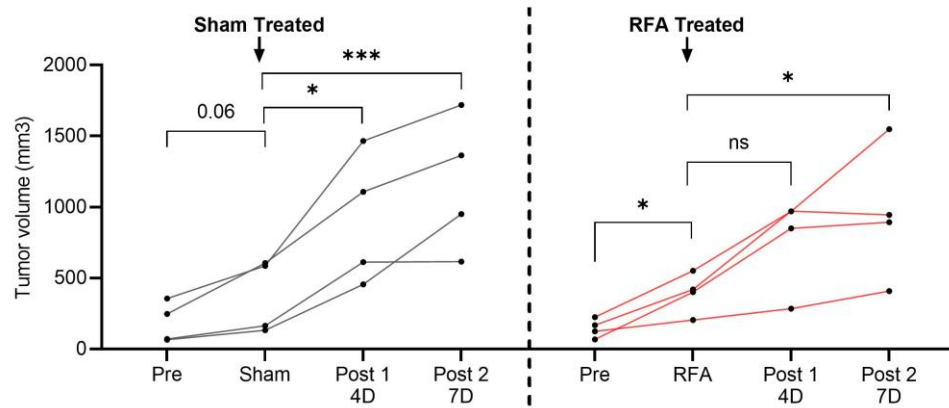
Affiliations + expand

PMID: 36147911 PMCID: PMC9486545 DOI: 10.3389/fonc.2022.995027

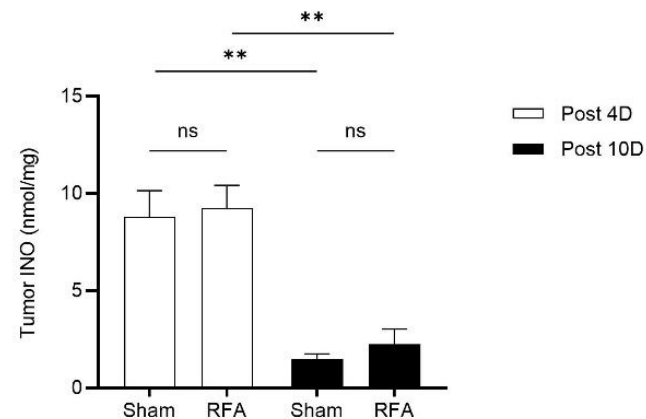
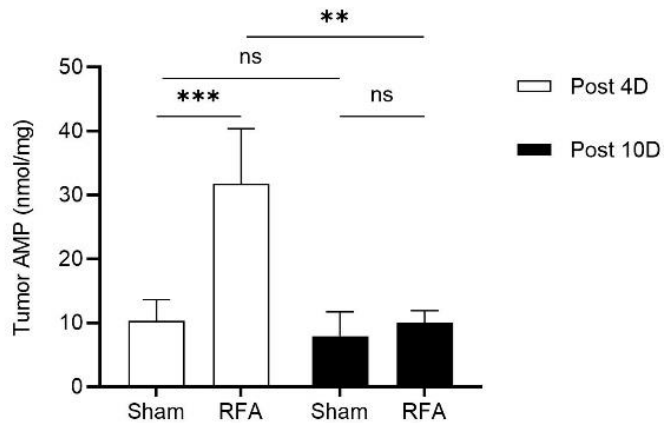
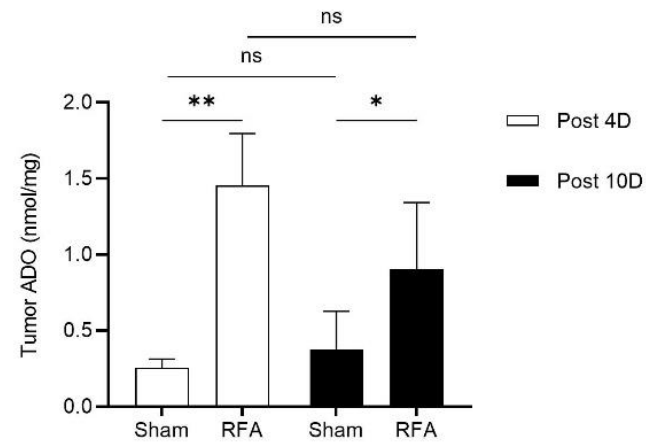
## Adenosine (ADO)/CD73 pathway



# RFA increases adenosine and inosine generation in KPC subcutaneous tumors



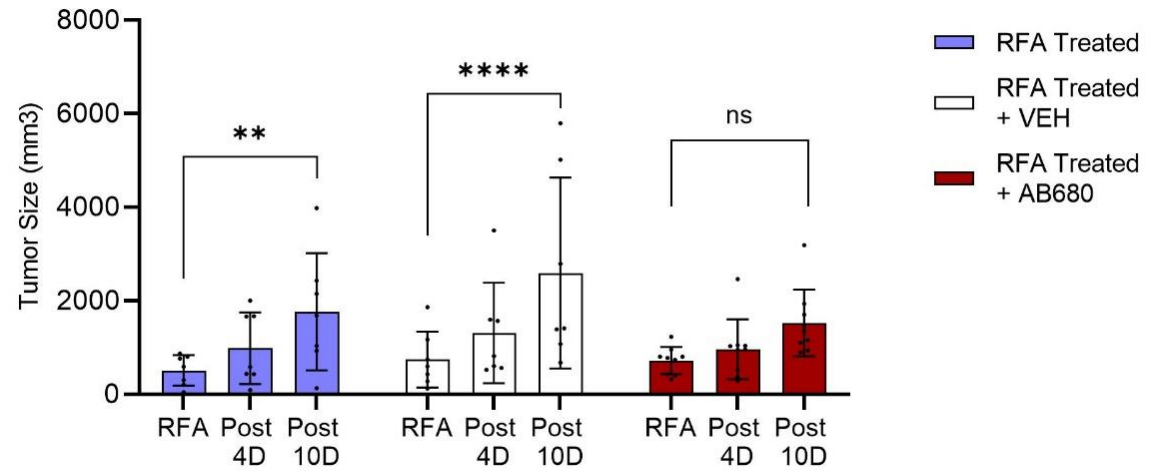
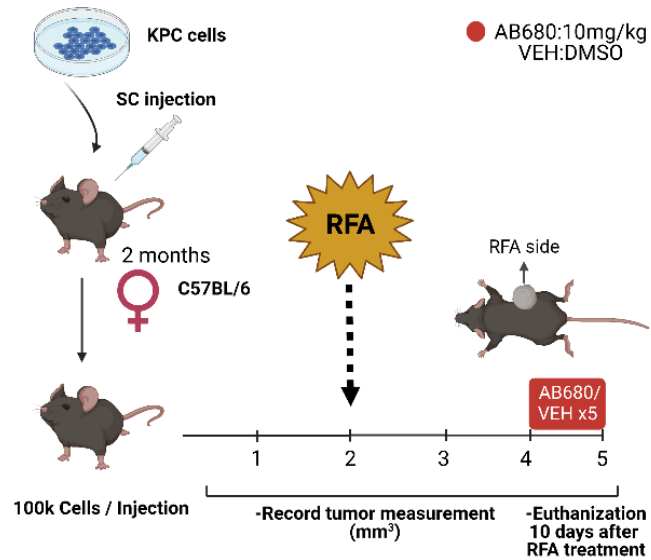
RFA-induced growth inhibition was not sustained after 4D  
 → LOCALLY treated tumors



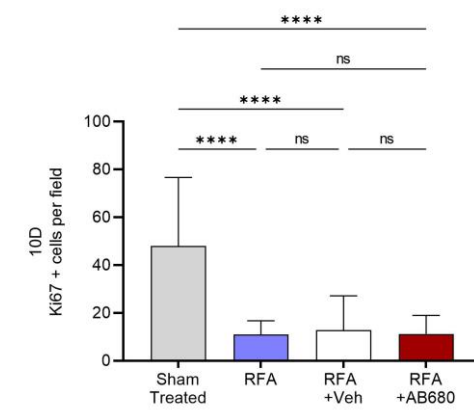
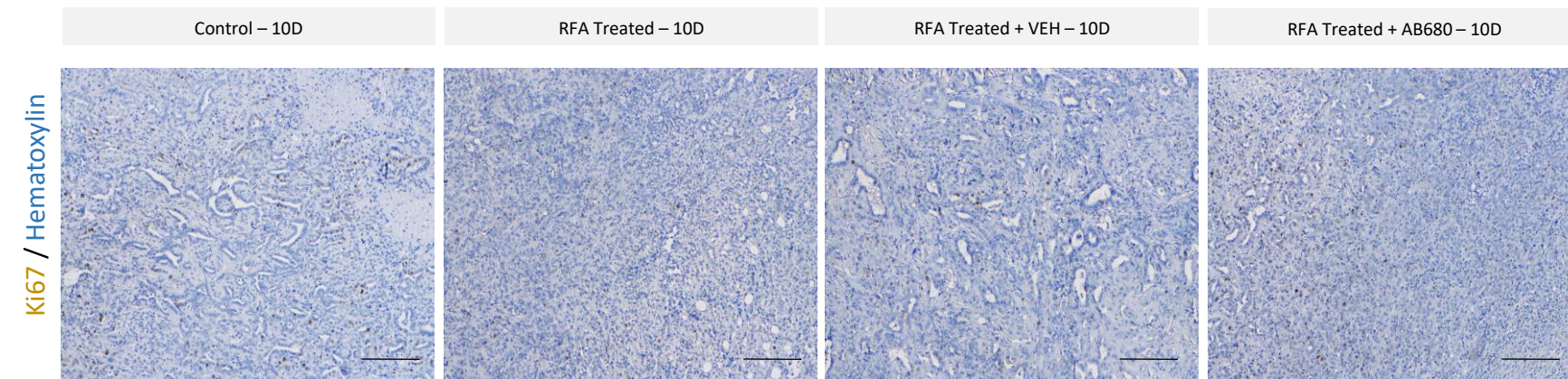
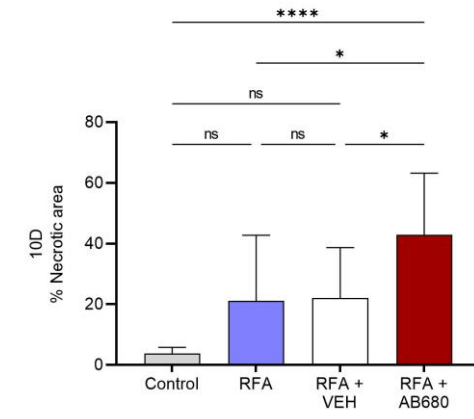
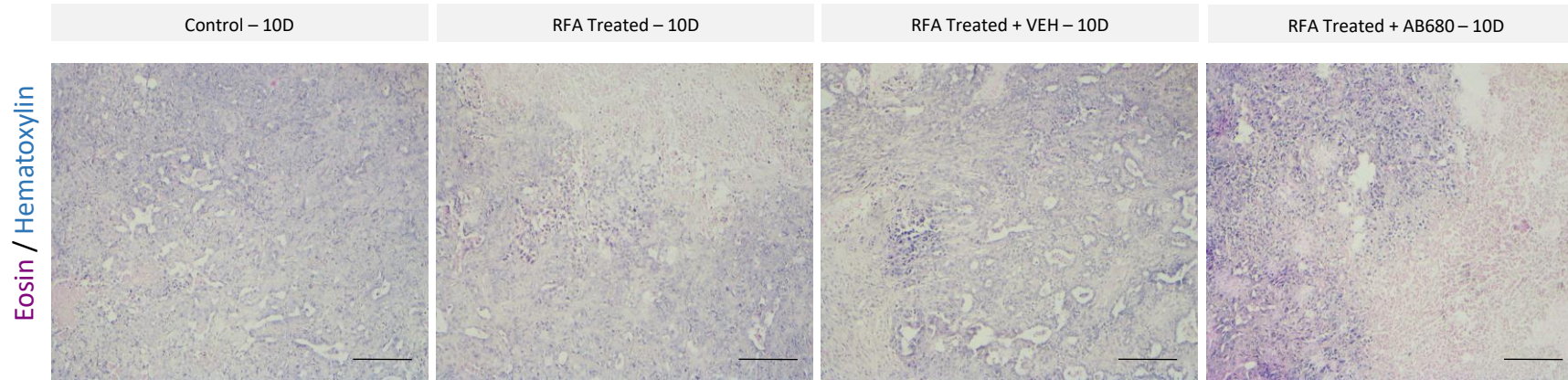
Mills Lab, McGovern Medical School



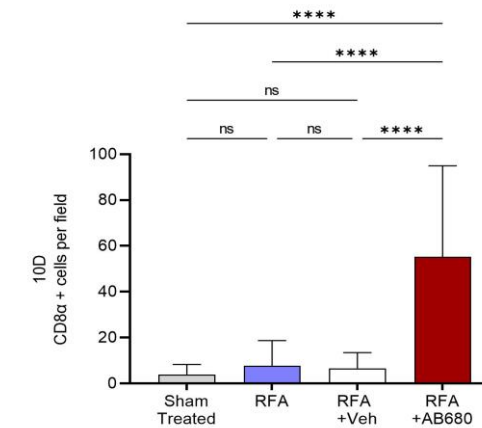
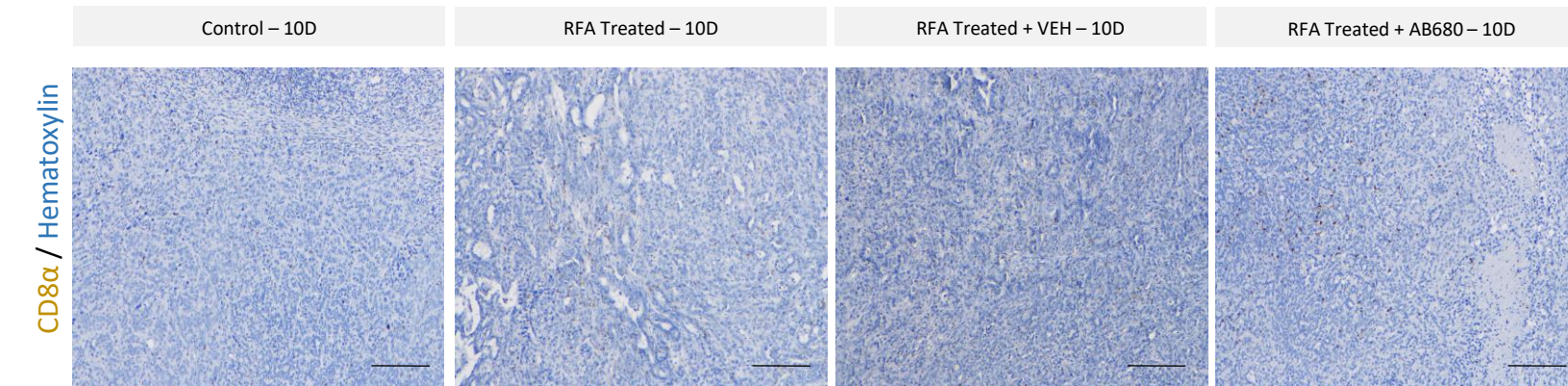
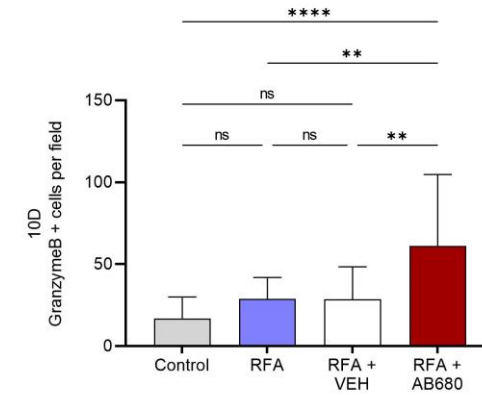
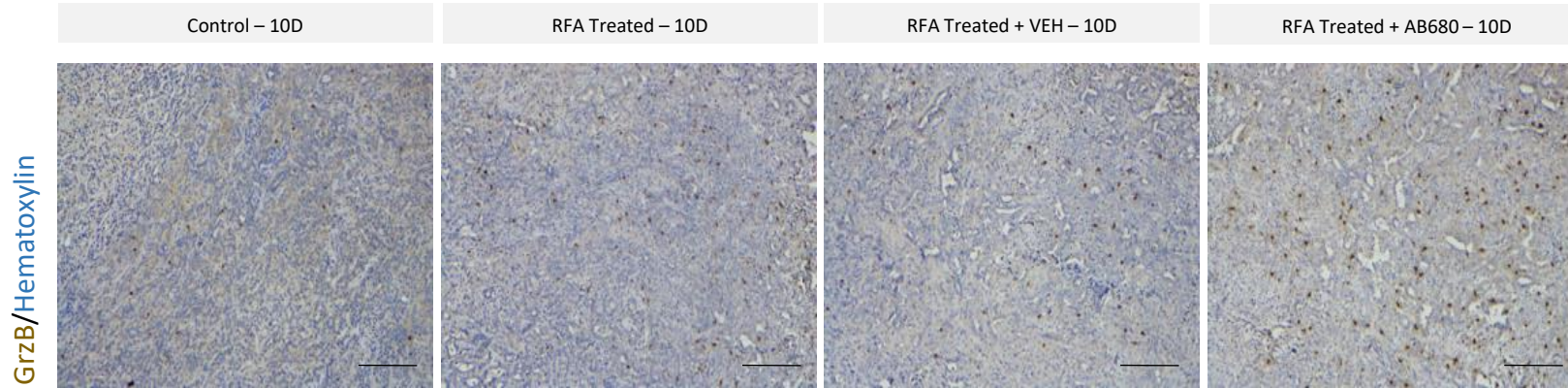
# Inhibition of CD73+RFA *in vivo* potently restricted tumor enlargement



# Inhibition of CD73+RFA *in vivo* increased necrosis and anti-tumor immunity



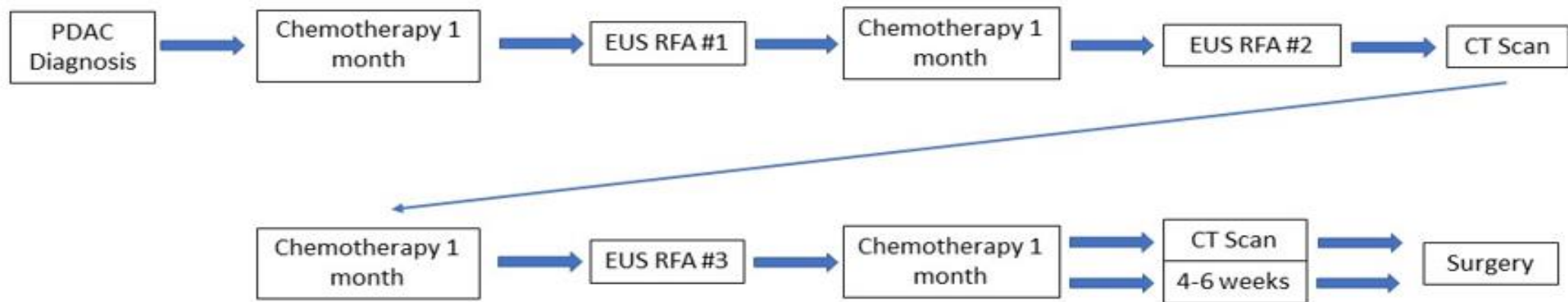
# Inhibition of CD73+RFA *in vivo* increased anti-tumor immunity



➤ **Clinical trial → Endoscopic Ultrasound PANcreatic CANcer RaDiofrequeNcy AbLation (PANCARDINAL-1)**

<https://clinicaltrials.gov/ct2/show/NCT04990609>

Objectives: Endoscopic Ultrasound (EUS) Radiofrequency ablation (RFA) plus standard-of-care Neoadjuvant chemotherapy (NAC) in the treatment of Pancreatic Ductal Adenocarcinoma (PDAC).

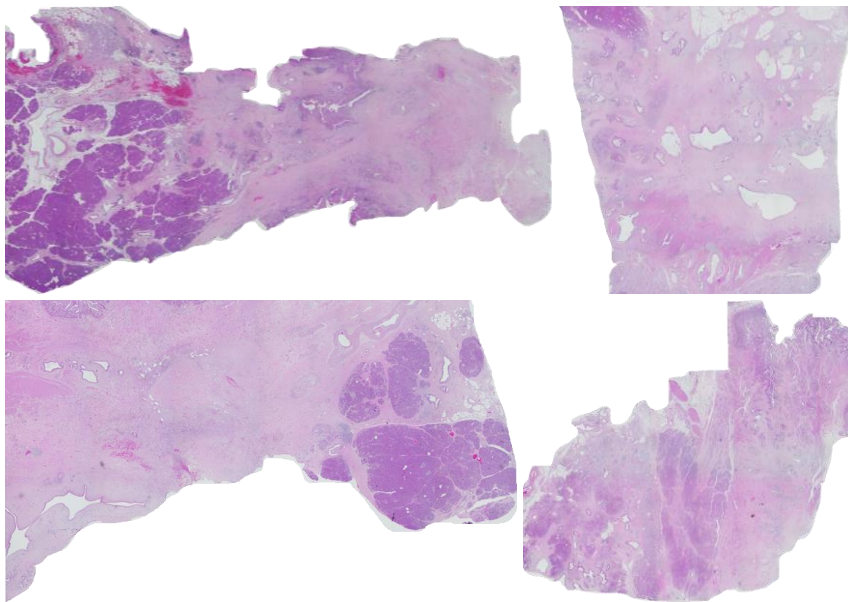


➤ **Clinical trial → Endoscopic Ultrasound PANcreatic CANcer RaDiofrequeNcy AbLation (PANCARDINAL-1)**

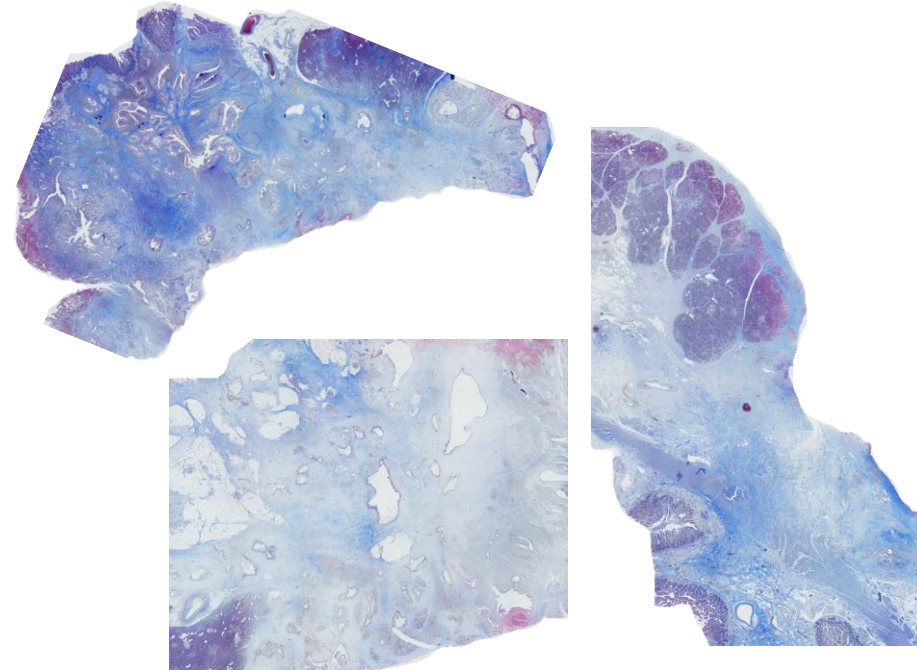
<https://clinicaltrials.gov/ct2/show/NCT04990609>

Objectives: Endoscopic Ultrasound (EUS) Radiofrequency ablation (RFA) plus standard-of-care Neoadjuvant chemotherapy (NAC) in the treatment of Pancreatic Ductal Adenocarcinoma (PDAC).

**Human RFA stains  
H&E | Trichrome Composites**



Increased necrosis adjacent to treated areas  
Residual tumor cells



Increased collagen deposition

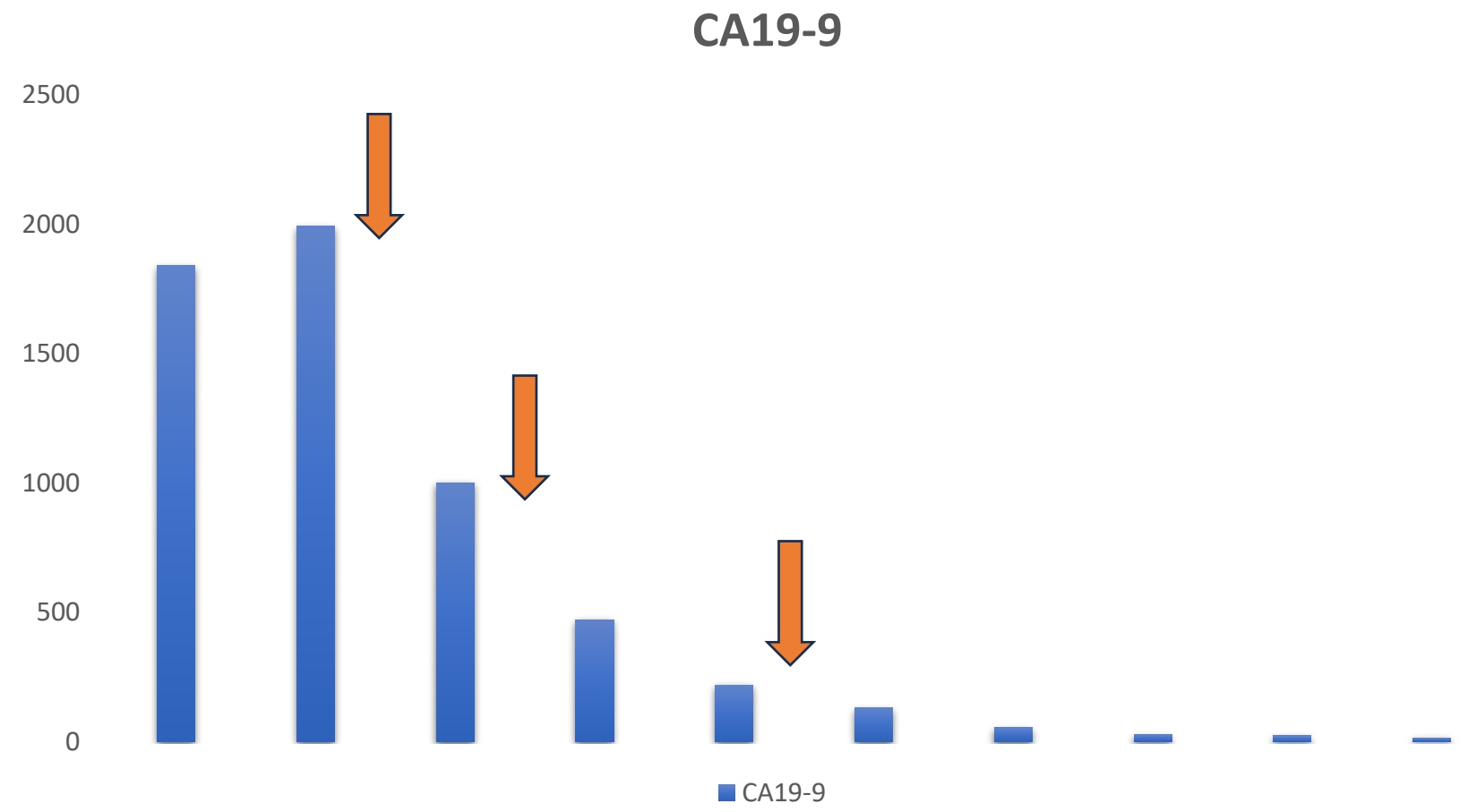
# EUS RFA – Lessons Learned

- PANCARDINAL-1 Trial Enrollment 22/30
- EUS RFA Prospective Registry Enrollment 48/50
  - Locally advanced PDAC
  - Metastatic PDAC
  - Neuroendocrine tumors
  - Metastatic lesions to pancreas
- 210 EUS RFA procedures; 3 procedures per patient (1-9)
- 4 serious adverse events; mild post procedure pain after 35% of procedure
- > 6 ablation per procedure associated with post procedure pain, nausea and vomiting
- 1 post ERCP pancreatitis (Neuroendocrine tumor)
- 2 cases of cholangitis including liver abscess (PDAC patient without biliary stent)
- 1 case of GI Bleeding from duodenal ulcer

# PANCARDINAL Trial



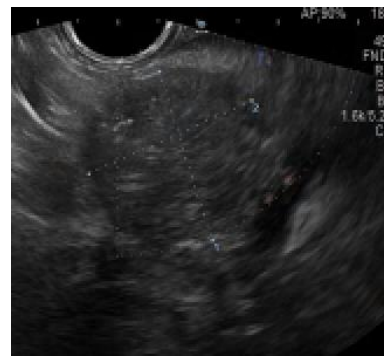
# EUS RFA-Lessons Learned: Tumor Marker Response





# EUS RFA-Lessons Learned: Abscopal Effect

	Pancreatic Tail Mass	Liver Metastasis
	3.4 x 2.4	3.3 x 2.5
S/p 2 EUS-RFA (PDAC only)	2.8 x 2.0	1.4 x 1.9



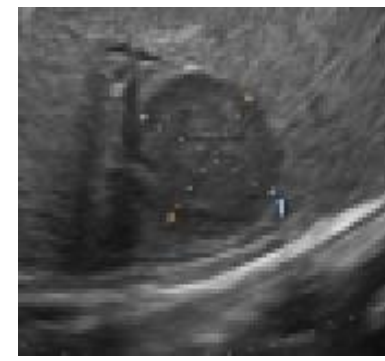
PDAC



EUS-RFA



Post EUS-RFA

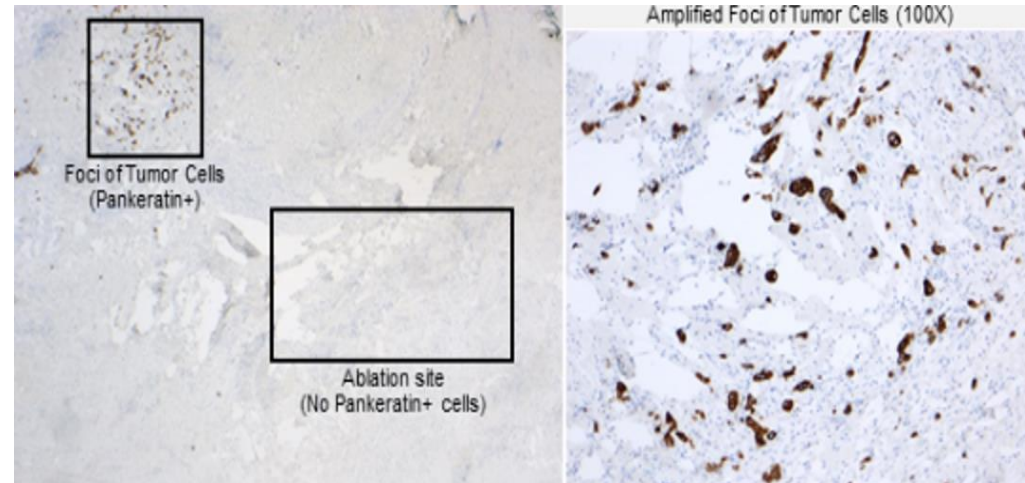
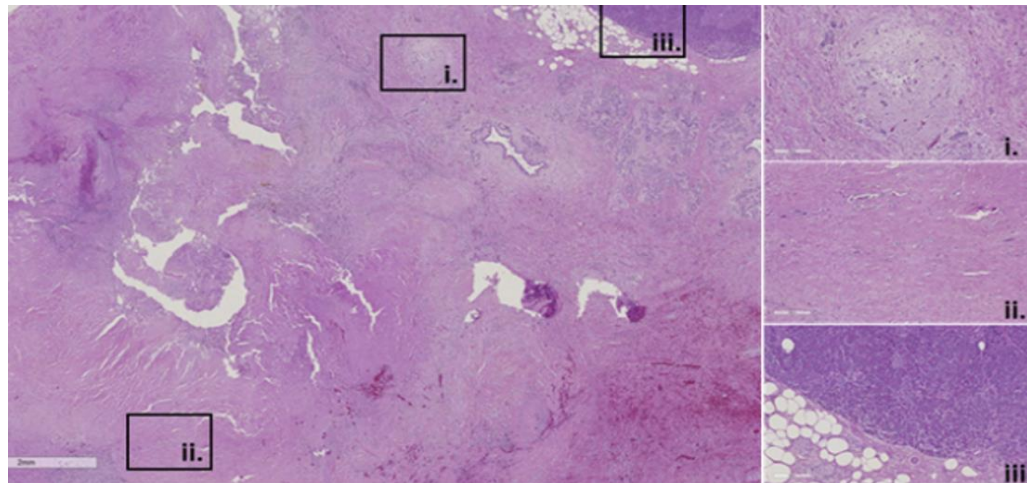
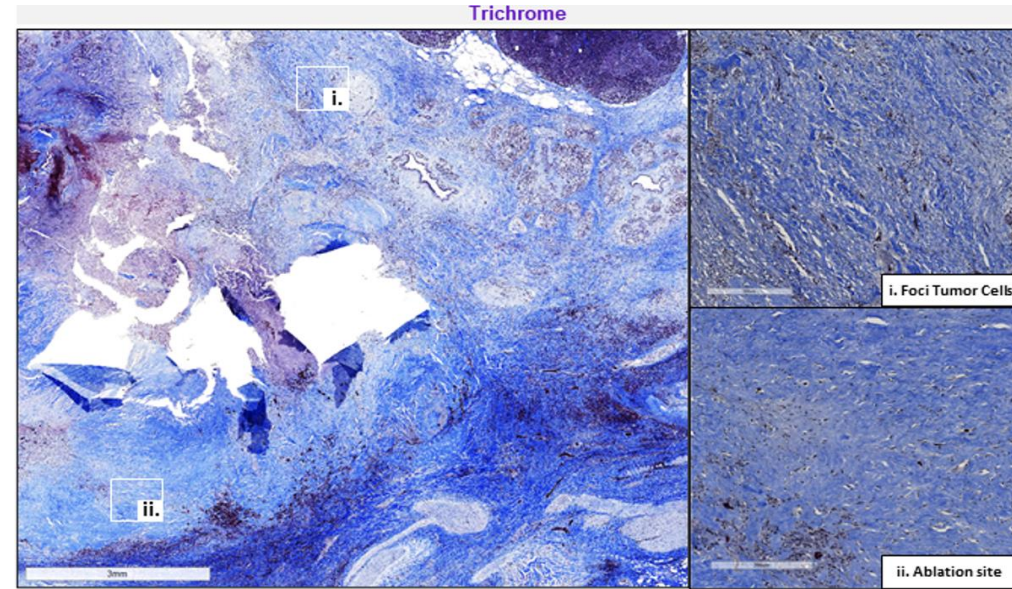
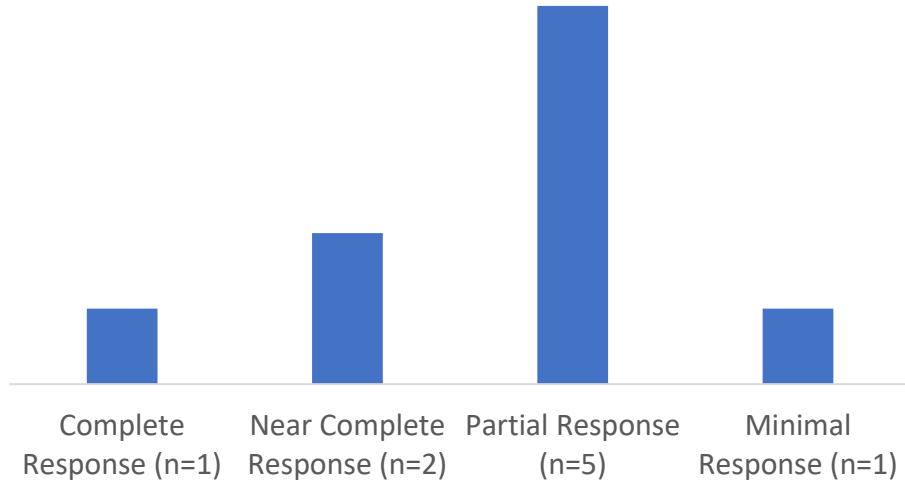


Liver Metastasis

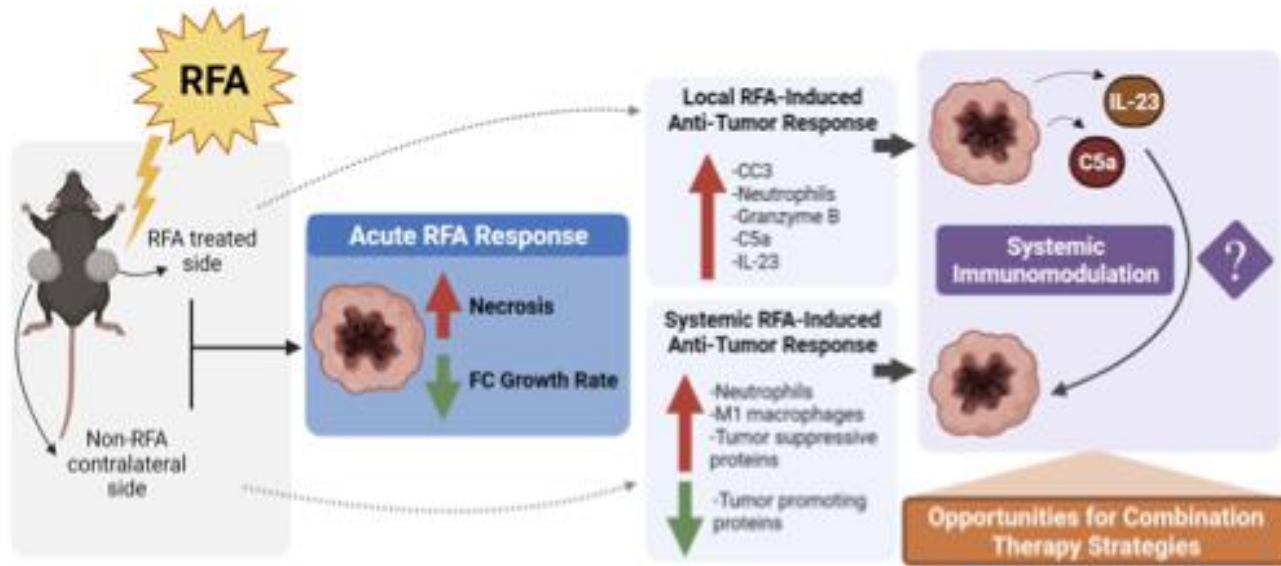


EUS-RFA

# EUS RFA-Lessons Learned: Pathological Response



# Conclusions



- RFA-treated and distant tumors presented a reduction in their growth rate after RFA treatment
- RFA induces changes in the stroma including the vasculature → RFA induces changes in infiltrating immune cells in RFA-treated and distant tumors
- RFA is capable of modulating cytokine secretion
- RFA should be considered for the treatment of metastatic PDAC (evidence of abscopal effect), but some resistance mechanisms are observed:
- **RFA induced accumulation local/circulating adenosine and PD-L1**

**Opportunity to target CD73 or PD-L1 and propose a combined therapy with RFA**

“The questions are always more important than the answers.” – Randy Pausch  
Professor, Carnegie Mellon | Author, The Last Lecture



## Pancreatic Cancer Research Team

### Bailey-Lundberg Lab

Erika Faraoni, PhD  
Lincoln Strickland  
Frank Chen  
Nicolette Mardik

### Former Lab Members

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Baylee O'Brien  
Trent Clark  
Amanda Warner  
Rachael Bland, MS  
Arun Mani, PhD  
Amrutha Imadi, MD  
Kishore Polireddy, PhD  
Melissa Pruski  
Guanghui Zhu, MD, PhD  
Audrey Hendley, PhD  
Neal Jones, MD  
Eric Yoon, MD  
Logan Oliver, MD  
Gary Chen, MD  
Naveen Manisundaram, MD

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Nirav Thosani, MD  
Curtis Wray, MD  
Mairin Joseph-Talreja, MD  
Julie Rowe, MD  
Putao Cen, MD  
Tinting Mills, PhD



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NCI R21 CA249924-01  
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