Advances in the Immunotherapy management of Pancreas Cancer
2019 Atlanta Pancreas Cancer Conference
October 5, 2019

Dan Laheru, M.D.
Professor of Oncology
Ian T. MacMillan Professorship in Clinical Pancreatic Cancer Research
Co-Director, Gastrointestinal Cancer Program
Co-Director, Skip Viragh Center for Pancreatic Cancer Research and Clinical Care
Co-Director, Translational Research Communities, Institute for Clinical Translational Research
Member, Miller-Coulson Academy of Clinical Excellence
Member, Bloomberg-Kimmel Institute for Cancer Immunotherapy
Sidney Kimmel Comprehensive Cancer Center
The Johns Hopkins University School of Medicine
Baltimore, Maryland USA
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

• Elizabeth Jaffee
• Dung Le
• Lei Zheng
• Mark Yarchoan
• Valerie Lee
• Bob Anders
• Luis Diaz (MSK)
  • Nilo Azad
  • John Cameron
  • Chris Wolfgang
  • Matt Weiss
  • Joe Herman (MDA)
  • Ralph Hruban
  • Elliot Fishman
  • Beth Onners
  • Elizabeth Sugar

• Skip Viragh Center for Pancreatic Cancer Research and Clinical Care
• Duncan and Nancy MacMillan
• Jim and Fran McGlothlin Foundation
• Bloomberg-Kimmel Institute for Immunotherapy
• Aduro BioTech, Inc.
• BMS Oncology
• Merck
• NIH/R21 (CA1266058)
• NIH/GI SPORE (2P50 CA062924)
• SU2C /Lustgarten Foundation pancreas cancer immunotherapy dream team
• Swim across America
Immunotherapy approvals in solid tumors

![Bar chart showing the number of approved immunotherapy drugs in solid tumors from 2010 to 2019. The number of approvals increased significantly in 2017 and 2018.](chart.png)
T Cell Therapy: From Development to Approval

1987: Discovery of CTLA-4 (Brentjens et al., Nature 1987)
1992: Discovery of PD-1 (Ishida et al., EMBO 1992)
1996: Blockade of PD-1/PD-L1 leads to anti-tumor response in mice (Cowl et al., PNAS 2002)
2000: 1st FDA approval for CAR-T for pediatric B cell ALL
2003: 1st FDA approval for CAR-T for refractory lymphoma
2011: Discovery of Iplilimumab for unresectable and stage IV melanoma
2012: 1st human trial and response with anti-CTLA-4 (melanoma) (Hodi et al., PNAS 2003)
2014: 1st human trial and response with anti-PD-1
2015: FDA approval Nivolumab and Pembrolizumab (anti-PD-1) for unresectable and stage IV melanoma (2nd line)
2017: CAR-T FDA Approval for adult relapsed or refractory lymphoma

Preclinical Development
Clinical Development
FDA Approval

Courtesy: Dr. Neeha Zaidi
Assistant Prof JHU
“Cold” versus “Hot” tumors

Pancreatic cancer

Melanoma

VS

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

![Graph showing response rates for ‘cold’ and ‘hot’ tumors across different GI malignancies.]

- Colon (MMR-p): 7
- Pancreatic: 17
- Esophageal/Gastric (PD-L1+): 20
- HCC: 44
- Melanoma: 40 (MMR-d)
- Colon (MMR-d): 78 (MMR-d)

Note: The graph illustrates the difference in response rates between ‘cold’ and ‘hot’ tumors across various GI malignancies.
Mutational load can be quantified to better predict who will respond to current immunotherapies.
The inflammatory response in pancreatic cancer is a progressive, dynamic process, interrelated with cancer genetics and leads to immune quiescence: “cold tumor.”
Pembrolizumab for microsatellite instability high or mismatch repair deficient cancers

1<sup>st</sup> tissue agnostic approval
Luis Diaz
head of solid tumor Oncology MSK

Dung Le
Associate Professor of Oncology, JHH
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

<table>
<thead>
<tr>
<th>Colorectal Cancers</th>
<th>Non-Colorectal Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort A</strong></td>
<td><strong>Cohort B</strong></td>
</tr>
<tr>
<td>Deficient in</td>
<td>Proficient in</td>
</tr>
<tr>
<td>Mismatch Repair</td>
<td>Mismatch Repair</td>
</tr>
<tr>
<td>(n=28)</td>
<td>(n=25)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cohort C</strong></td>
<td></td>
</tr>
<tr>
<td>Deficient in</td>
<td></td>
</tr>
<tr>
<td>Mismatch Repair</td>
<td></td>
</tr>
<tr>
<td>(n=30)</td>
<td></td>
</tr>
</tbody>
</table>

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

Clinical benefit of pembrolizumab treatment according to mismatch repair status

Target Lesion Measurements

Durability of Disease Control

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

Pancreatic cancer

Melanoma

Courtesy of Liz Jaffee
Durvalumab ± Tremelimumab for Patients with Metastatic Pancreatic ca

95 Patients assessed for eligibility

30 Excluded
28 Did not meet eligibility criteria
1 Refused to participate
1 Died

65 Randomized

32 Randomized to durvalumab + tremelimumab therapy
32 Received study treatment

32 Excluded
28 Died
2 Discontinued study treatment owing to closure of part A
2 Chose to discontinue study treatment

32 Included in efficacy analysis
32 Included in safety analysis

33 Randomized to durvalumab monotherapy
32 Received study treatment
1 Did not receive study treatment owing to worsening disease

33 Excluded
31 Died
1 Discontinued study treatment owing to closure of part A
1 Chose to discontinue study treatment

33 Included in efficacy analysis
32 Included in safety analysis

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

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

OR= 3.1% (1/32) in the doublet versus 0% (0/33) in the durvalumab alone arm
Naturally Non-Immunogenic Cancers Require a 2-Step Process to Reprogram the TME and Optimize Immunotherapy

**STEP 1**
- Neoantigen targeted vaccines
- Oncolytic viruses
- Epigenetic modifier to uncover neoantigens
- Radiation to release antigens
- Chemotherapy to release antigens
- Other Vaccine strategies

**STEP 2**
- Manipulate stroma
  - CD40
  - CD137
  - OX40
- Agonist activation
  - PD1/PDL1
  - CTLA4
  - TGFb
  - IDO

**Checkpoint blockade**

*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?

Pre-study Screen/randomization

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Surgery (PD)</th>
<th>2nd Vaccine</th>
<th>Adjuvant Chemoradiation and Chemotherapy</th>
<th>3rd Vaccine</th>
<th>4th Vaccine</th>
<th>5th Vaccine</th>
<th>6th Vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2</td>
<td>-1</td>
<td>0</td>
<td>4</td>
<td>8</td>
<td>12</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24</td>
<td>28</td>
<td>32</td>
<td>38</td>
<td>42</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52</td>
<td>54</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Week

**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)

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

Vaccine Can Reprogram the Tumor Microenvironment

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

OS<1.5 yr  
CD8 T Cells  
2 weeks after vaccination  

OS>3 yr
Development of post vaccination intra-tumor tertiary lymphoid aggregates is associated with survival

![Graph showing the relationship between tumor aggregates and survival time](image)

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

CD8 T cell activation in lymphoid aggregates produce IFNγ which upregulates T cell inhibitory signals like PD-L1.
Ipilimumab + Vaccine Improves Survival In Advanced Pancreatic Cancer Patients
(PI: Dung Le)

Projected Survival Curves 12/1/2011

Survival Correlation with Enhancement in CD8+ Mesothelin-Specific T Cell Repertoire

- 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*

- Tumor antigens
- GM-CSF
- Antigen uptake & Activation
- Tumor Cell Destruction

**LADD Listeria**
*Live-attenuated *Listeria monocytogenes*

- Δ*actA*
- Δ*inlB*
- Mesothelin
Median Survival Measured from First Dose of CRS-207

7 Pts

CRS-207

4 Pts

OS: 5 ± 2 mos

GVAX + CRS-207

3 Pts

OS: 17 ± 6 mos

Legend:

CRS-207 Only
GVAX Only
GVAX + CRS-207

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

Subjects with metastatic pancreatic cancer; failed or refused chemotherapy

2:1 randomization

Arm A, n=60

Arm B, n=30

- 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 Dung
## Baseline Characteristics

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

Overall Survival – Full Analysis Set

mOS
Arm A (Cy/GVAX/Nivo): 6.0 months
Arm B (Cy/GVAX): 3.4 months

\( p = 0.0057 \) (one-sided)

HR 0.4477

Extended OS in Per Protocol Analysis
Subjects Who Received at 3 Doses (One Dose of CRS-207)

mOS
Arm A (Cy/GVAX/Nivo): 9.7 months
Arm B (Cy/GVAX): 4.6 months

p = 0.0167 (one-sided)
HR 0.5290

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).
<table>
<thead>
<tr>
<th>Event-no. (%)</th>
<th>Event</th>
<th>N=51</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td></td>
<td>16 (31)</td>
<td></td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Rash</td>
<td>5 (10)</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Arthralgias</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea/colitis</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Amylase/lipase</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transaminitis</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Endocrine Disorders</td>
<td>Hyper/hypothyroidism</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pneumonitis</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Myocarditis</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Acute kidney injury</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Thrombocytopenia</td>
<td>1 (2)</td>
<td></td>
</tr>
</tbody>
</table>
GVAX + CRS-207 Prime Boost Vaccination with Programmed Death-1 (PD-1) Blockade
GVAX + CRS-207 Prime Boost Vaccination with Programmed Death-1 (PD-1) Blockade

Baseline

Week 30
Phase 2b randomized, multicenter study of GVAX pancreas and CRS-207 compared to chemotherapy in patients with previously treated metastatic pancreatic adenocarcinoma (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

Arm A, Cy/GVAX + CRS207
Arm B, CRS-207 alone
Arm C (physician choice among 5 single chemo)

* Additional courses if clinically stable

Le D et al: CCR May 24, 2019
# Patient demographics (primary cohort)

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

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

Le D et al: CCR May 24, 2019
Kaplan Meier median OS

Le D et al: CCR May 24, 2019
Nivolumab plus Ipilimumab and CRS-207 with or without GVAX Pancreas Vaccine (with Cyclophosphamide) in Patients with Pancreatic Adenocarcinoma:

**Metastatic Cohort**
Subjects with previously treated metastatic pancreatic cancer

Randomize 1:1
N=63

- Nivolumab 240mg - **Day 1**, Cycles 1,2,3,4,5 and 6
- Ipilimumab-1mg/kg – **Day 1**, Cycles 1,3,5
- Cyclophosphamide – **Day 1**, Cycles 1 and 2
- GVAX – **Day 2** Cycles 1 and 2
- CRS-207 – **Day 1**, Cycles 3,4,5 and 6

- Nivolumab-240mg - **Day 1**, Cycles 1,2,3,4,5 and 6
- Ipilimumab-1mg/kg – **Day 1**, Cycles 1,3,5
- CRS-207 – **Day 2**, Cycles 1,2,3,4,5 and 6

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

50 Patients with resectable PDA

1:1:2 randomization

After combining Arm A and Arm B the current trial has enrolled 25 patients.

Arm A (Vaccine alone)

Arm B (Cy/GVAX+anti-PD-1)

Arm C (Cy/GVAX+anti-PD-1+anti-CD137)

4 doses, q4w

https://clinicaltrials.gov/ct2/show/NCT02451982
GVAX Vaccine/anti-PD-1 Antibody (Pembrolizumab) with Stereotactic Body Radiation following induction chemotherapy for locally Advanced PDAC

Enrollment (54 pts)

Core Biopsy

SBRT

unresectable

Resectable > Surgery

CT, PET

CT, PET

Resected tumors

CT

CT

CT

CT

until metastasis

Core Biopsy

Pembrolizumab

CY/GVAX

Chemotherapy

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

Resected tumors

Primary endpoint: metastasis free survival

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

Val Lee
Instructor of Oncology, JHH
# Demographics

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

<table>
<thead>
<tr>
<th>Outcomes after first scan</th>
<th>N = 38* (%)</th>
<th>Historical N=461</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic</td>
<td>4 (11%)</td>
<td></td>
</tr>
<tr>
<td>Locally Advanced</td>
<td>9 (27%)</td>
<td>72%</td>
</tr>
<tr>
<td>Surgical Candidate</td>
<td>25 (66%)**</td>
<td>28%</td>
</tr>
</tbody>
</table>

*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)

<table>
<thead>
<tr>
<th>Surgical outcomes</th>
<th>N = 18</th>
<th>Historical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic intraop</td>
<td>6 (25)</td>
<td>28%</td>
</tr>
<tr>
<td>Locally advanced intraop</td>
<td>3 (12)</td>
<td>28%</td>
</tr>
<tr>
<td>Resected</td>
<td>15 (60)</td>
<td>72%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pathologic Response</th>
<th>N = 15</th>
<th>Historical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0 (complete response)</td>
<td>0 (0)</td>
<td>6%</td>
</tr>
<tr>
<td>Grade 1 (marked response)</td>
<td>7 (47)</td>
<td>32%</td>
</tr>
<tr>
<td>Grade 2 (cancer outgrown by fibrosis)</td>
<td>7 (47)</td>
<td>39%</td>
</tr>
<tr>
<td>Grade 3 (poor/no response)</td>
<td>1 (7)</td>
<td>16%</td>
</tr>
</tbody>
</table>

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 on trial
- Median 5.4 months (Range 0-20 months)

Medium metastasis free survival: >12 months

Historically, 7.7 months

Time to Develop Metastasis

Median Survival: 375
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.