Emerging Strategies for the Immunotherapy of Pancreatic Cancer

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Disclosure Information

Elizabeth M. Jaffee, M.D.

I have the following financial relationships to disclose

I will be discussing the investigational use of:

- GVAX
- Listeria Monocytogenes – mesothelin

Both licensed to Aduro Biotech with potential to receive royalties
Cancer Immunotherapy Comes of AGE

- FDA approved a prostate cancer vaccine (sipuleucel-T) targeting a specific cancer antigen

- FDA approved a checkpoint inhibitor ipilimumab targeting the T cell inhibitory signal CTLA-4

- PD-1/PD-L1 pathway blockade agents are showing efficacy in solid tumors

- FDA approved the first PD-1 blocking antibody pembrolizumab for ipilimumab resistant melanoma
What have we learned from these successes?

- Immune checkpoint agents act on T cells
- Only a minority of tumors have natural T cells
  - 50% of melanomas
  - 20-30% RCCS
  - 10-20% lung and colorectal tumors
- For most cancers immune modulation alone is not enough – a T cell generating agent is also needed
- More studies are needed to better understand all of the inflammatory signals involved in regulating immune responses within each tumor’s microenvironment
Single agent vaccines/immune checkpoints not enough even for “immunologic” cancers! We still have lots of room for improvement!

Provenge: Compared with placebo in metastatic patients

Yervoy: Yervoy vs. GP100 vaccine vs. Yervoy + GP100 vaccine

Autologous PBL exposed to cytokines and antigen

Ipilimumab=anti-CTLA-4
GP100=antigenic peptide vaccine
50% of Melanomas have spontaneous infiltration of effector T cells

Explains why immune checkpoint inhibitors work more often in this cancer without vaccines
Combinations are needed to achieve the full potential of the immune system to recognize and kill all cancers

- Vaccines are the most efficient way to induce T cells
- Understanding all of the signals that regulate immune responses to the different cancers will determine the best combinations
Immune-Modulatory Receptors & Ligands Regulating T Cells: Emerging and in the Clinics

Biologic roles NOT redundant

Differential up-regulation by different tumor types
The inflammatory response in the TME is a progressive, dynamic process, interrelated with cancer genetics.

Telomere Shortening ➔ Kras mutation ➔ P16 Cyclin D1 ➔ TP53 DPC4 BRCA2 ➔ mesothelin
These new “immune checkpoint” agents act on T cells

For most cancers immune modulation alone is not enough – a T cell generating agent is also needed

Different cancers may have different checkpoint pathways that predominate
IT'S A BALANCE:
NOT AN ALL OR NONE SITUATION!

NEW BALANCES BETWEEN PRO-CARCINOGENIC
BY BERNSTEIN'S ANTI-CANCER AND ANTI-INFLAMMATION CANCER IMMUNE RESPONSES CANCER GROWTH

Tumor Inflammation

Antigen specific T cells
Dendritic cells
Th1 T cells
TLR ligands
Activated monocytes
Cancer specific antibodies
Chemotherapy
Radiation
Methylation agents
Androgen ablation
Angiogenic inhibitors

Regulatory T cells
Th17 T cells
Regulatory Dendritic Cells
Regulatory Monocytes
Regulatory Mast Cells
Regulatory Granulocytes
Inhibitory Cytokines/Chemokines
Vascular Factors (VEGF)
Stromal Factors
Tumor Factors (STATS, TFG-beta)

Vaccines
Immune Modulating Agents
What makes immunologically quiescent tumors different from immunologically active cancers like melanoma that respond to immunotherapy?
The Prototype of Immunologically Quiescent Tumors

Pancreatic Cancer

National Cancer Institute: SEER Survival Monograph
Effector T cell infiltration NOT usually a natural response to cancers like pancreatic cancer.
But even in cancers like pancreatic cancer the immune system can be provoked!
A dendritic cell recruiting vaccine provokes T cells: 2 genetically modified allogeneic tumor cell lines expressing GM-CSF

(Neo)adjuvant Pancreatic Cancer Vaccine Study Provides New Evidence for ANTITUMOR Immunity
Cancer Immunology Research, 2014

**Cyclophosphamide to deplete Tregs**

<table>
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<th>Pre-study Screen/randomization</th>
<th>1st Vaccine</th>
<th>Surgery (PD)</th>
<th>2nd Vaccine</th>
<th>Adjuvant Chemoradiation and Chemotherapy</th>
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**Arm A:** Vaccine alone  
**Arm B:** Vaccine + low dose IV Cy  
**Arm C:** Vaccine + metronomic Cy
Lymphoid Aggregates found in 2 location patterns in vaccinated patients 2 weeks after a single vaccine

Intratumoral

Peri-tumoral
Lymphoid aggregates in PDAs are composed of organized T and B cell zones and a Germinal Centre-like structure.
Lymphoid aggregates are composed of myeloid-derived antigen-presenting cells

**CD20**

**CD3**

**CD56**

**CD1a**

**CD68**

**CD163**

**CD83**

**DC-LAMP**
Development of lymphoid aggregates involves lymphoid neogenesis

Lymphatic vessel marker

Chemokine involved in lymphoid Neogenesis
Lymphoid Aggregates Are Sites of Immune Activation and Regulation – Not Cytoloyisis

A
- CD3
- CD20
- CD45RO
- CD45RA

B
- CD4
- Tbet
- CXCR3
- CD69
- Foxp3
- Granzyme B
PD-1/PD-L1 pathway is upregulated in vaccine induced lymphoid aggregates

Co-localization
Foxp3+ cells are decreased and Teff/Treg ratios are increased in non-aggregate intratumoral areas of PDAs from patients with OS>3 yr vs <1.5 yr. T cells can also be found infiltrating between lymphoid aggregates.
Microdissection and microarray analysis of intratumoral lymphoid aggregates from responders vs non-responders identifies gene signatures associated with response.
Decreased Tregs - increased Th17 - decreased PDL1 correlate with improved survival
Vaccination induces increased numbers of IFNγ producing T cells infiltrating the tumor microenvironment.

CD4⁺ and CD8⁺ T cells

CD8⁺/FoxP3⁺ T cells
Vaccines can induce tumor infiltrating lymphocytes in traditionally “non-immunogenic” tumors

- Tumor infiltrating lymphocytes in turn secrete IFNg and other cytokines that upregulate the PD-1/PD-L1 and other immune modulating pathways

- But vaccine induced infiltrating T cells likely get down regulated by suppressive mechanisms within the tumor – (PD-1/PD-L1, CTLA-4 and others)

- Vaccines must be given with agents that modulate these suppressive mechanisms to activate the T cell response
Clinical study supporting the need for combining a T cell activating vaccine with T cell modulating agents in pancreatic cancer patients

Dr. Dung Le
**Phase Ib: Ipilimumab 10 mg/kg Alone or Ipi + Vaccine**
Le, et al., J Immunother 2013

**INDUCTION PHASE**
- **Weeks**
  - 1
  - 2
  - 3
  - 4

**MAINTENANCE PHASE**
- **Weeks**
  - 1*
  - 4
  - 7*
  - 10
  - 14*
  - 18
  - 22*
  - 34*
  - 46*
  - 58*

- **Vaccine** = $2.5 \times 10^8$ Panc 6.03 + $2.5 \times 10^8$ Panc 10.05 tumor cells
- **Tumor assessments (TA)**
- **Maintenance Phase Dosing And/Or TA q 12 weeks if SD or better at Week 22**
Ipilimumab + Vaccine Improves Survival In Advanced Pancreatic Cancer Patients

Projected Survival Curves 12/1/2011

- Metastatic patients having failed >2 chemotherapies
- Phase II multicenter study under development
- 7/15 patients in combo arm with clinical and/or biomarker response
- 0/15 in single Ipi arm with clinical and/or biomarker response
Radiographic Regressions After 14 Weeks Of Treatment with Ipilimumab (Ipi) + Vaccine

Baseline

Week 7 Ipi/Vaccine

Week 14 Ipi/Vaccine
CA19.9 Changes with Ipilimumab+vaccine treatment

Began steroids
For hypophysitis

Off steroids but no further treatment
No progression at 65 weeks
No progression as of 75 weeks with declining CA19.9

Remains on study with
ON THE HORIZON

• New vaccine approaches to induce better T cells
  - Listeria monocytogenes targeting tumor antigens
  - DNA, peptide, DC, Listeria platforms delivering individual patient specific mutations

• Combinations of immune checkpoint inhibitors with vaccines
  - Anti-CTLA-4 + GVAX vaccine (enrolling)
  - Anti-PD-1 + GVAX prime/Listeria Boost (Initiation Dec 9, 2014)

• Combinations of immune activating agents with methylation targeting agents or radiation
  - Both uncover antigens and inflammatory signals within the tumor micro-environment

• Engineered T Cells (CARS) that target GI cancer tumor antigens
TWO VACCINES MAY BE BETTER THAN ONE!
PRIME/BOOST STUDY – 2 synergistic mechanisms

GVAX Pancreas
Irradiated, whole-cell tumor vaccine

Tumor antigens

Dendritic Cell

Antigen uptake & Activation

T Cell Destruction

LADD Listeria
Live-attenuated *Listeria monocytogenes*

ΔactA
ΔinlB

Mesothelin
Key Features

- Complete deletion of 2 virulence genes (actA, inlB)
- Mesothelin expression cassette stably inserted into the chromosome at inlB locus
- No antibiotic resistance genes
- Antigen expression/secretion induced inside APCs
- Induction of robust innate and antigen-specific adaptive immunity
Preclinical Data Supporting GVAX as Prime and Listeria as Boost Vaccine
RESULTS: Phase 2 Trial: Multi-Center, Open-label, Randomized, Controlled
Le et al, GI ASCO 2014; Oral Abstract #177
Le et al, Journal of Clinical Oncology, in press

Subjects with metastatic pancreatic cancer; failed or refused chemotherapy

Arm A, n=60
Arm B, n=30

2:1 randomization

24 months follow-up

Primary objective: 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
Improved OS in GVAX/CRS-207 Combo

Median OS
Arm A: 6.1 months
Arm B: 3.9 months

p=0.0172 (one-sided)
HR 0.5930

Follow up study enrolling nationally

Dung Le, et al. and AduroBiotech: Abstract # Oral Abstract #177
Le, et al., Journal of Clinical Oncology, in press
Percent Change From Baseline in the CA19.9 Biomarker
Ongoing studies to address critical questions

- 3 arm study comparing prime/boost vs Listeria-mesothelin vs SOC
  - Randomized 1:1:1
  - 240 metastatic patients who failed 2\textsuperscript{nd} or 3\textsuperscript{rd} line chemotherapy
  - 23 sites in US
  - Enrolling

- Chemotherapy versus GVAX/ipilimumab in FOLFIRINOX stable patients
  - Randomized 1:1
  - 42 patients per arm
  - 3 sites in US
  - Enrolling

- Prime/boost vs prime/boost + anti-PD-1 mAb (Nivolumab)
  - Randomized 1:1
  - 88 patients who failed 1 prior chemotherapy
  - 5 sites in US
  - Begins enrolling January 2015
FINAL POINT: Improving Survival with Combination Therapy

% Survival

Time

Control

Standard Chemotherapy

Checkpoint Blockade

Combination

Combinations needed for the big therapeutic leap!
Acknowledgements

Lei Zheng
Eric Lutz
Dung Le
Dan Laheru

Sara Solt
Guanglan Mo

Immunopathology Lab
Bob Anders
Rajni Sharma

Clinical Research Team
Barish Edil
Chris Wolfgang
Ralph Hruban

Trang Nguyen
Rich Schulick
Carol Judkins
Raka Bhattacharya
Tianna Dauses
Joe Herman
John Cameron

NCI GI Spore
Viraggh Pancreatic Cancer Center
Aduro Biotech
Increased Th17A expression in lymphoid aggregates confirmed by FACS and IHC