Advances in the Immunotherapy management of Pancreas Cancer
2019 Atlanta Pancreas Cancer Conference
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Disclosures

- Off label use: pancreas GVAX and CRS-207 (Aduro Biotech, Inc)
- Off label use: Nivolumab (BMS oncology)
- Off label use: Pembrolizumab (Merck)
- Off label use: Ipilimumab (BMS)
- Off label use: Urelumab (BMS)

Objectives

- Understand the challenge of developing immunotherapy for pancreatic cancer
- Understand the special case of Microsatellite Instability (MSI-H, MMR-d) high tumors and how this would apply to pancreatic cancer
- Learn how we might be able to induce tumor infiltrating T cells in pancreatic cancer
- Review some of the early studies focusing on immunotherapy for pancreatic cancer

Acknowledgements

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- Beth Onners
- Elizabeth Sugar

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- BMS Oncology
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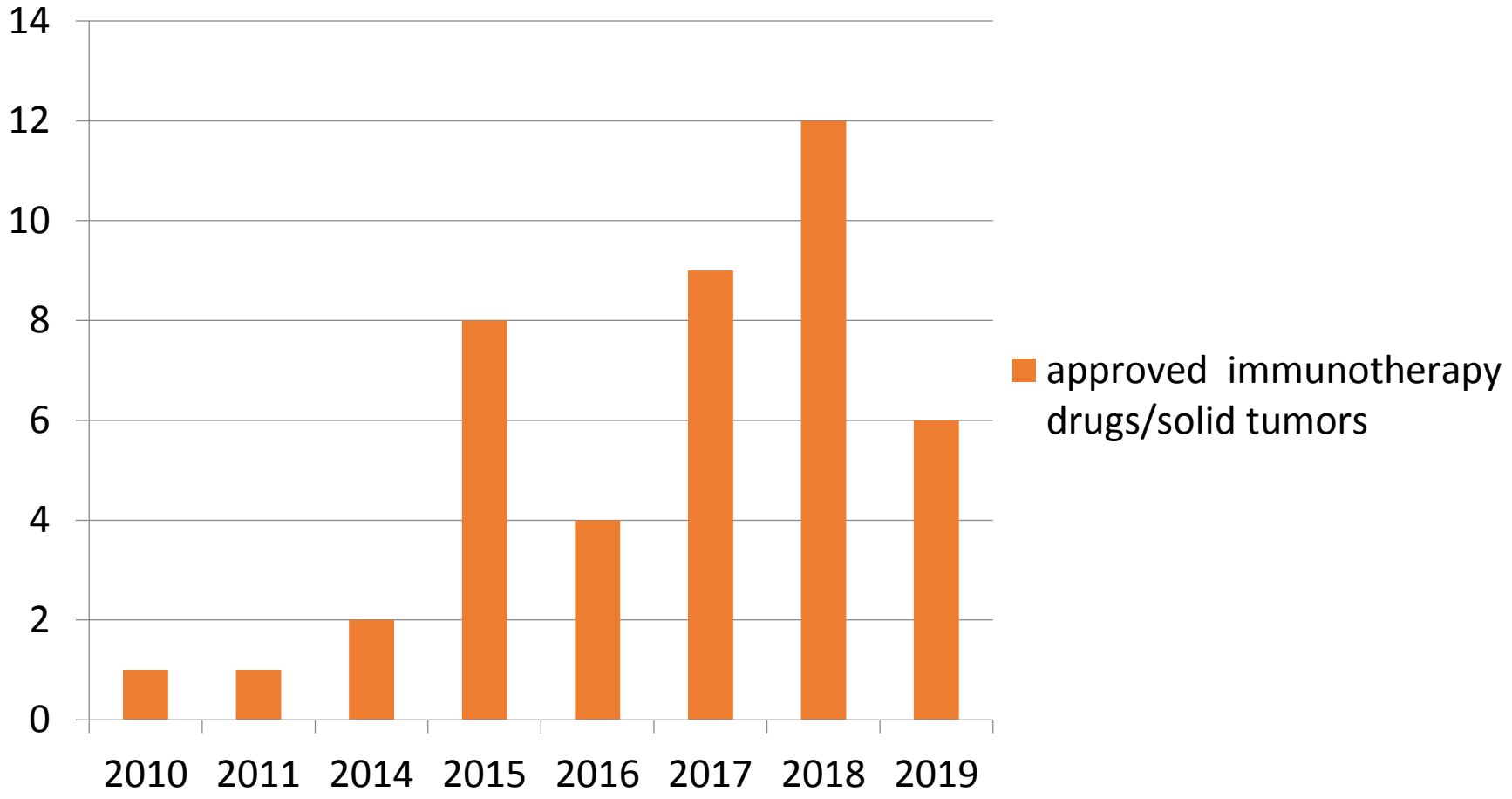
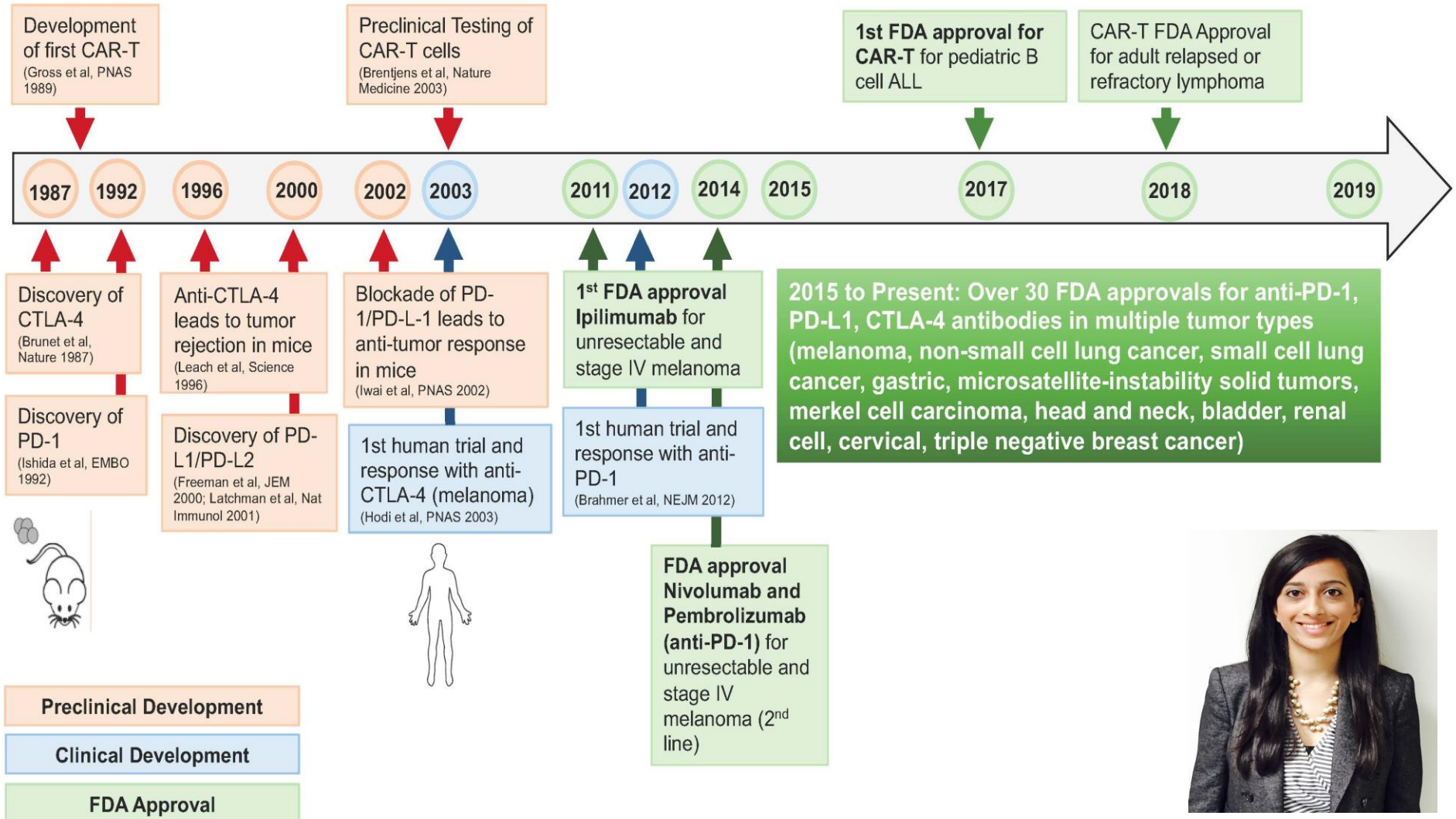
- NIH/GI SPORE (2P50 CA062924)
- SU2C /Lustgarten Foundation pancreas cancer immunotherapy dream team
- **Swim across America**

Immunotherapy approvals in solid tumors

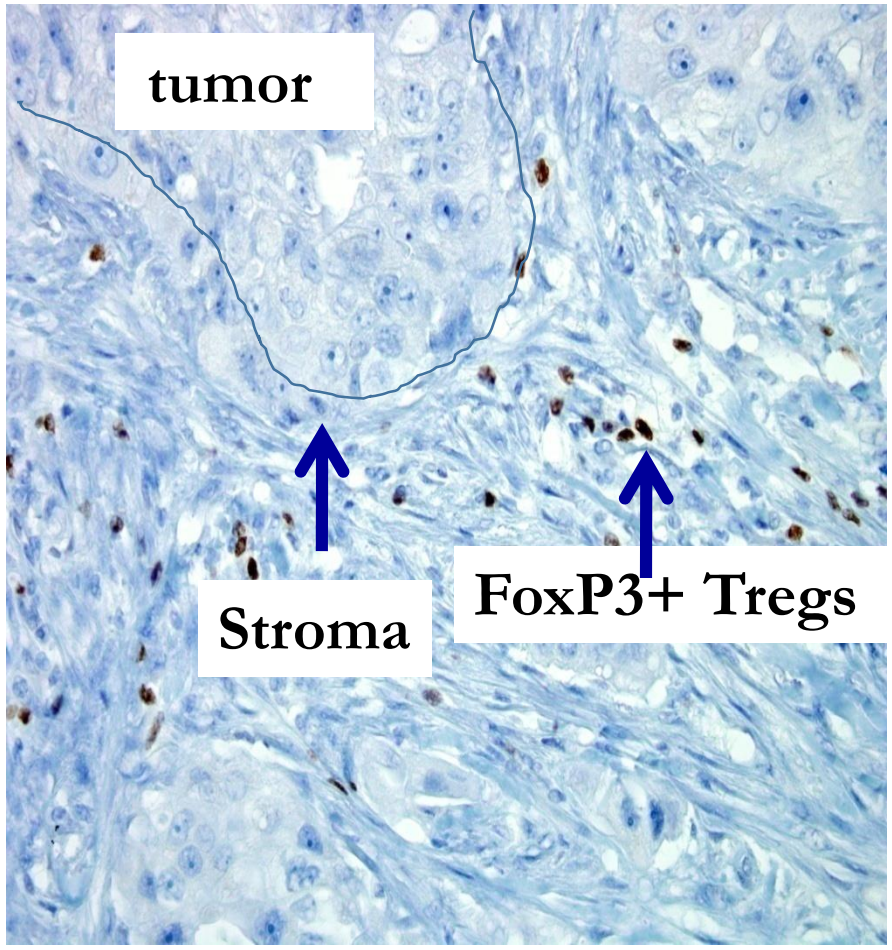


T Cell Therapy: From Development to Approval



Courtesy: Dr. Neeha Zaidi
Assistant Prof JHU

“Cold” versus “Hot” tumors



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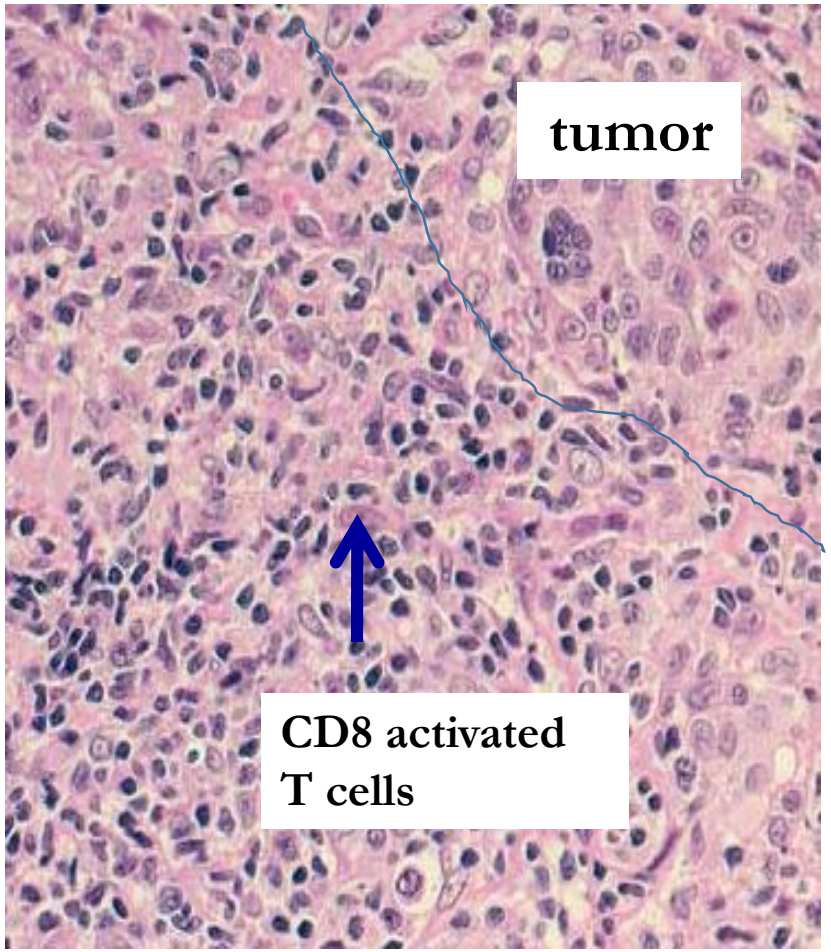


Pancreatic cancer

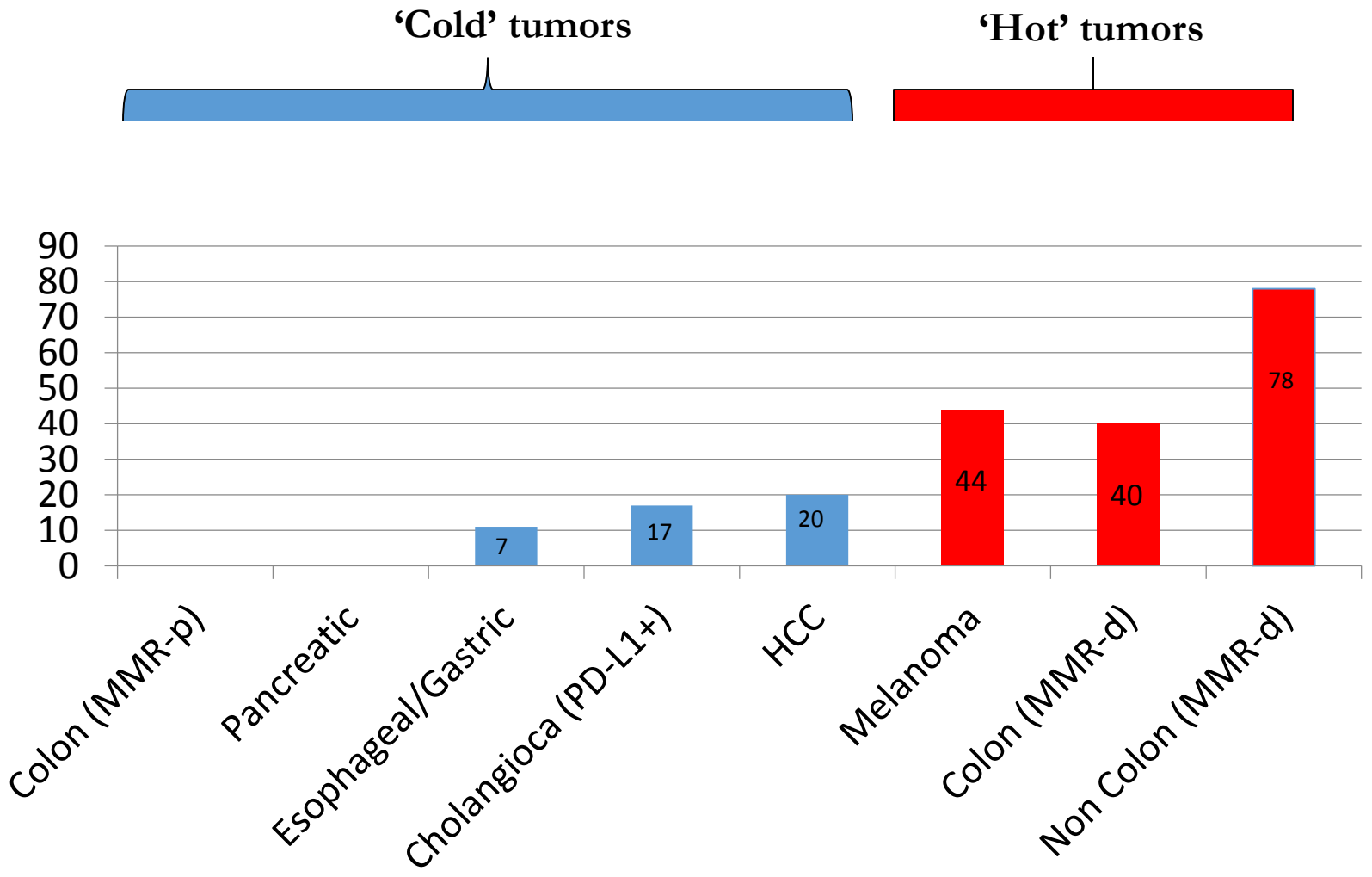
Melanoma

Courtesy of Liz Jaffee

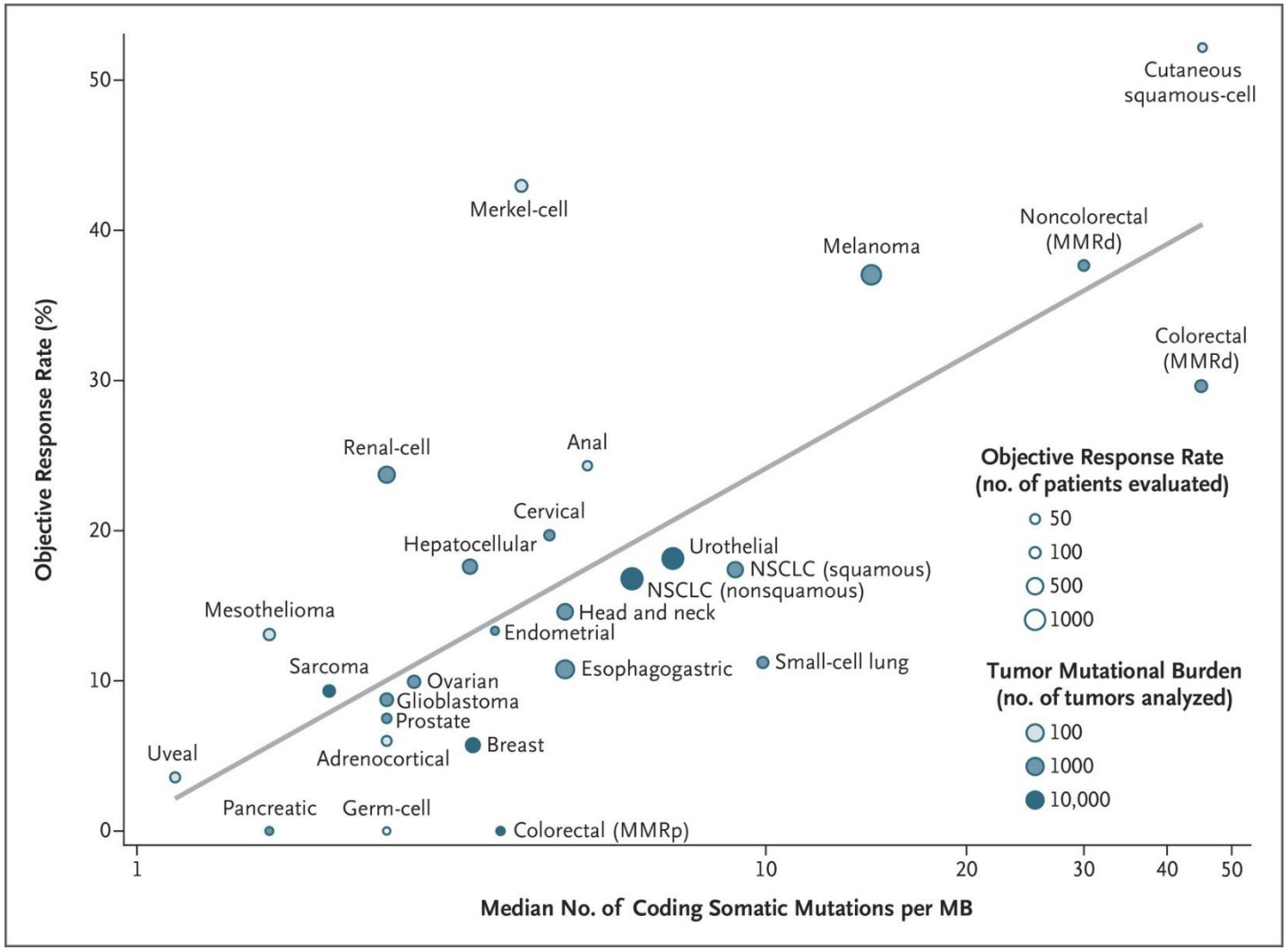
Challenges

- The tumor microenvironment of immunotherapy resistant cancers such as pancreatic cancers have multiple immune suppressive signals that need to be bypassed to achieve clinical responses
- Bio-markers are not adequate to identify the patients who will respond to immunotherapy
- Responses to immunotherapy can take months to observe and patients with metastatic pancreatic cancer don't have that kind of time to wait

Anti-PD-1: Low Single-Agent Response Rates in "cold" GI Malignancies



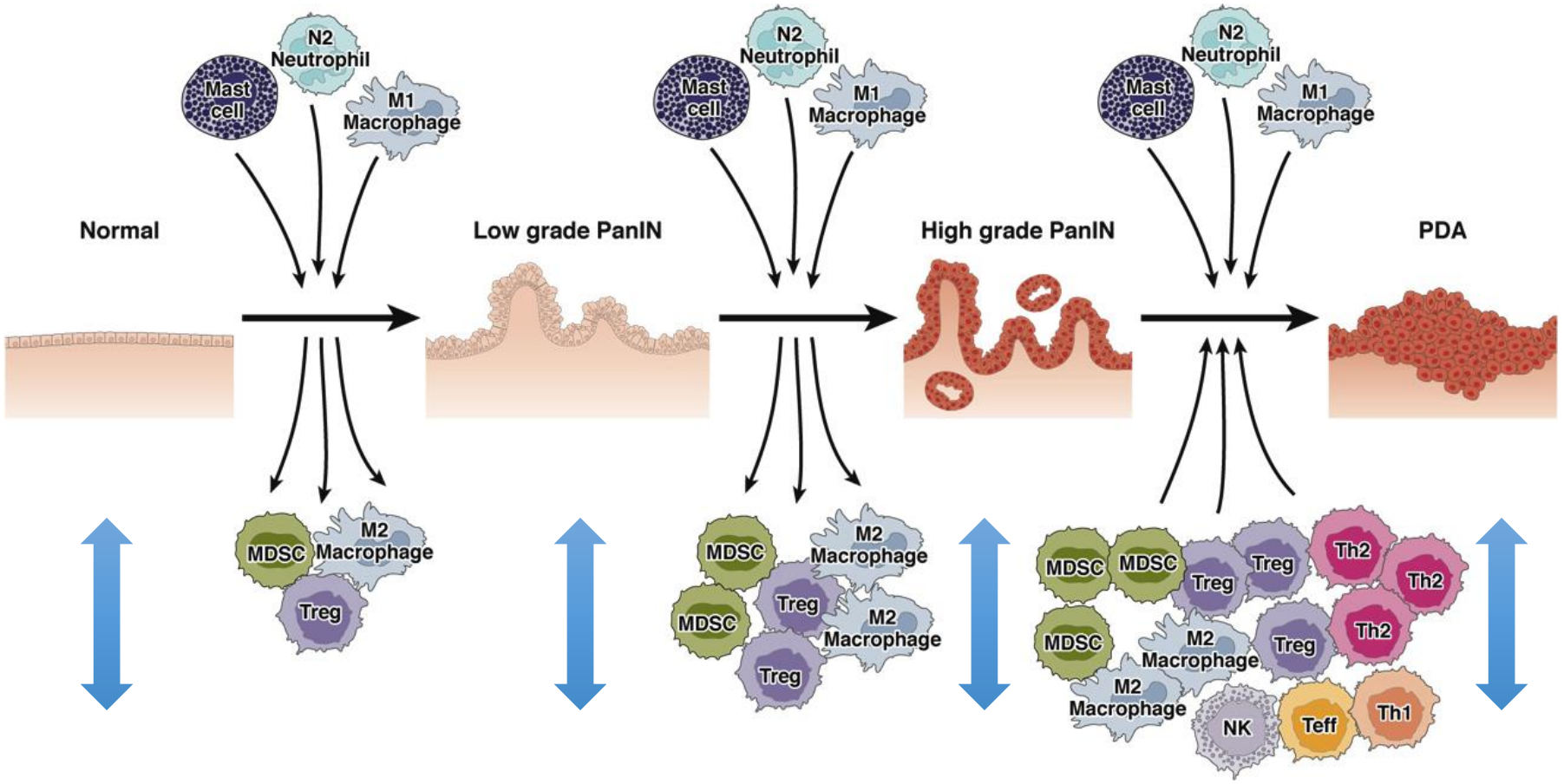
Mutational load can be quantified to better predict who will respond to current immunotherapies



Mark Yarchoan
Assistant Professor , JHH

Mark Yarchoan NEJM 9-2017

The inflammatory response in pancreatic cancer is a progressive, dynamic process, interrelated with cancer genetics and leads to immune quiescence : "cold tumor"



Telomere Shortening → Kras mutation → P16 Cyclin D1 → TP53 DPC4 BRCA2 → mesothelin

Pembrolizumab for microsatellite instability high or mismatch repair deficient cancers

1st tissue agnostic approval

Luis Diaz
head of solid tumor Oncology MSK

Dung Le
Associate Professor of Oncology, JHH

Hypothesis

- Mutations have been shown to encode proteins that can be recognized and targeted by the immune system
- Average tumor has dozens of somatic mutations; mismatch repair-deficient tumors harbor thousands of mutations
- Mismatch repair-deficient tumors are infiltrated with T cells
- Immune augmentation with PD-1 blockade may be highly effective in mismatch repair-deficient tumors

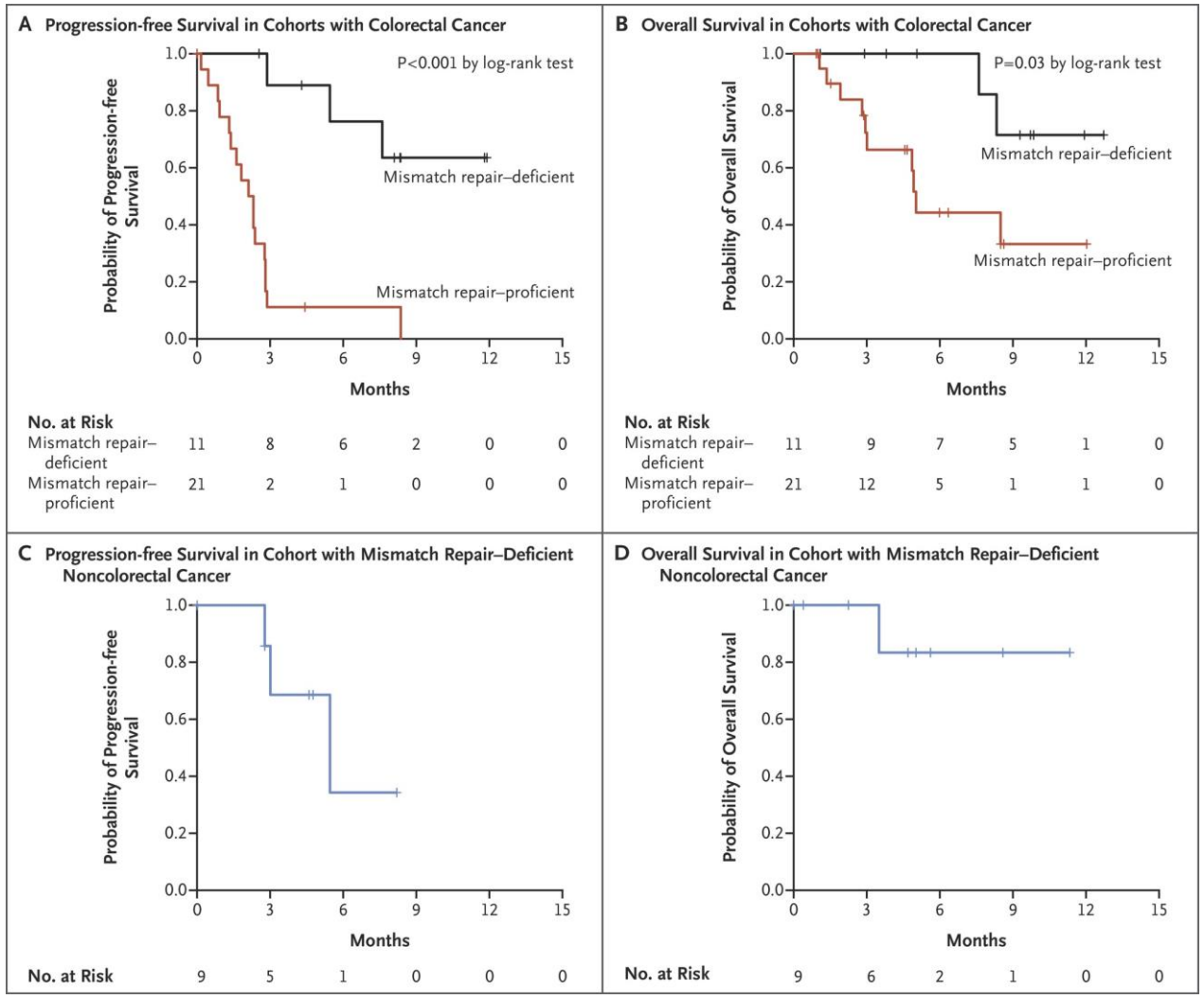
Keynote-016: Study Cohorts

Colorectal Cancers		Non-Colorectal Cancers
Cohort A Deficient in Mismatch Repair (n=28)	Cohort B Proficient in Mismatch Repair (n=25)	Cohort C Deficient in Mismatch Repair (n=30)

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks

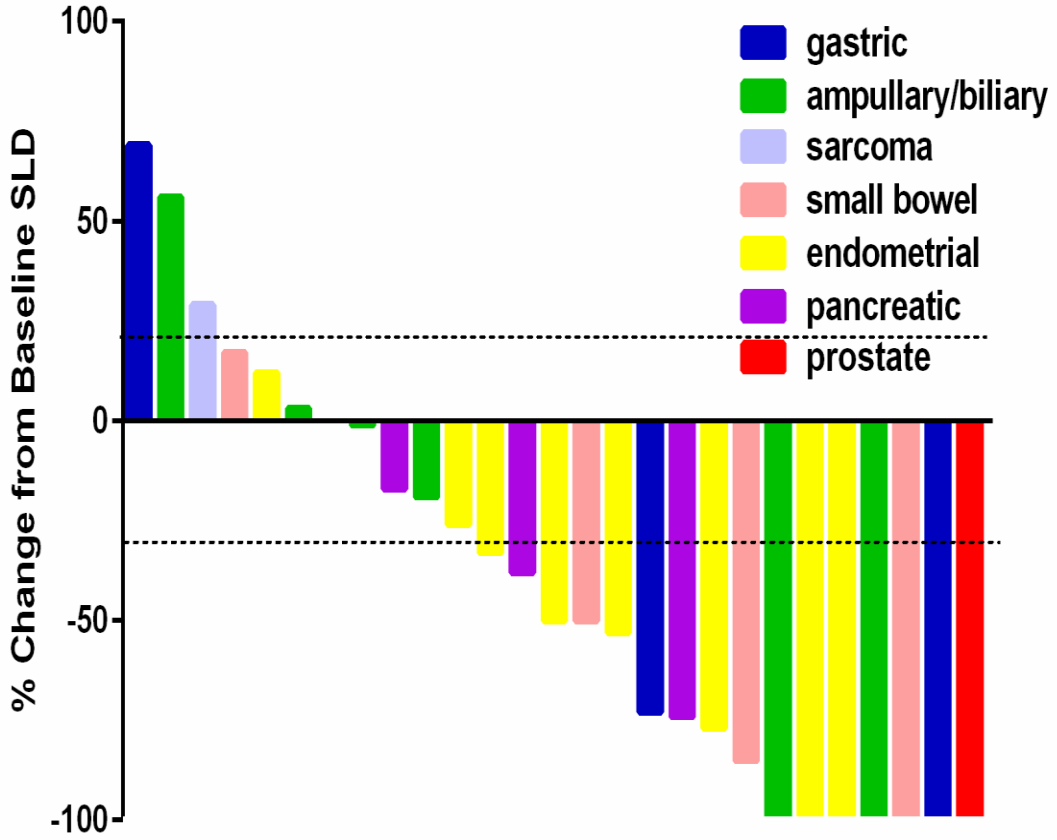
Le D et al: NEJM 2015;372:2509-20.

Clinical benefit of pembrolizumab treatment according to mismatch repair status



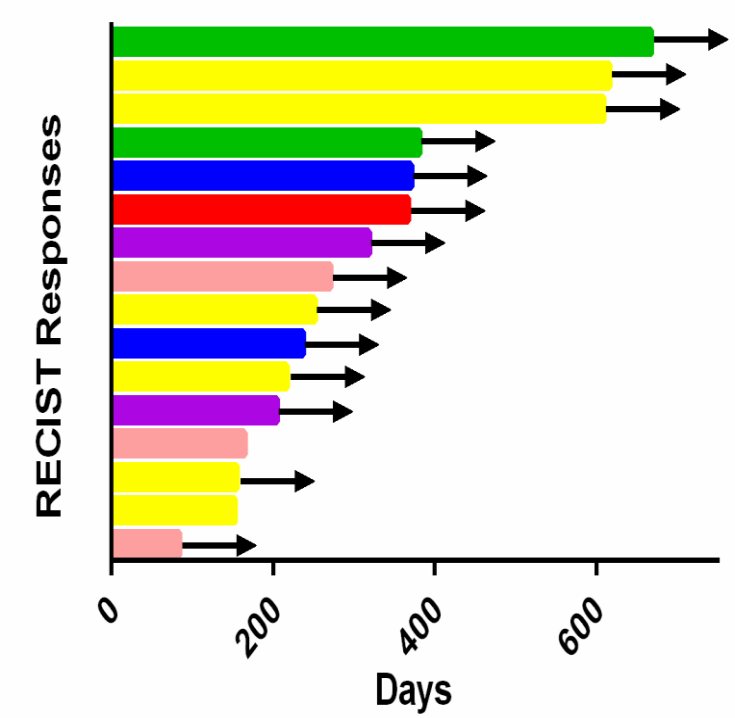
Le D et al: NEJM 2015;372:2509-20

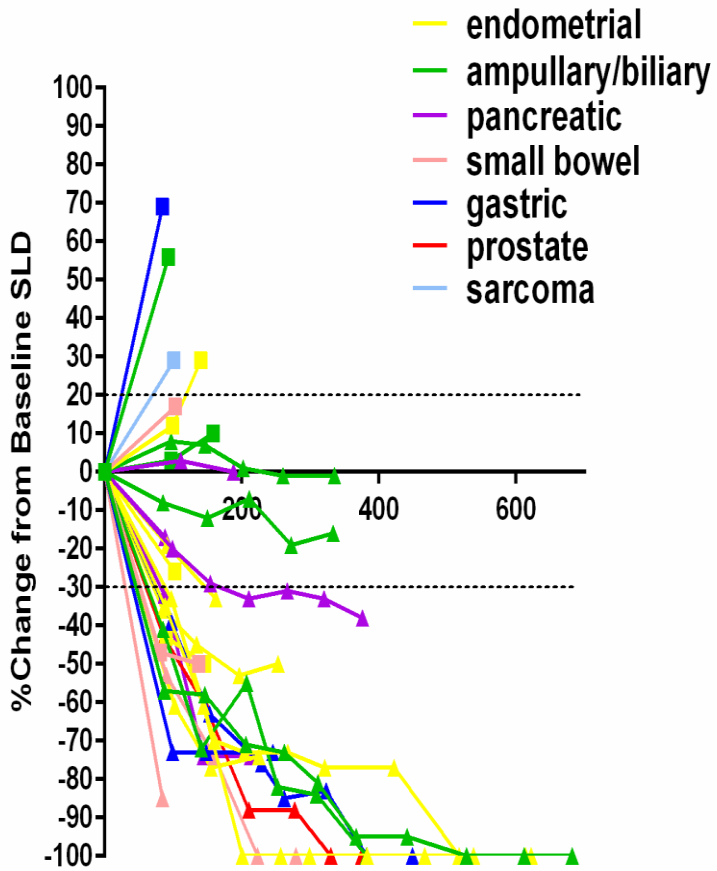
Target Lesion Measurements



Diaz LA, et al. ASCO 2016. Abstract 3003.

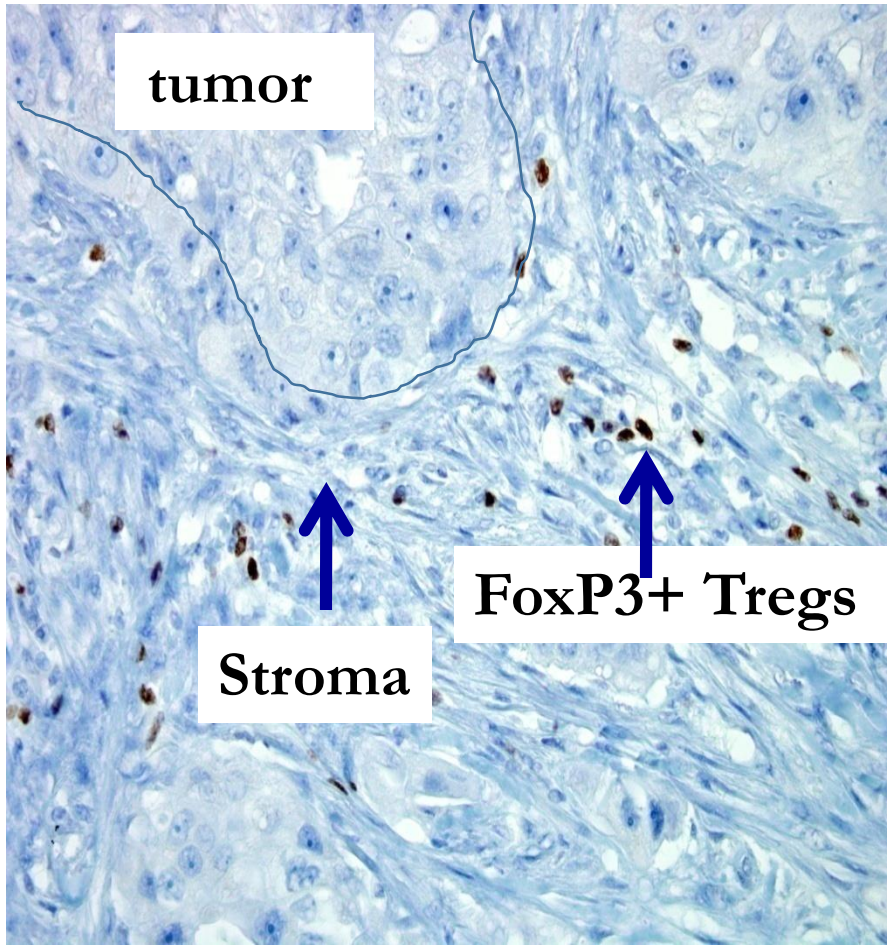
Durability of Disease Control





Diaz LA, et al. ASCO 2016. Abstract 3003.

How can we convert an immunologically unresponsive tumor into one that responds to immune checkpoint therapy?



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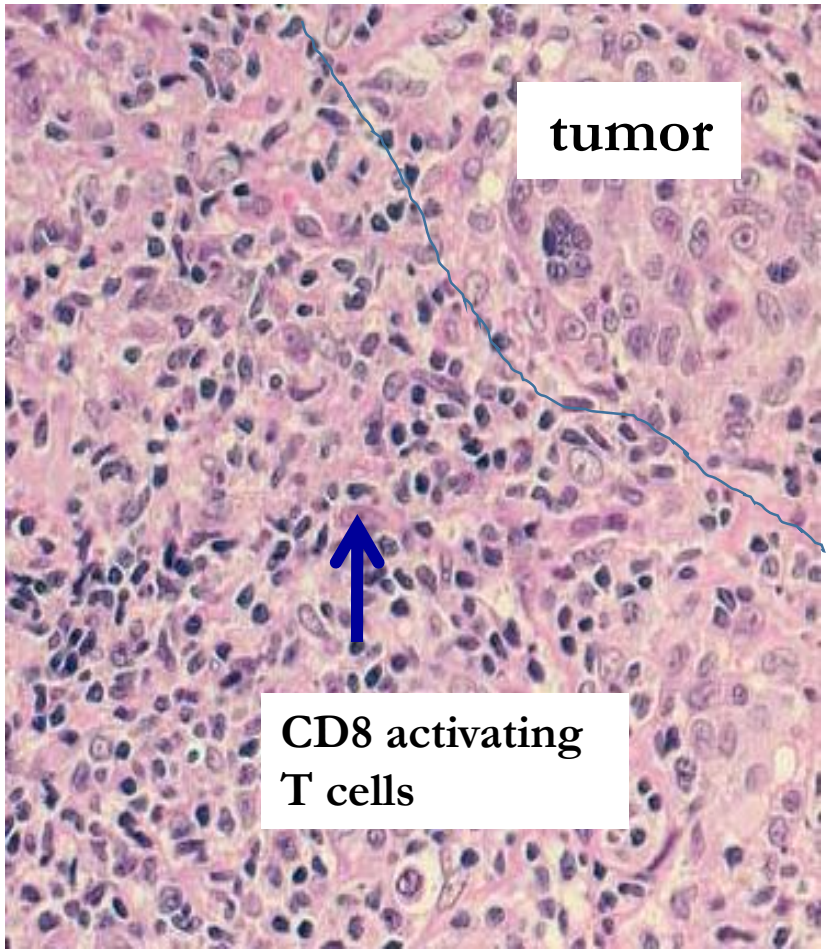
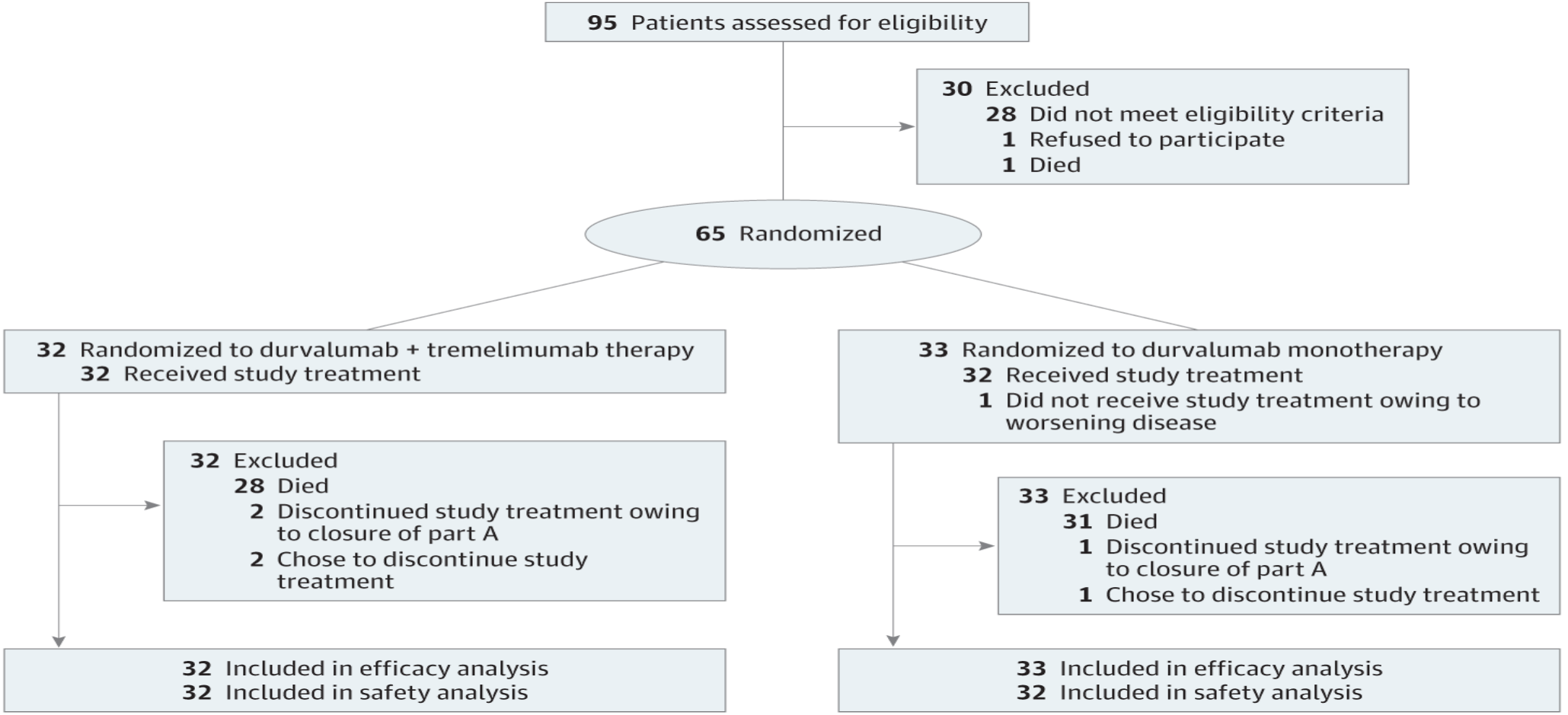


Pancreatic cancer

Melanoma

Courtesy of Liz Jaffee

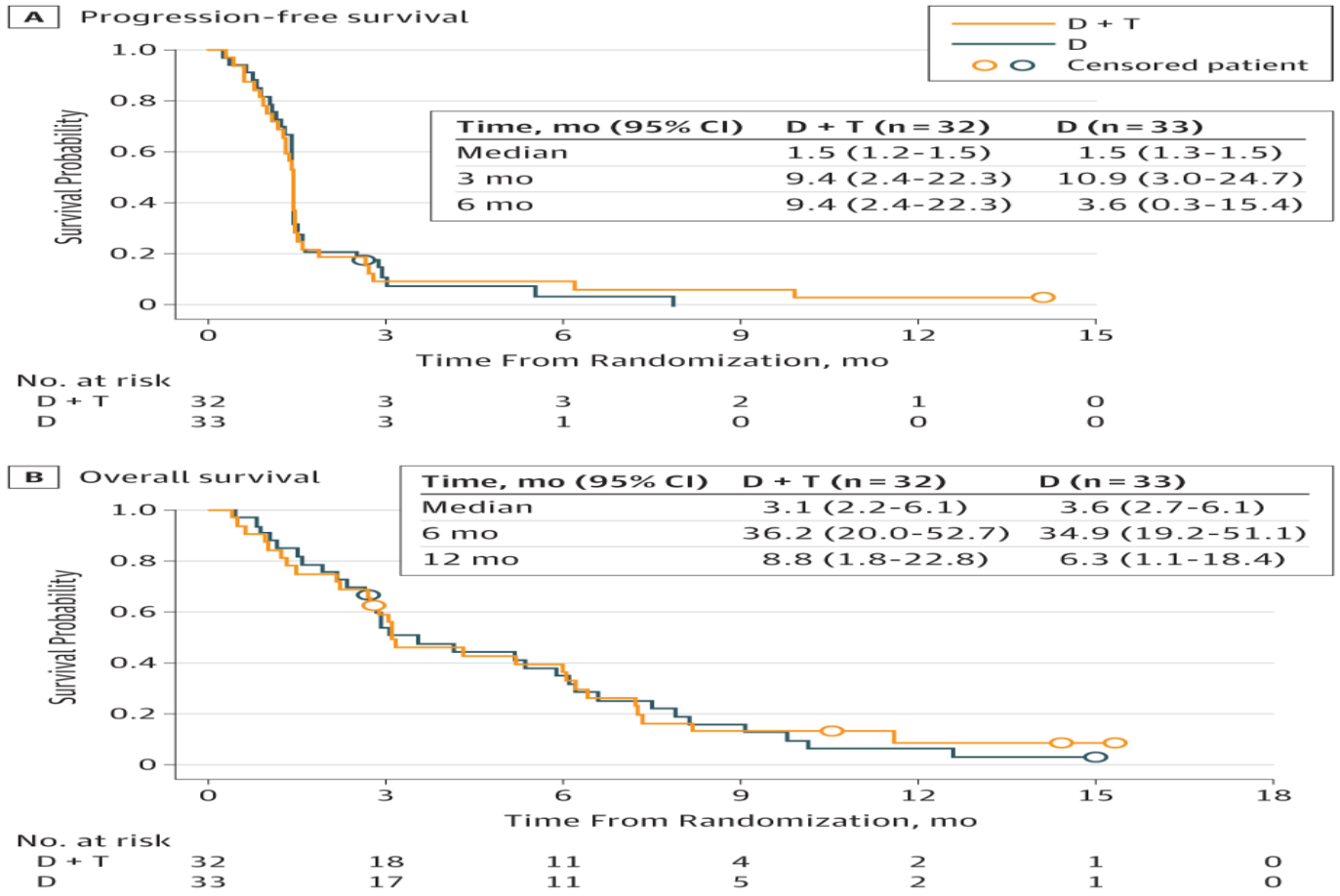
Durvalumab ± Tremelimumab for Patients with Metastatic Pancreatic ca



Threshold for continuation to part B was an OR= 10%

O'Reilly E et al: JAMA Oncology 2019 July 18

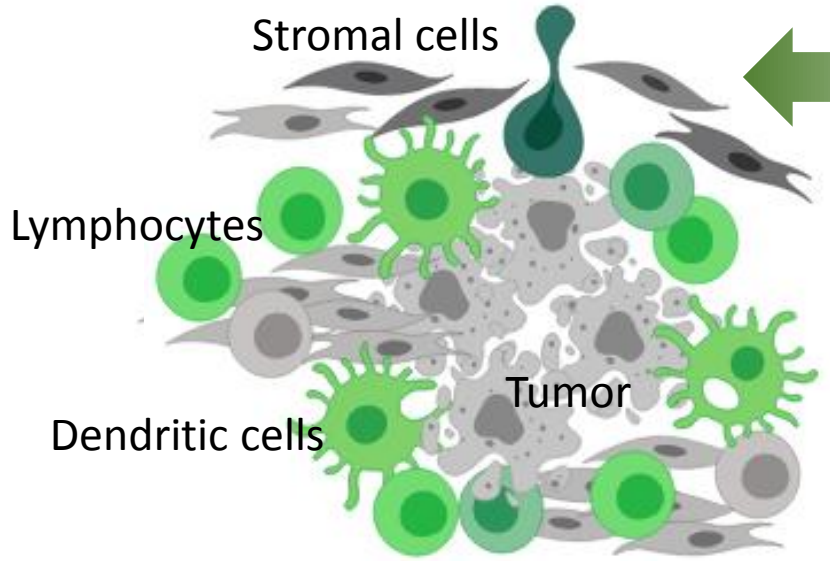
Durvalumab ± Tremelimumab for Patients with Metastatic Pancreatic ca



OR= 3.1% (1/32) in the doublet versus 0% (0/33) in the durva alone arm

O'Reilly E et al: JAMA Oncology 2019 July 18

Naturally Non-Immunogenic Cancers Require a 2-Step Process to Reprogram the TME and Optimize Immunotherapy



STEP 2

Manipulate stroma

CD40
CD137
OX40

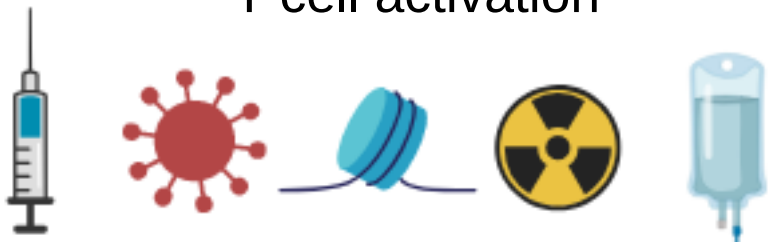
Agonist activation

PD1/PDL1
CTLA4
TGFb
IDO

Checkpoint blockade

STEP 1

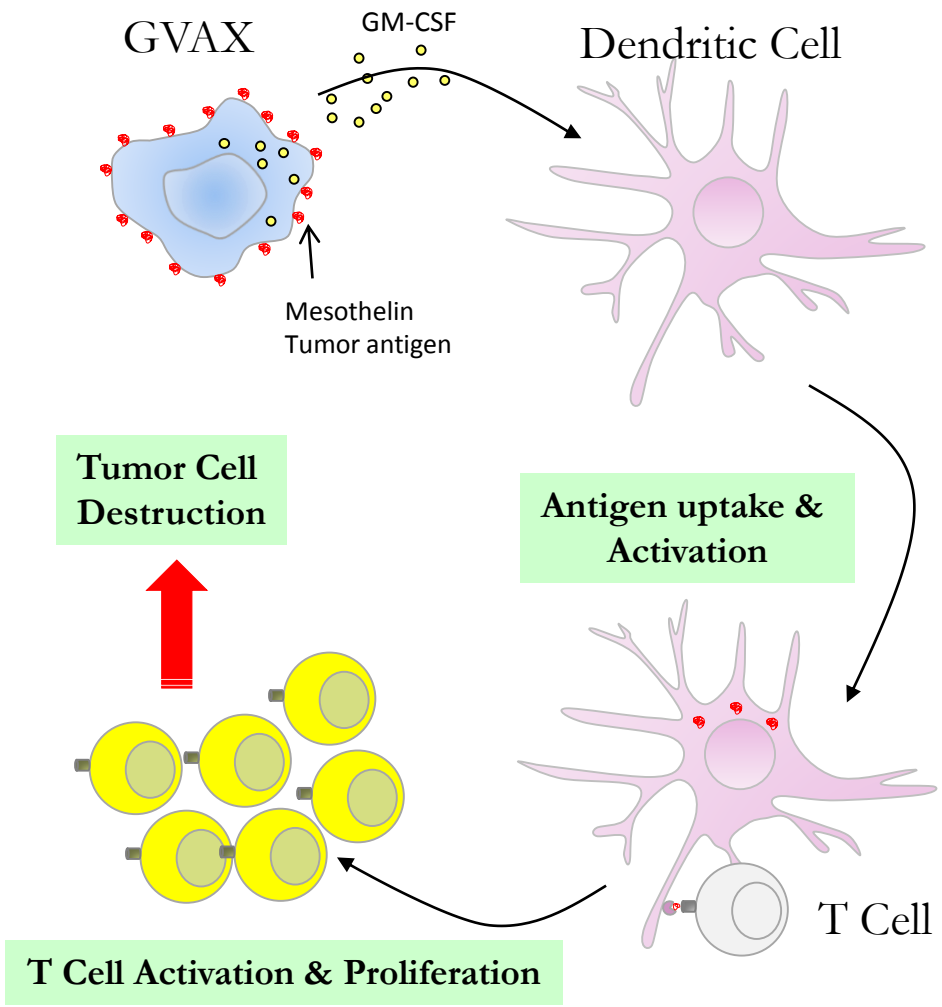
T cell activation



- Neoantigen targeted vaccines
- Oncolytic viruses
- Epigenetic modifier to uncover neoantigens
- Radiation to release antigens
- Chemotherapy to release antigens
- Other Vaccine strategies

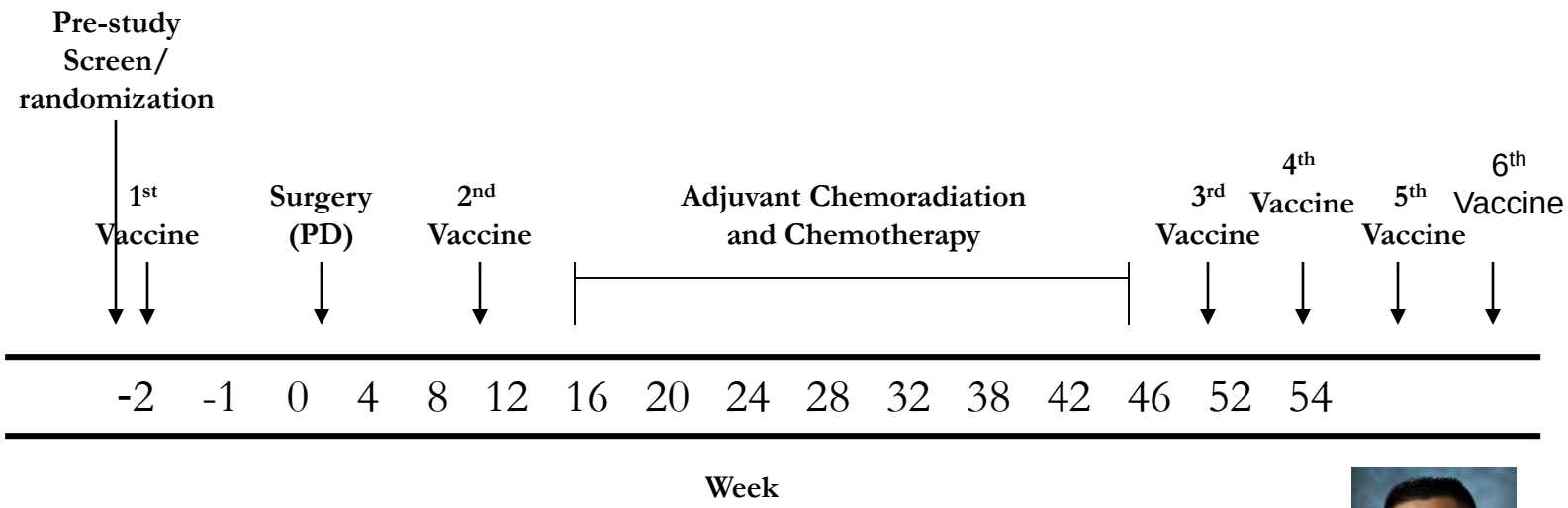
Courtesy Dr. Won Ji Ho

GVAX: GM-CSF Secreting Whole Tumor Cell Vaccine



- Allogeneic pancreatic cancer cell vaccine expressing GM-CSF
- Developed by JHU (Liz Jaffee)
- Off-the-shelf product
- Excellent safety profile in multiple clinical trials
- Induces mesothelin-specific cellular immunity

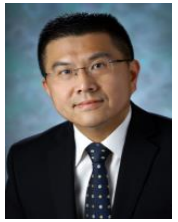
A (Neo)adjuvant Pancreatic Ductal Adenocarcinoma (PDA) Vaccine Study
Can a Vaccine Modulate the Tumor Microenvironment?



Arm A: Vaccine alone (29 patients)

Arm B: Vaccine plus
a single low dose IV Cyclophosphamide (28 pts)

Arm C: Vaccine plus
daily oral metronomic cyclophosphamide (30 pts)

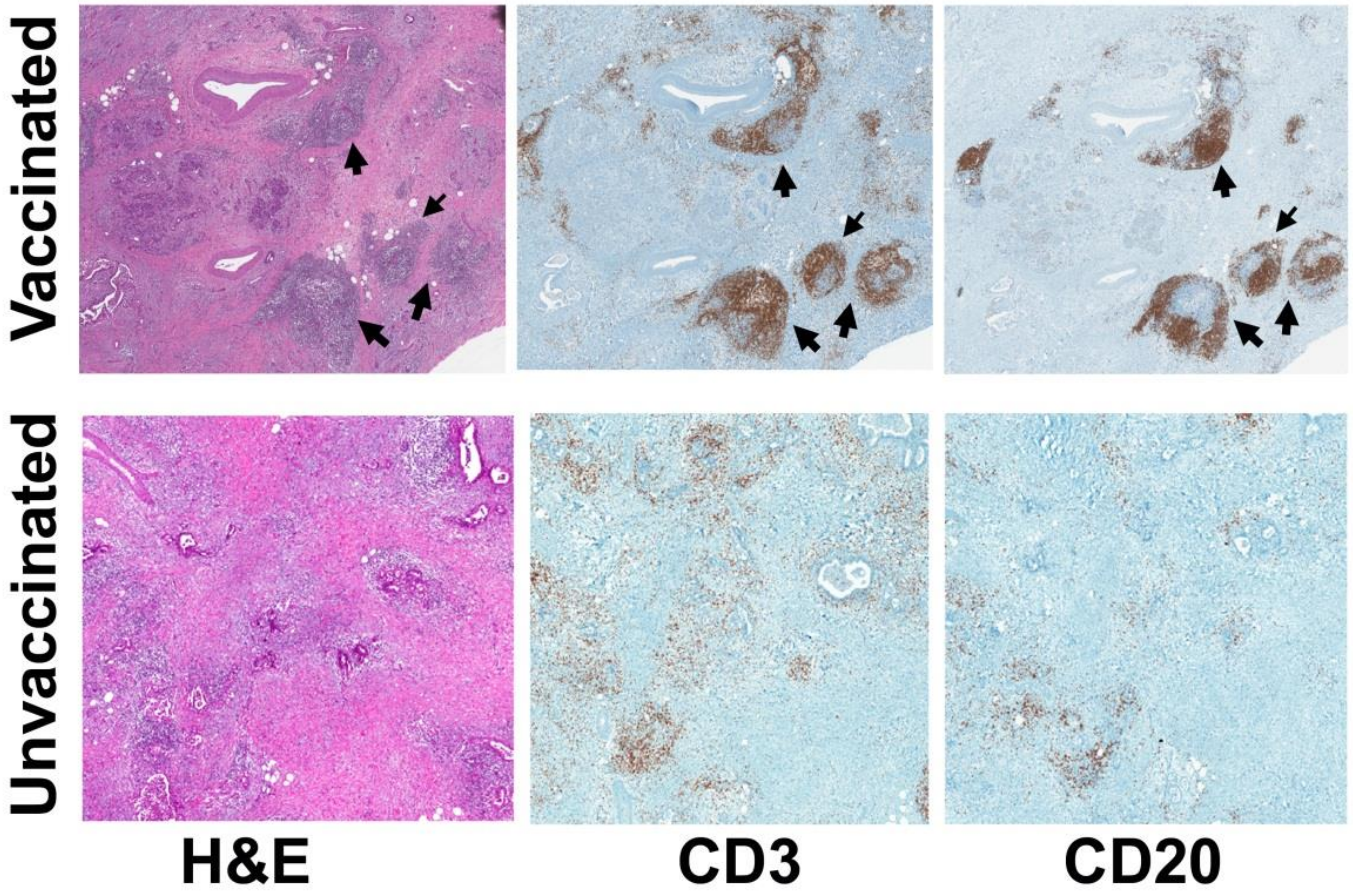


Lei Zheng
Assoc Prof, JHH

Lutz E et al: Cancer Immunol Res 2014:2(7):616-31

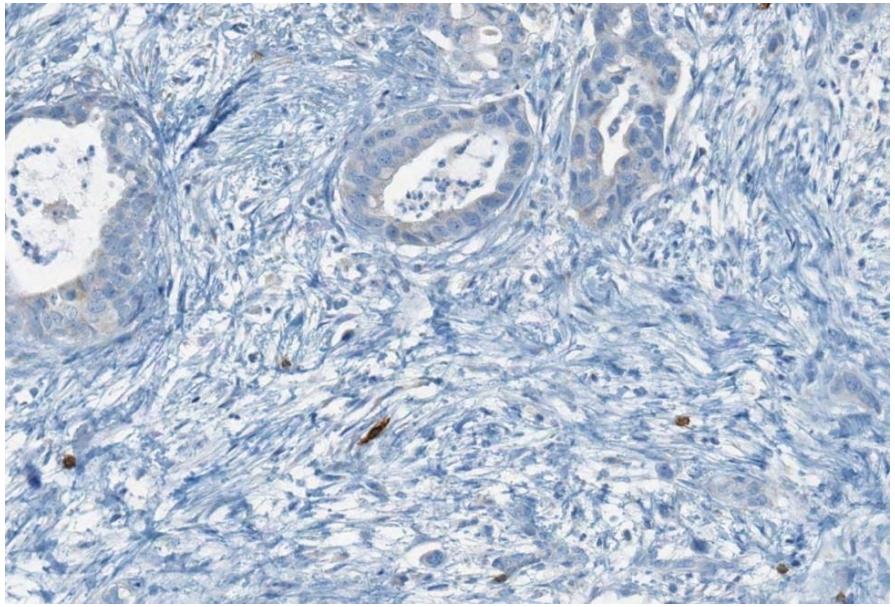
Intra-tumoral Lymphoid Aggregates Form in 85% PDAC Tumors within Two Weeks Following Vaccination

Vaccine Can Reprogram the Tumor Microenvironment

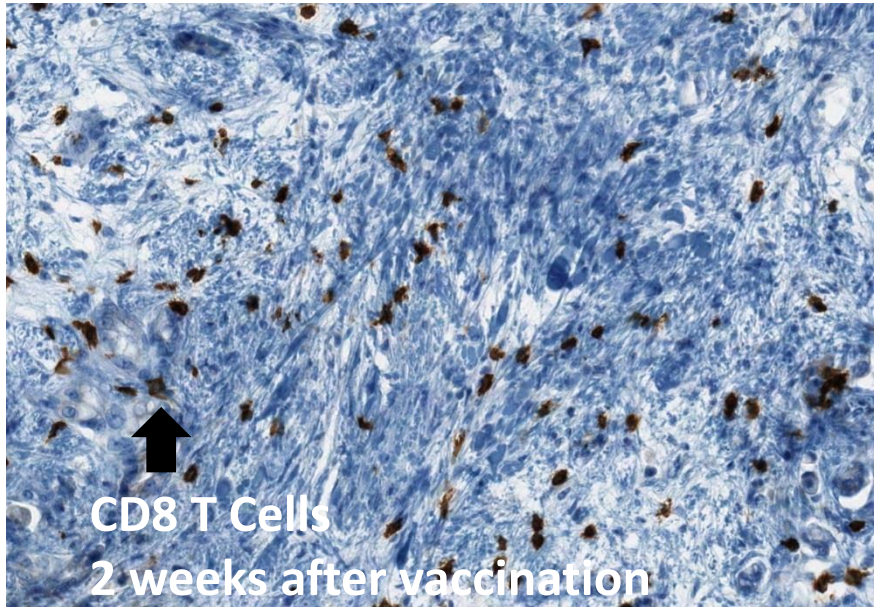


Lutz E et al: Cancer Immunol Res 2014:2(7):616-31

Patients live longer when CD8 T cells leave the lymphoid aggregates and infiltrate the tumor

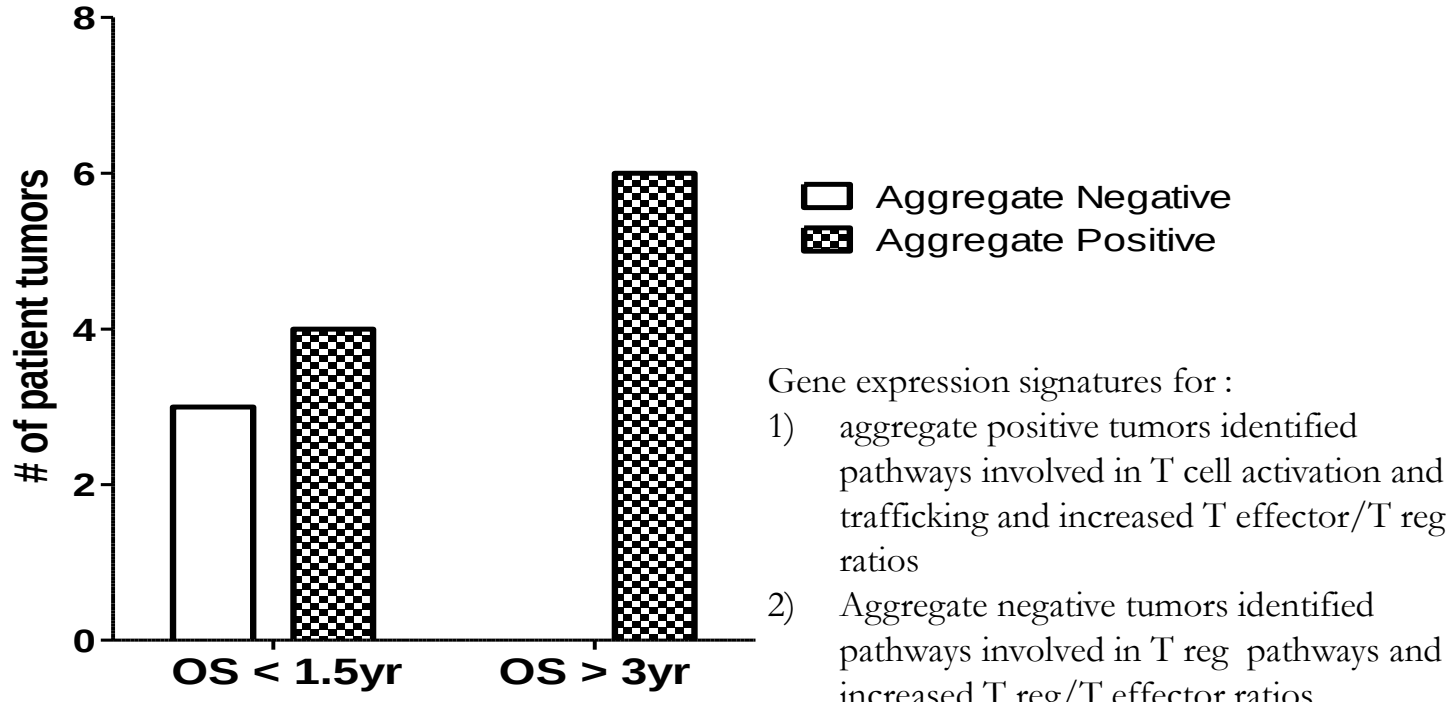


OS<1.5 yr



OS>3 yr

Development of post vaccination intra-tumor tertiary lymphoid aggregates is associated with survival

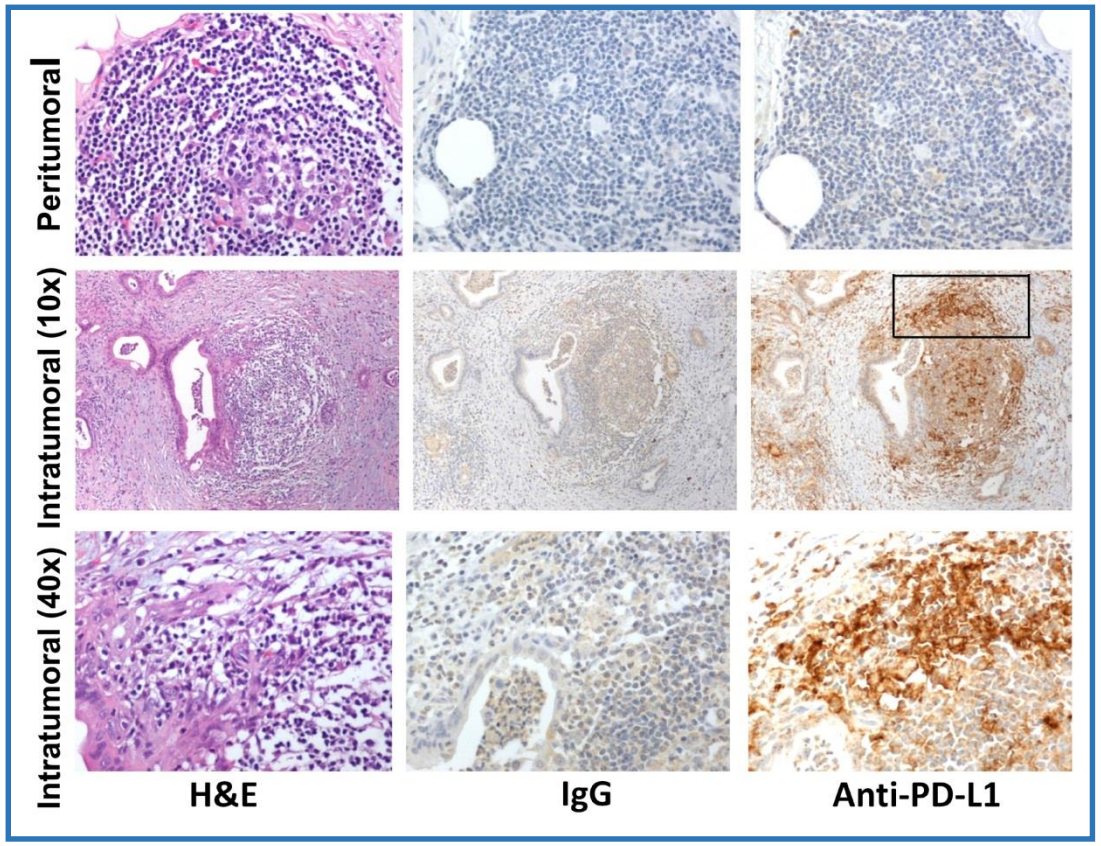


Gene expression signatures for :

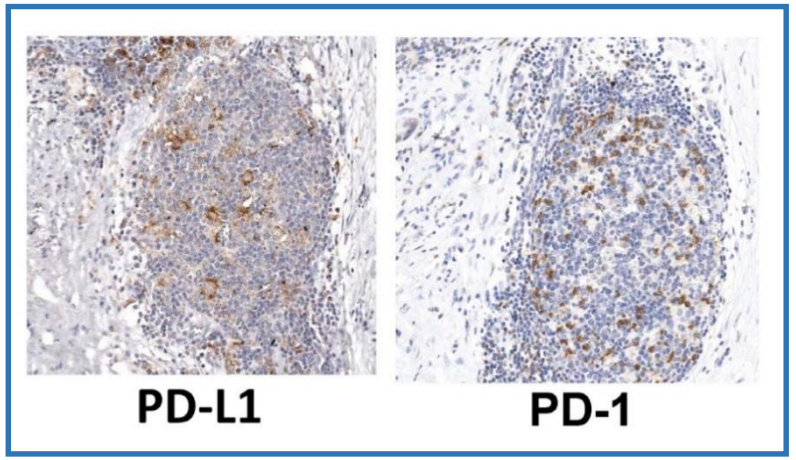
1) aggregate positive tumors identified pathways involved in T cell activation and trafficking and increased T effector/T reg ratios
2) Aggregate negative tumors identified pathways involved in T reg pathways and increased T reg/T effector ratios

Lutz E et al: Cancer Immunol Res 2014:2(7):616-31

CD8 T cell activation in lymphoid aggregates produce IFNɣ which upregulates T cell inhibitory signals like PD-L1



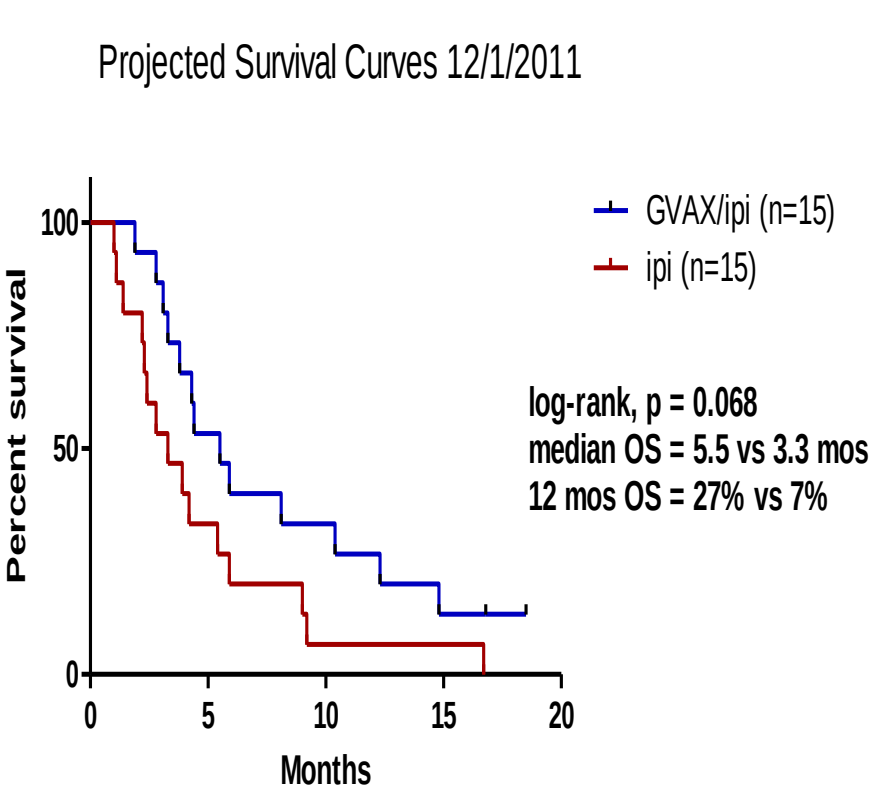
Co-localization

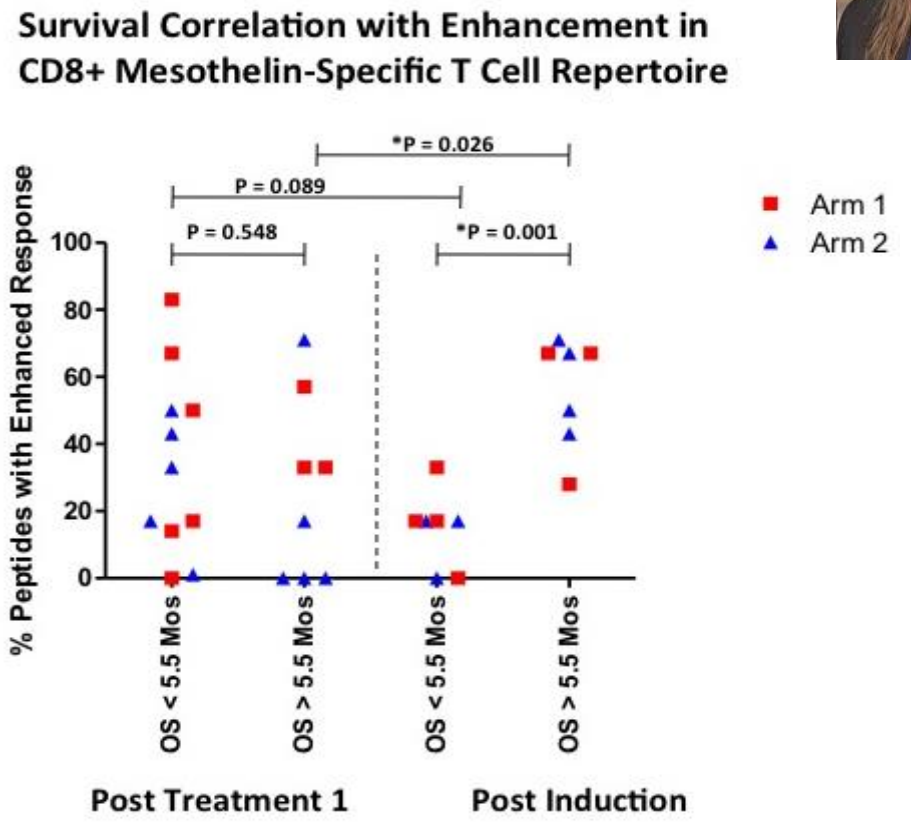


Activated T cells → IFNɣ production → PD-L1/PD-1

Ipilimumab + Vaccine Improves Survival In Advanced Pancreatic Cancer Patients

(PI: Dung Le)

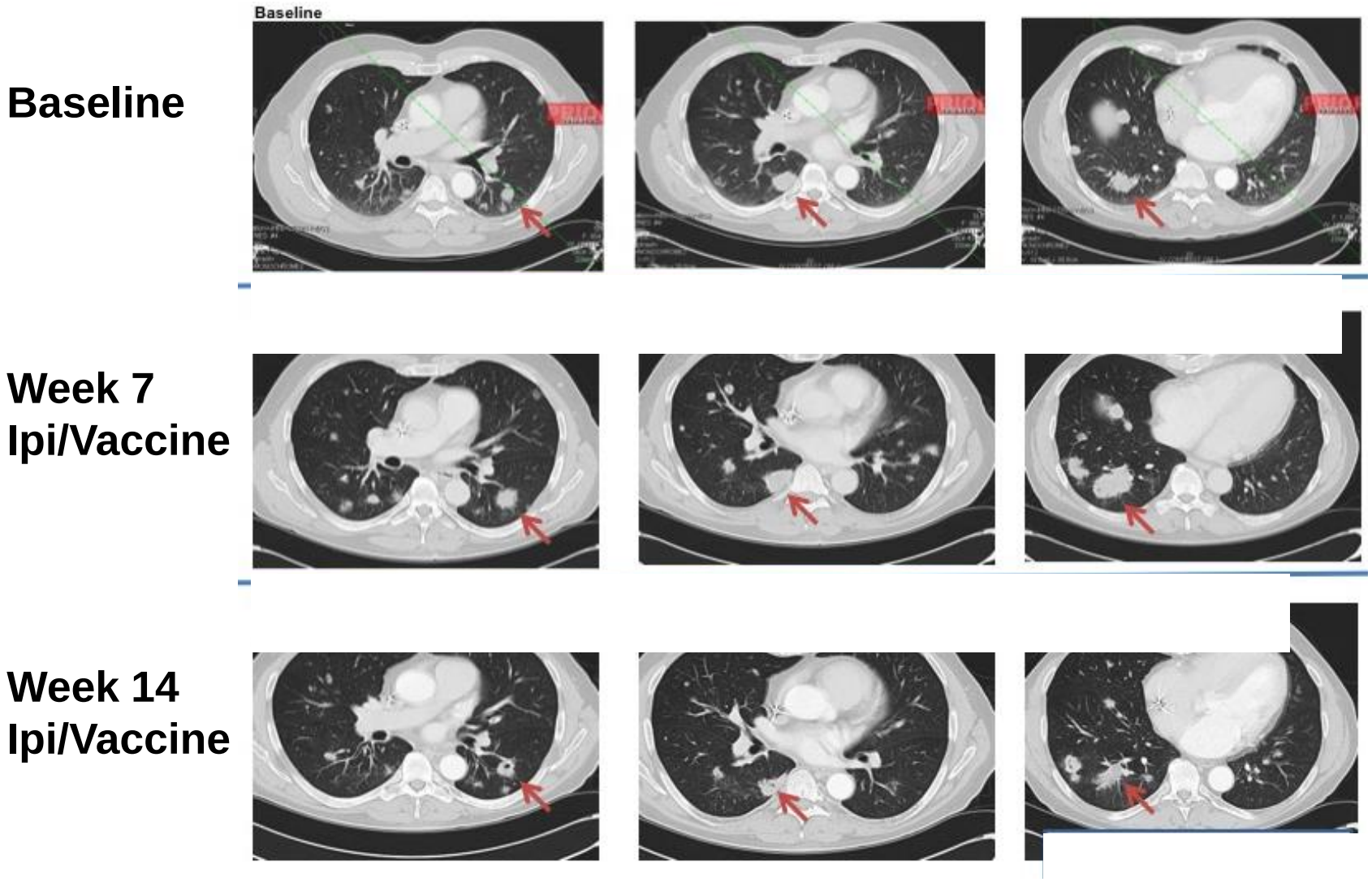




- Metastatic patients having progressed with >2 chemotherapies
- 7/15 patients in the ipi+GVAX combo arm with radiographic and/or CA19-9 response
- 0/15 in the Ipi alone arm with radiographic or CA19-9 response

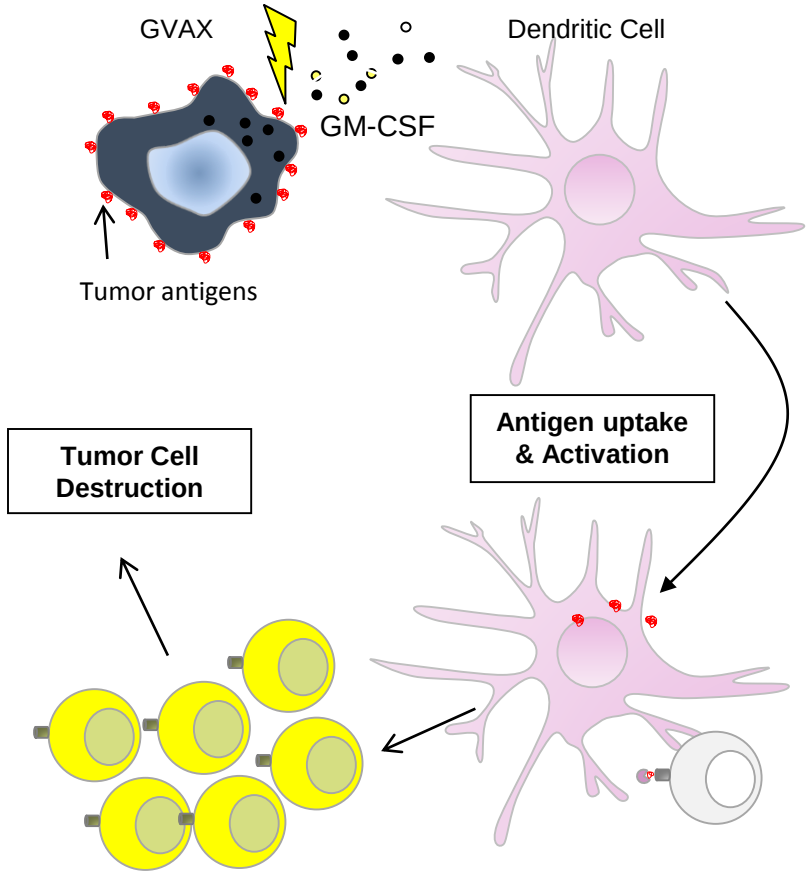
Le et al. Journal of Immunotherapy 2013

Radiographic Regressions After 14 Weeks Of Treatment with Ipilimumab (Ipi) + Vaccine

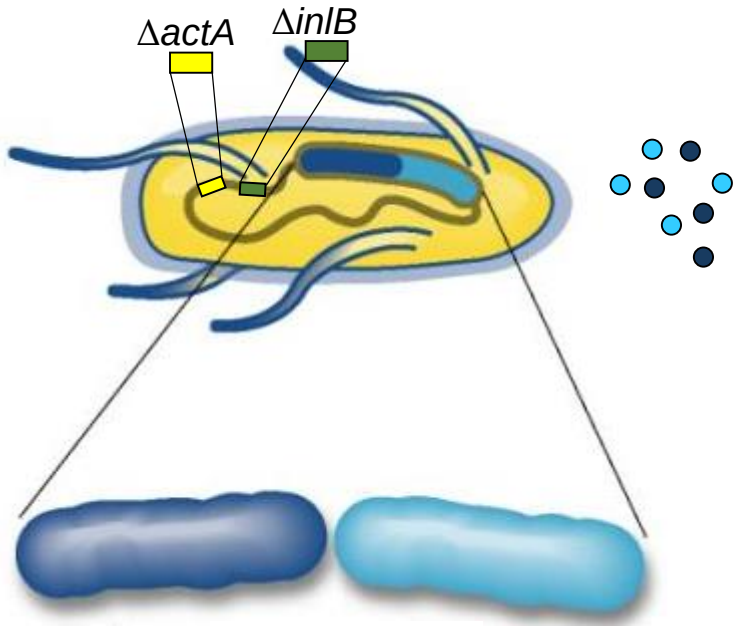


Two Vaccines May Be Better Than One: Prime/Boost Study : 2 synergistic mechanisms

GVAX Pancreas
Irradiated, whole-cell tumor vaccine

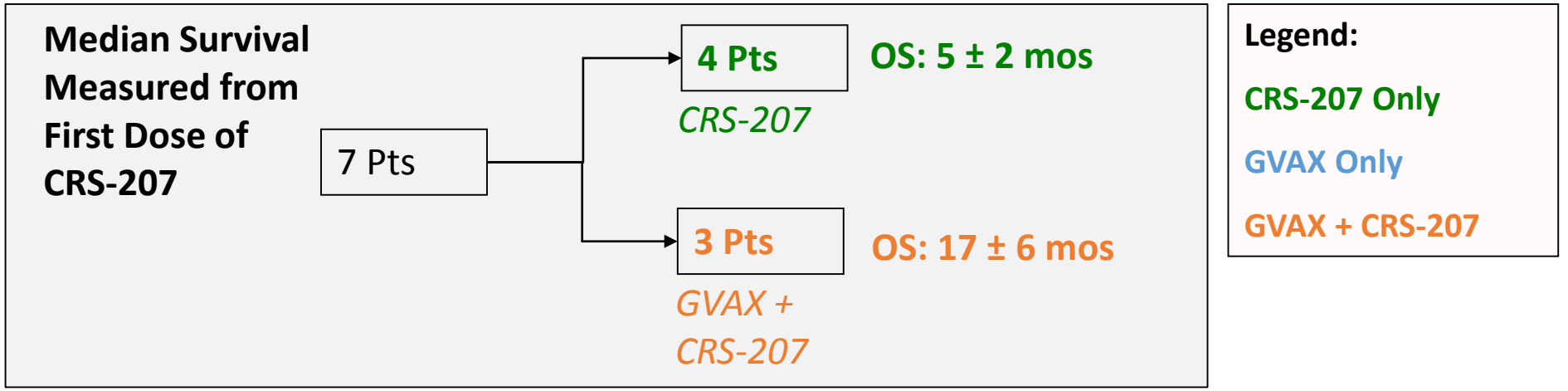


LADD Listeria
Live-attenuated *Listeria monocytogenes*



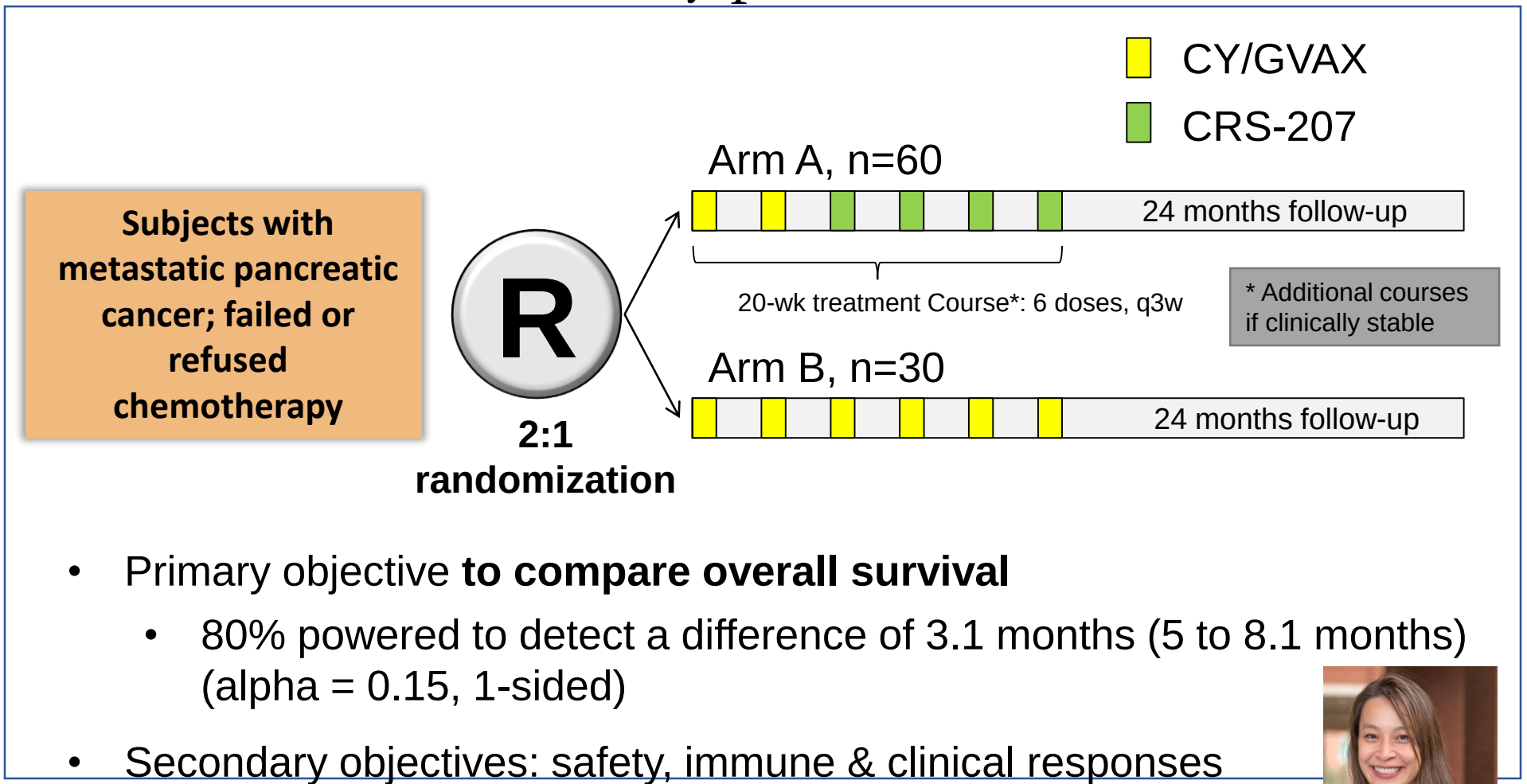
Mesothelin

Phase I clinical data suggests GVAX Prime / Listeria Boost



Laheru et al: Clin Cancer Res 2012: 18(3) 858-68

Randomized Phase 2 Trial: GVAX/CRS-207 v. GVAX for chemo refractory pancreatic ca



- Primary objective **to compare overall survival**
  - 80% powered to detect a difference of 3.1 months (5 to 8.1 months) (alpha = 0.15, 1-sided)
- Secondary objectives: safety, immune & clinical responses

Le D et al: JCO 2015:33(12):1325-33

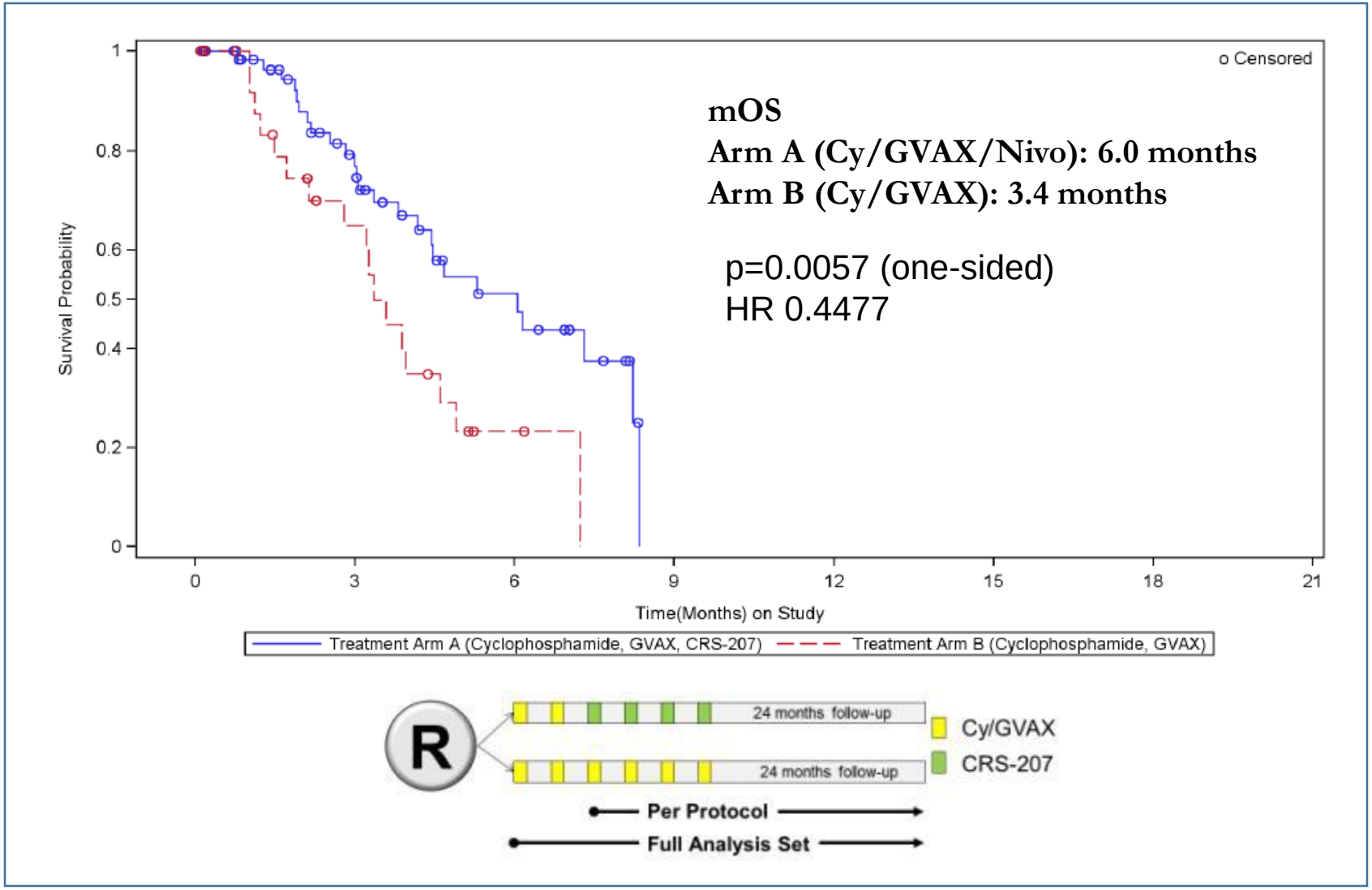
Dung Le

Baseline Characteristics

Number of Subjects (% of Treated)	ARM A (N=61)	ARM B (N=29)	P-value
Age-yr			0.9135
Median	63	67	
Range	45-87	46-80	
Sex - no. (%)			0.3782
Male	34 (56%)	19 (66%)	
Female	27 (44%)	10 (34%)	
ECOG - no. (%)			0.627
0	39 (64%)	17 (59%)	
1	22 (36%)	12 (41%)	
Sites of metastases - no. (%)			0.5066
Liver	39 (64%)	22 (76%)	
Lung Only	14 (23%)	4 (14%)	
Other	8 (13%)	3 (10%)	
Disease status at study entry - no. (%)			0.9102
Stable Disease	12 (20%)	6 (21%)	
Progressive Disease	49 (80%)	23 (79%)	
Prior chemotherapy metastatic regimens - no. (%)			0.7005
0	11 (18%)	4 (14%)	
1	18 (30%)	11 (38%)	
2+	32 (52%)	14 (48%)	
Previous surgical resection - no. (%)			0.7383
Yes	23 (38%)	12 (41%)	

Le D et al: JCO 2015:33(12):1325-33

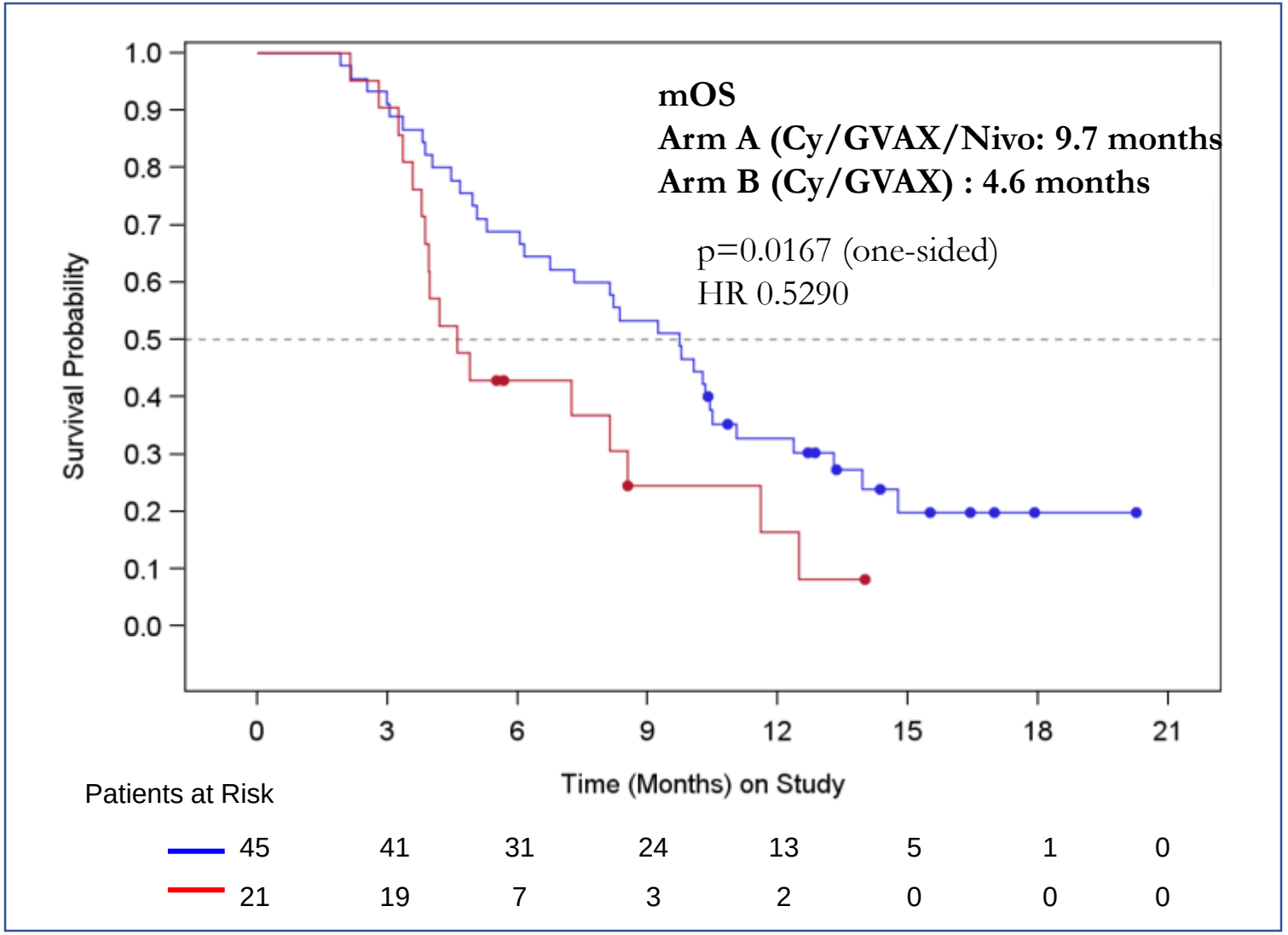
Overall Survival – Full Analysis Set



Le D et al: JCO 2015:33(12):1325-33

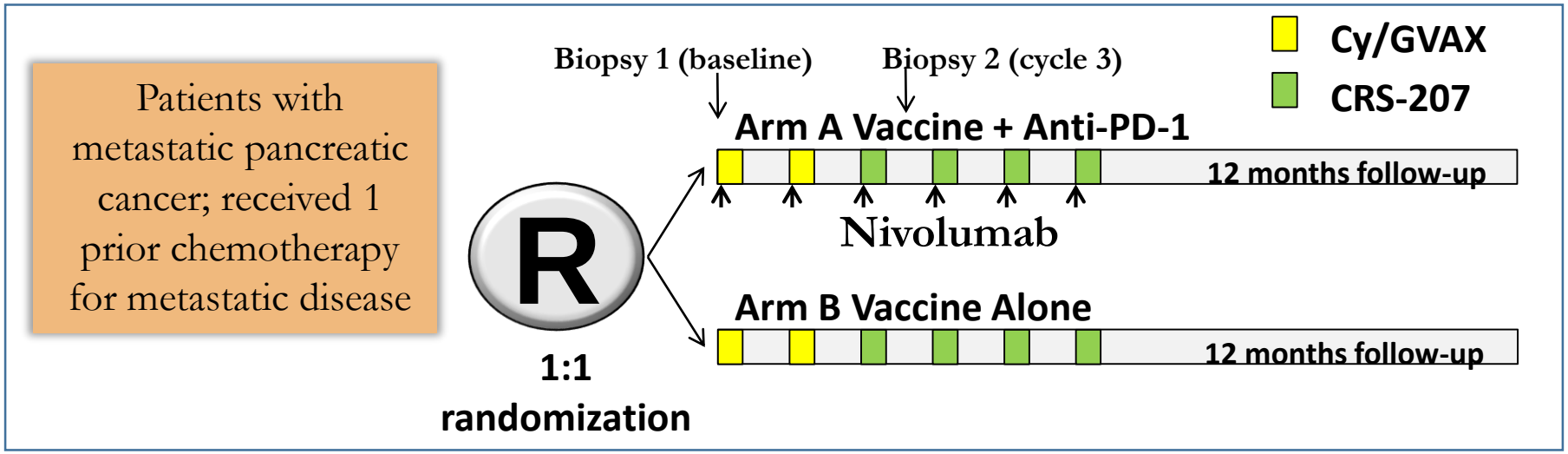
Extended OS in Per Protocol Analysis

Subjects Who Received at 3 Doses (One Dose of CRS-207)



Le D et al: JCO 2015:33(12):1325-33

A Randomized Phase 2 Study of the Safety, Efficacy, and Immune Response of GVAX Pancreas Vaccine (with Cyclophosphamide) and CRS-207 with or without Nivolumab in Patients with Previously Treated Metastatic Pancreatic Adenocarcinoma: "Stellar"



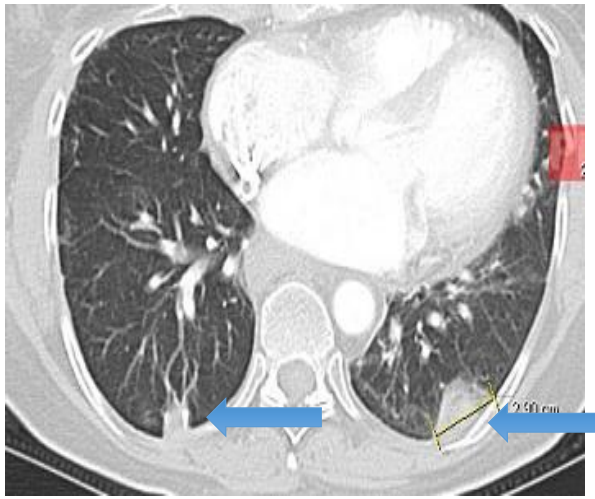
- 96 patients with previously treated, metastatic pancreatic cancer randomized 1:1 to 2 treatment arms
- Primary objective: study is 80% powered for primary endpoint of comparison of OS between Arms A and B (HR 1.66, 2-sided type 1 error rate 14%)
- Power is computed for a 2-stage group sequential design with a single interim analysis. An O'brien Fleming-like spending function will be used to account for one interim analysis (approximately 42 events).

Dung Le

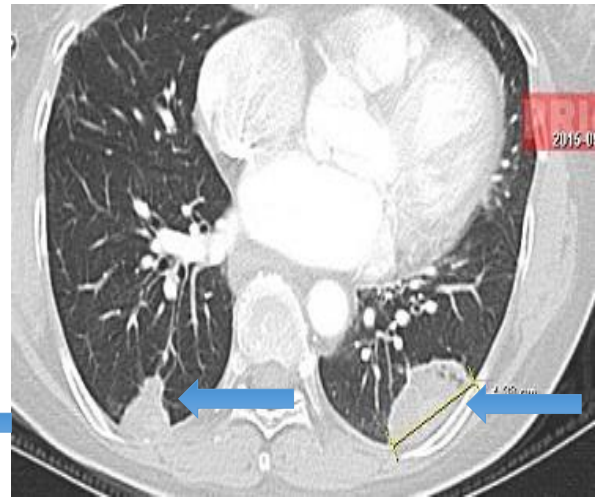
Immune Related Adverse Events

Event-no. (%)		All Grades N=51
Any		16 (31)
Dermatologic	Rash	5 (10)
Musculoskeletal	Arthralgias	2 (4)
Gastrointestinal	Diarrhea/colitis	2 (4)
	Amylase/lipase	2 (4)
	Transaminitis	2 (4)
Endocrine Disorders	Hyper/hypothyroidism	2 (4)
	Hyperglycemia	1 (2)
Respiratory	Pneumonitis	1 (2)
Cardiovascular	Myocarditis	1 (2)
Renal	Acute kidney injury	1 (2)
Hematologic	Thrombocytopenia	1 (2)

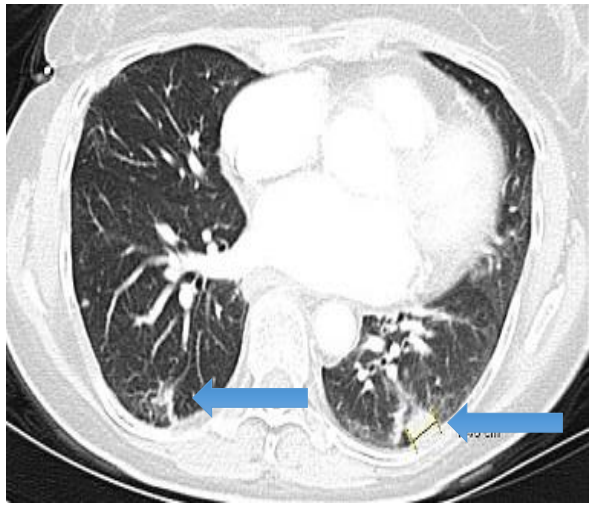
GVAX + CRS-207 Prime Boost Vaccination with Programmed Death-1 (PD-1) Blockade



Baseline

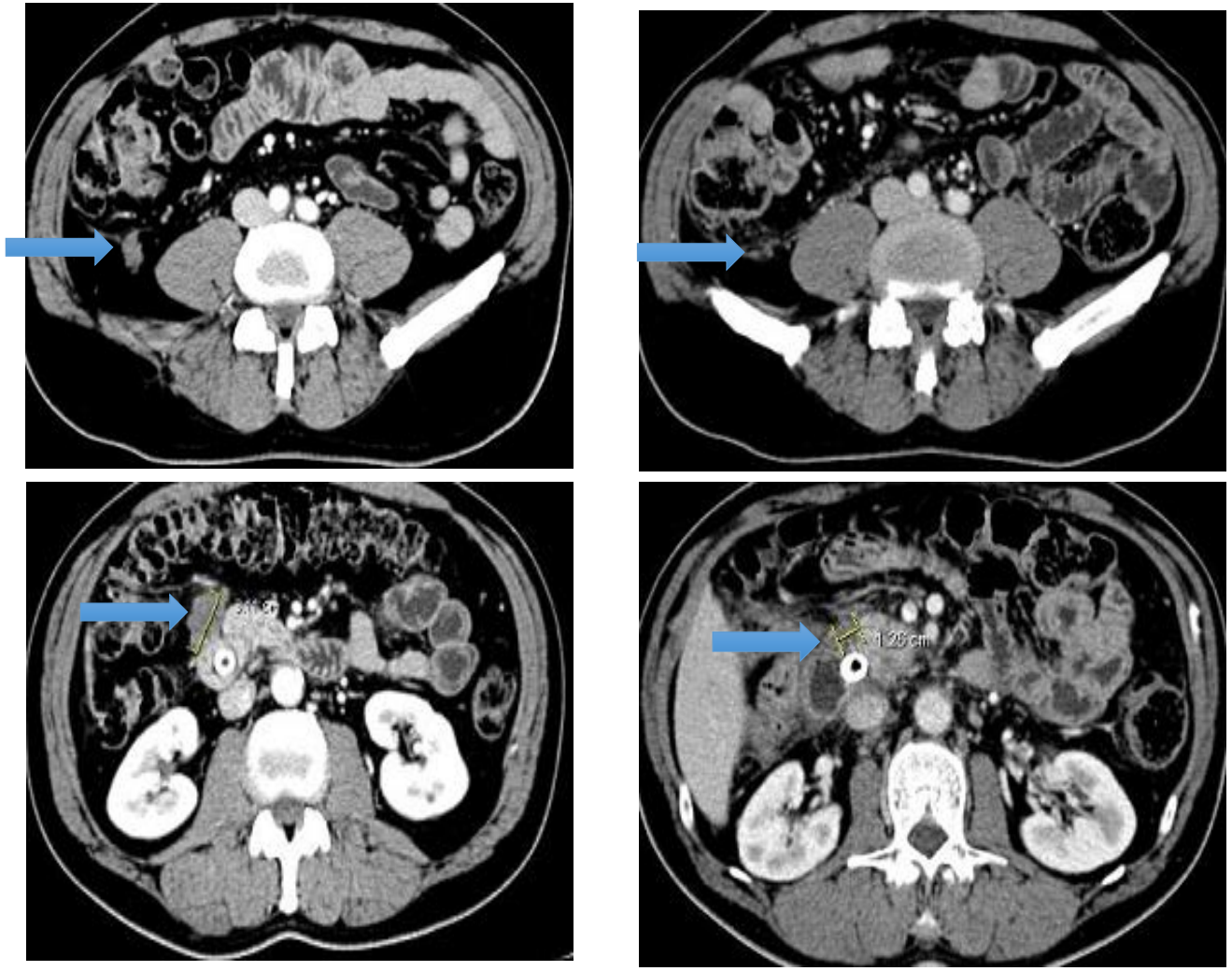


Week 10



Week 30

GVAX + CRS-207 Prime Boost Vaccination with Programmed Death-1 (PD-1) Blockade

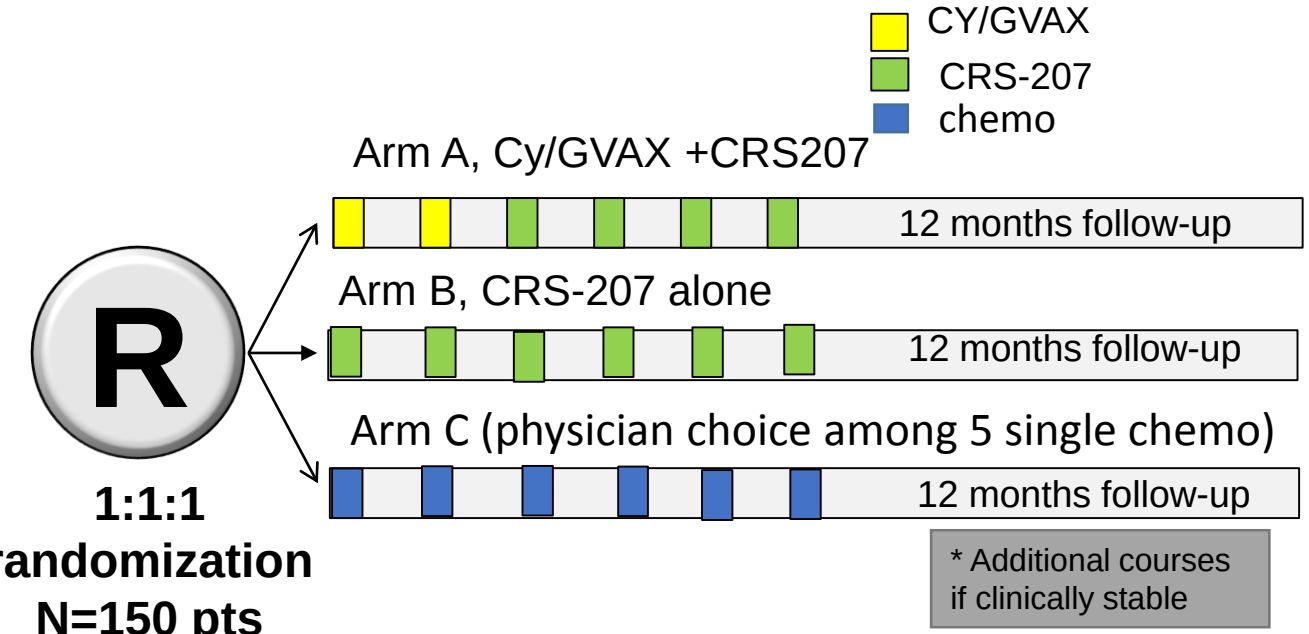


Baseline

Week 30

Phase2b randomized, multicenter study of GVAX pancreas and CRS-207 compared to chemotherapy in patients with previously treated metastatic pancreatic adenoca (ECLIPSE)

Subjects with metastatic pancreatic cancer; progressed ≥ 2 lines of chemotherapy (primary cohort) or progressed on 1 line of chemo second line cohort



1:1:1 randomization N=150 pts

- Primary objective **to compare overall survival in the primary cohort**
  - 80% powered to detect a difference of 2 months (Arm A of 6 mo to Arm C of months) (alpha = 0.15, 1-sided)
- Secondary objectives: safety, immune & clinical responses

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Dung Le

Patient demographics (primary cohort)

Primary Cohort	Cy/GVAX+ CRS207 Arm A (N=68)	CRS-207 ARM B (n=58)	Chemotherapy Arm C (N=43)	Total (N=169)
Age (years) mean	63.3	63.2	64	63.5
Gender (M/F)	37/31	29/29	17/26	83/86
Ethnicity (W/AA/Hispanic/A)	60/5/0/3	50/2/4/2	37/4/2/0	147/9/6/7
ECOG 0/1/2	26/42/0	15/43/0	17/25/1	58/110/1
Prior treatment (2/3/4/5/6/7)	30/16/12/7/2/1	36/16/4/2/0/0	17/13/7/5/1/0	83/45/23/14/3/1

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Patient demographics (second line cohort)

Second line Cohort	Cy/GVAX+ CRS207 Arm A (N=26)	CRS-207 ARM B (n=29)	Chemotherapy Arm C (N=11)	Total (N=66)
Age (years) mean	63.9	64.1	66.6	64.4
Gender (M/F)	11/15	19/10	6/5	36/30
Ethnicity (W/AA/Hispanic/A)	22/3/0/1	25/2/1/1	11/0/0/0	58/5/2/1
ECOG 0/1/2	10/16/0	13/16/0	6/5/0	29/37/0

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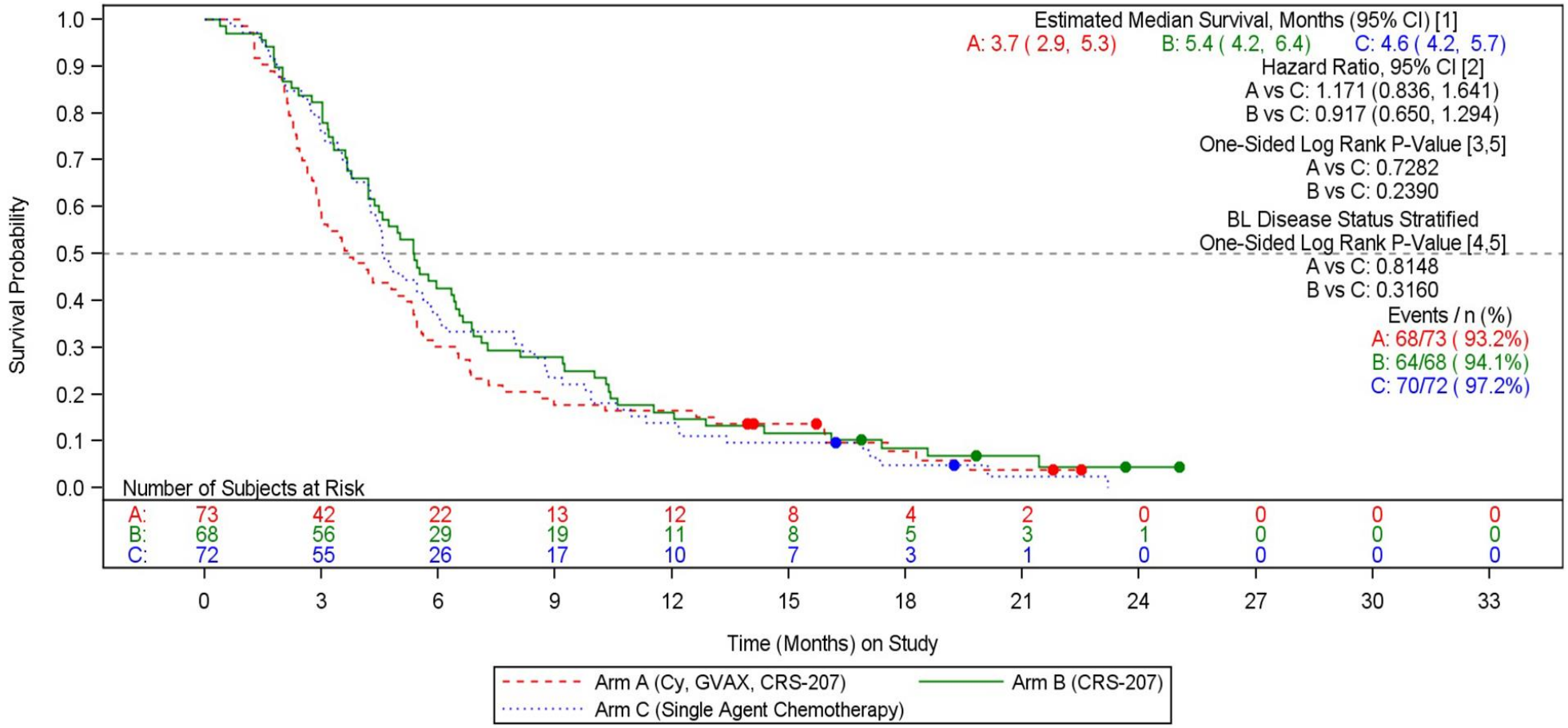
Kaplan Meier median OS



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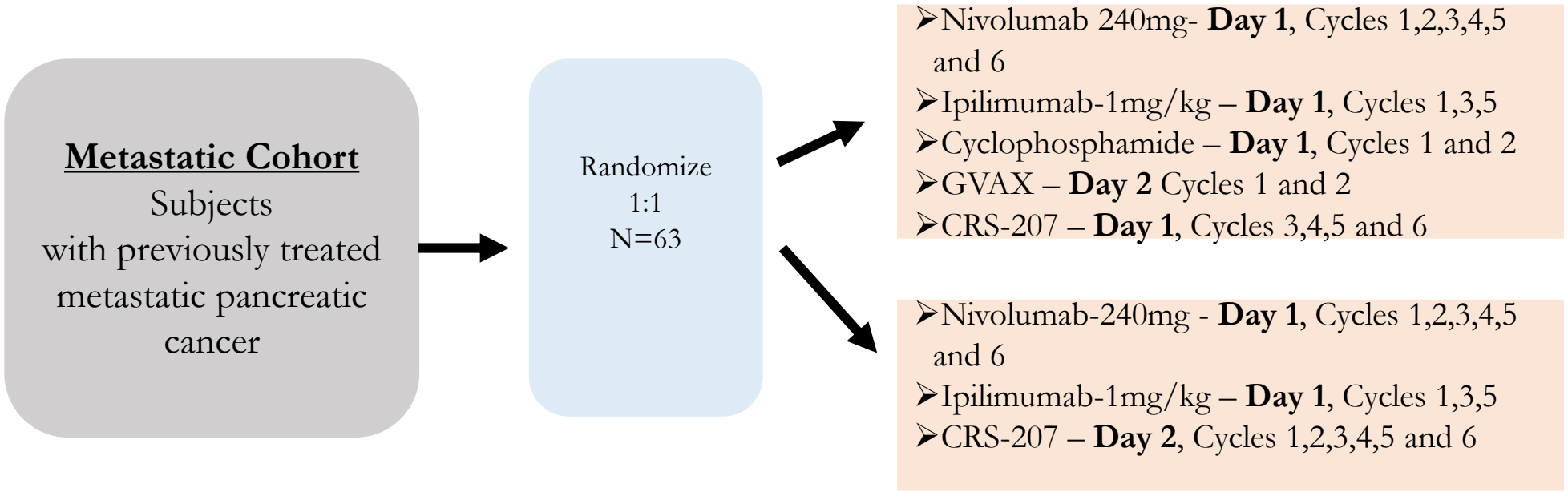
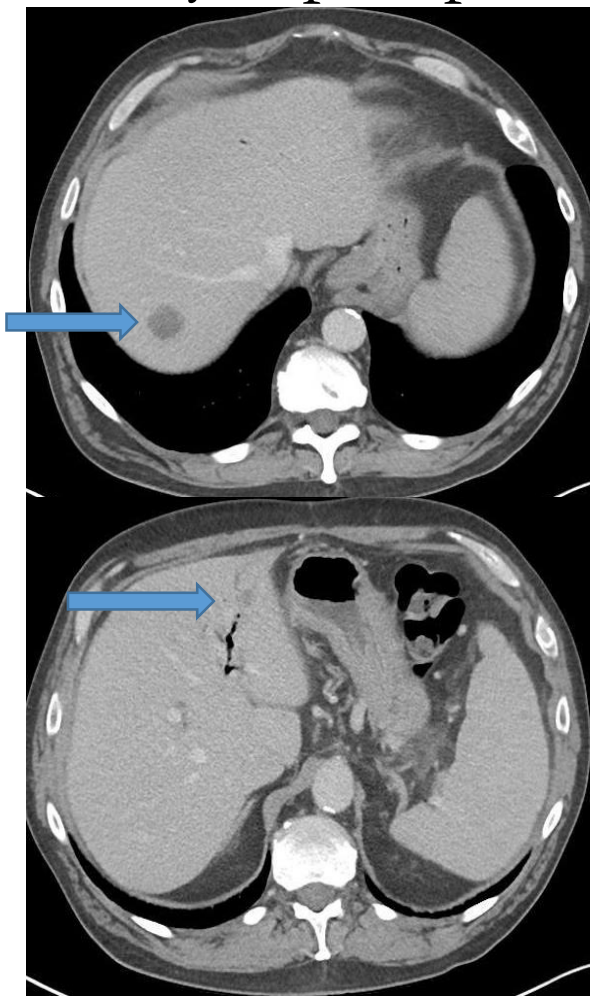
Nivolumab plus Ipilimumab and CRS-207 with or without GVAX Pancreas Vaccine (with Cyclophosphamide) in Patients with Pancreatic Adenocarcinoma:

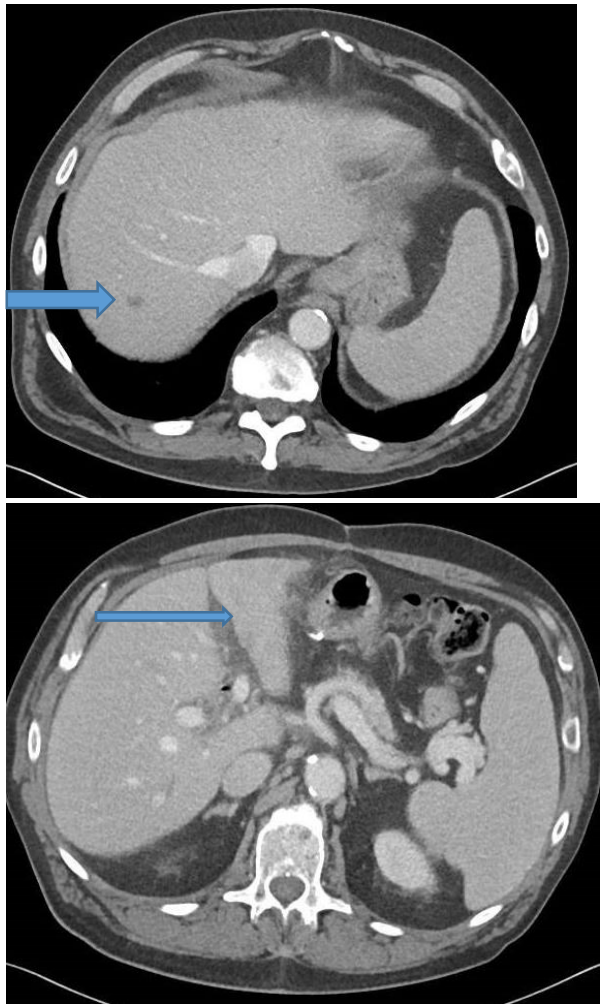


https://clinicaltrials.gov/ct2/show/NCT03190265

Nivolumab plus Ipilimumab and CRS-207 with or without GVAX Pancreas Vaccine (with Cyclophosphamide) in Patients with Pancreatic Adenocarcinoma:

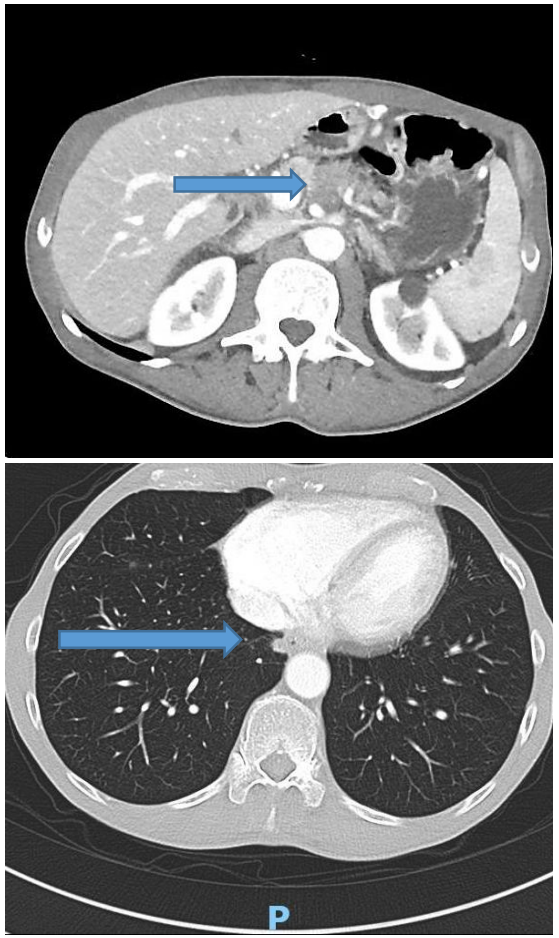


Baseline (6/25/2018)



Week 48 (5/28, 2019)

Nivolumab plus Ipilimumab and CRS-207 with or without GVAX Pancreas Vaccine (with Cyclophosphamide) in Patients with Pancreatic Adenocarcinoma:



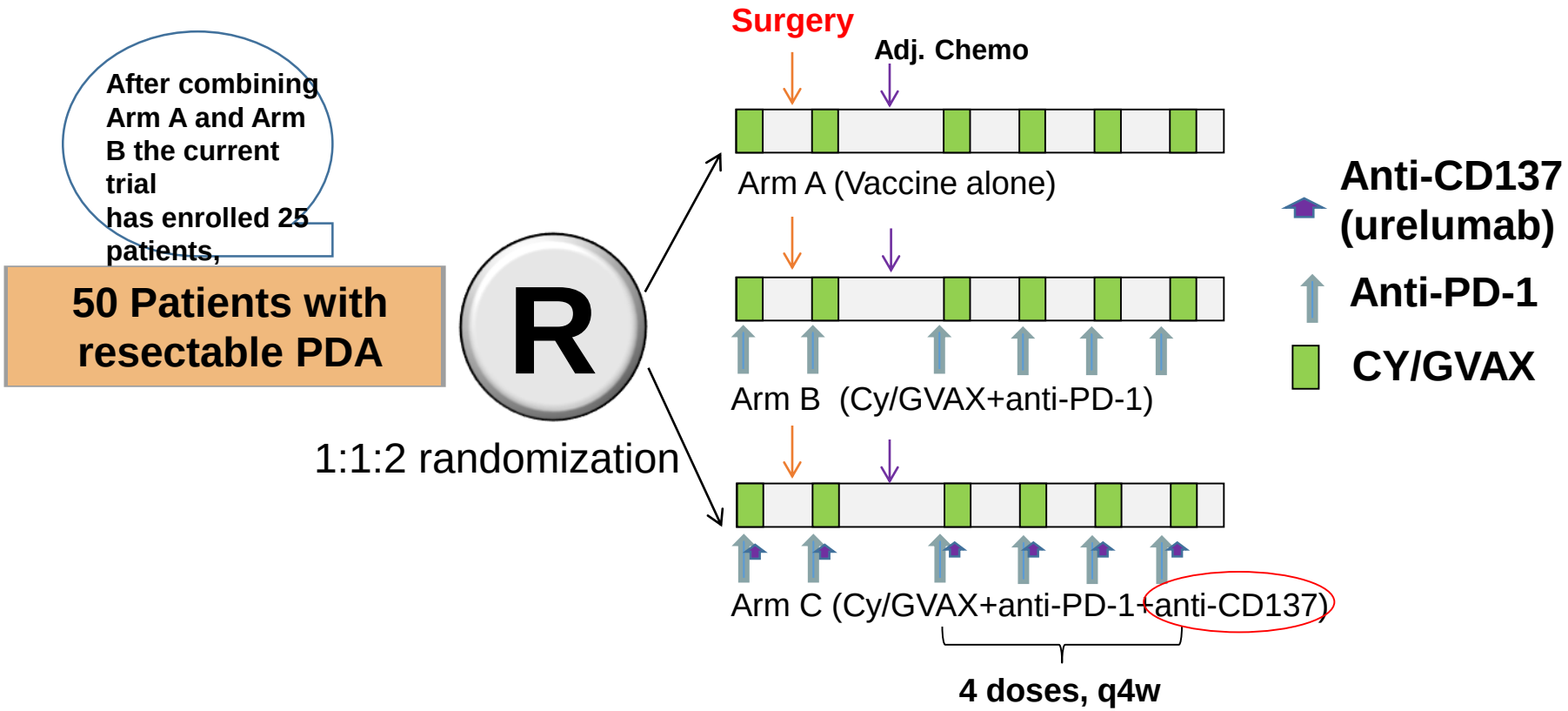
Baseline (7/30/2018)

Week 36 (April 8, 2019)

A randomized phase II clinical trial of neoadjuvant and adjuvant CY/GVAX vaccines with versus without anti-PD-1 antibody and/or anti-CD137 agonist antibody for resectable pancreatic cancer

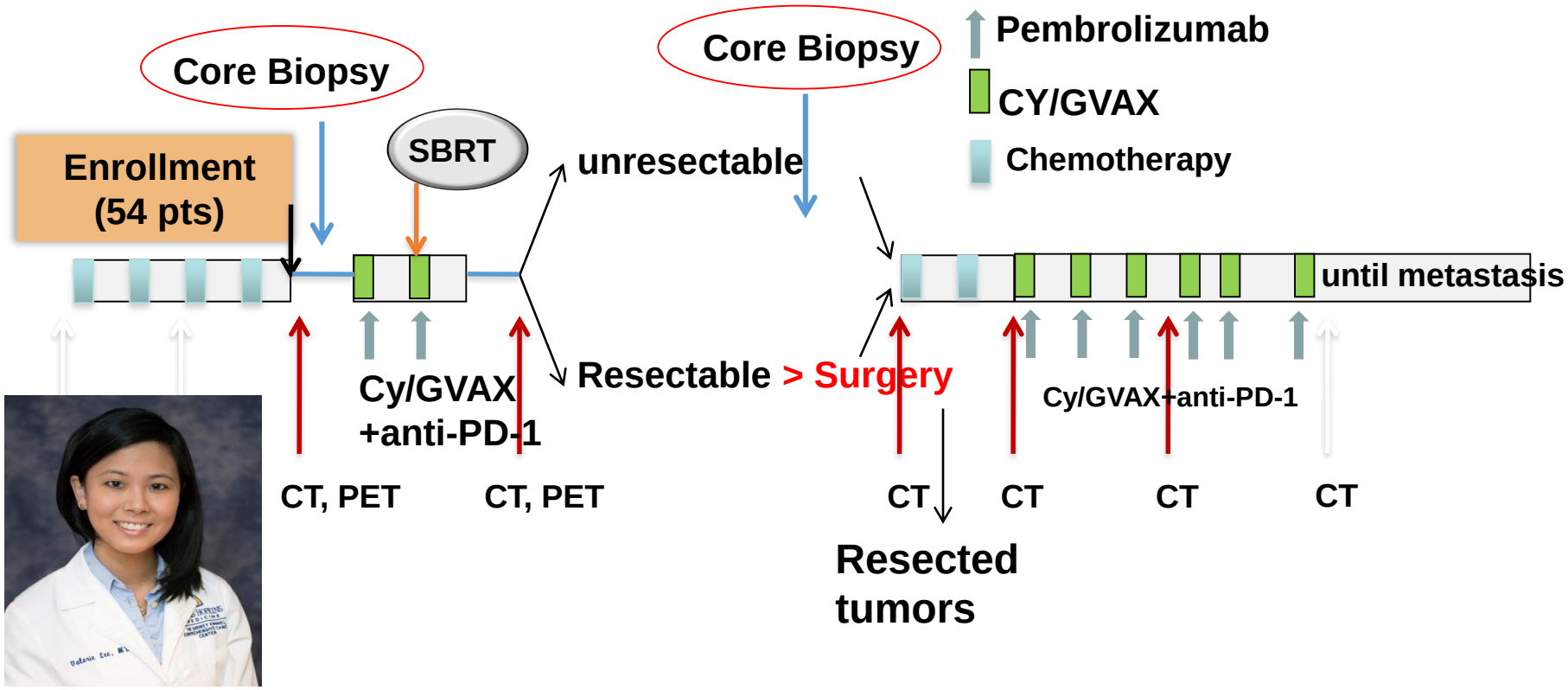
PI: Lei Zheng; Research Nurse: Carol Judkins; Data Manager: Jessica Hoare

Lei Zheng
Assoc Prof, JHU



https://clinicaltrials.gov/ct2/show/NCT02451982

GVAX Vaccine/anti-PD-1 Antibody(Pembrolizumab) with Stereotactic Body Radiation following induction chemotherapy for locally Advanced PDAC



Primary endpoint: metastasis free survival

Val Lee
Instructor of Oncology , JHH

https://clinicaltrials.gov/ct2/show/NCT02648282

Demographics

Characteristic	N = 42
Gender (N, %)	
Male	21 (50)
Female	21 (50)
Prior treatment (N, %)	
FOLFIRINOX	30 (71)
Gem/Abraxane	6 (14)
Both	6 (14)
Age (median, range)	63 (42-84)
Race/Ethnicity (N, %)	
Non-Hispanic White	36 (86)
African American	5 (12)
Asian	1 (2)
LAPC Stage (N, %)	
1	4 (10)
1-2	1 (2)
2	8 (19)
2-3	1 (2)
3	24 (57)
Undetermined	4 (10)
Location (N, %)	
Head/neck	21 (50)
Body	18 (43)
Tail	3 (7)

Surgical Outcomes

Outcomes after first scan	N = 38* (%)	Historical N=461
Metastatic	4 (11%)	72%
Locally Advanced	9 (27%)	
Surgical Candidate	25 (66%)**	28%

*One drop out prior to first scan due to thrombocytopenia, two patients on trial who has not yet reached first restaging scan

**One patient declined surgical intervention (would have required a total pancreatectomy)

Surgical outcomes	N = 18	Historical
Metastatic intraop	6 (25)	28%
Locally advanced intraop	3 (12)	
Resected	15 (60)	72%

Pathologic Response	N = 15	Historical
Grade 0 (complete response)	0 (0)	6%
Grade 1 (marked response)	7 (47)	32%
Grade 2 (cancer outgrown by fibrosis)	7 (47)	39%
Grade 3 (poor/no response)	1 (7)	16%

The overall resectability was 40% (15 of 38), which is higher than our historical control (20%, 84 of 461). ($p<0.01$).

Toxicity

- Immune-related adverse events requiring systemic steroids, all reversed:
  - Pneumonitis (1 case)
  - Arthritis (2 cases)
  - Dermatitis (1 case c/b steroid induced hyperglycemia)
  - Hepatitis (1 case; likely concurrent with disease progression)
  - Colitis (1 case after 2 doses pembro)

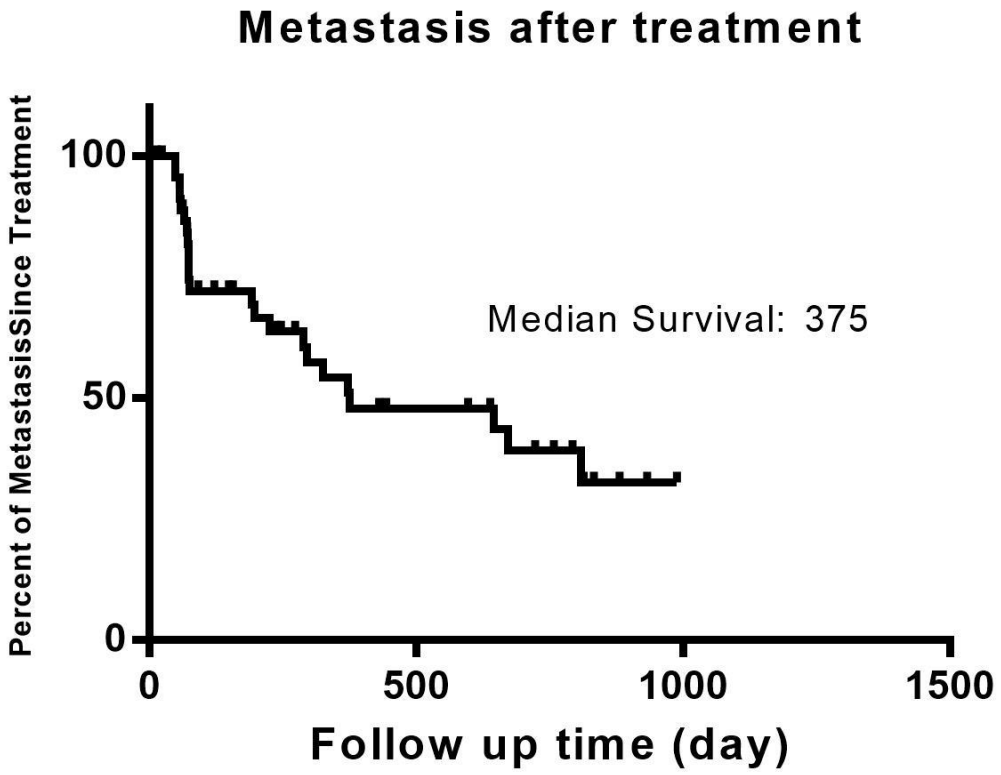
Time to Develop Metastasis

Time on trial

- Median 5.4 months (Range 0-20 months)

Medium metastasis free survival: >12 months

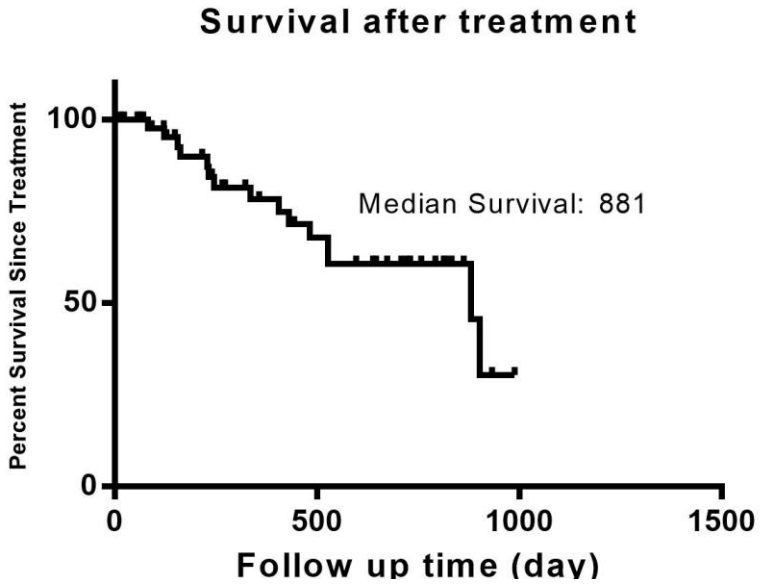
Historically, 7.7 months

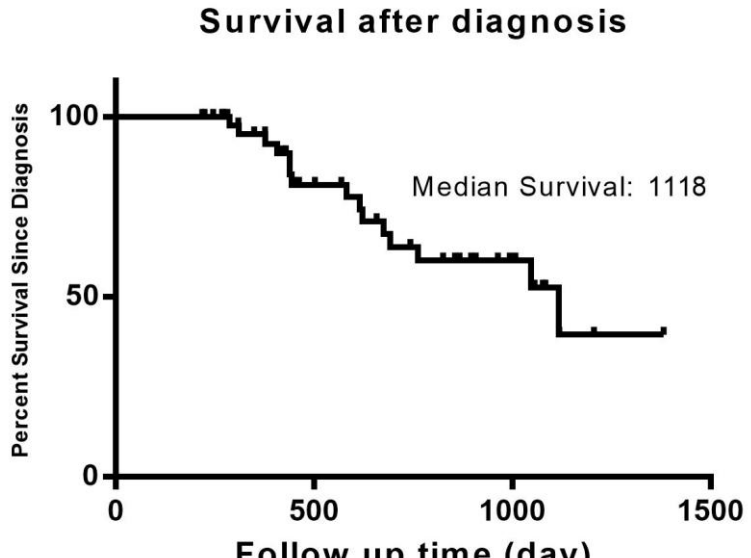


Overall Survival of All Patients

Medium Overall Survival: 29.4 months from the time of completion of pre-radiation chemotherapy and 37.2 months from diagnosis

Historically, 20 months from the time of diagnosis





Conclusions

- There is more hope for the future as we now have a better understanding of the biology, genetics and immunology of pancreatic cancer
- There remains a rationale for testing checkpoint blockade therapy in PDAC. However this strategy will likely need to include agents that will first trigger the trafficking of T cells into the otherwise T-cell-poor tumor so that T cells are available for activation by Immune checkpoint inhibitors.
- Other agents need to be further tested in combination that would effectively reprogram the otherwise immunosuppressive PDAC TME in order to optimize T cell function by turning off inhibitory signals
- There is much excitement in the field as new studies open to address contemporary questions