Yale Engage Cancer: Immuno-Oncology

Wednesday, October 21, 2020
11:00a.m – 12:30p.m
Scientist, scholars, and physicians . . .

- Engaged in research
- Engaged in policy
- Engaged in innovation
- Engaged in the clinic
Welcome

- **Charles Fuchs, M.D, MPH**, Richard Sackler and Jonathan Sackler Professor of Medicine (Medical Oncology) and Professor of Chronic Disease Epidemiology; Director, Yale Cancer Center and Physician-in-Chief, Smilow Cancer Hospital
- **Mario Sznol, M.D**, Professor of Medicine (Medical Oncology), Yale School of Medicine; Co-Leader, Cancer Immunology, Yale Cancer Center; Leader, Yale Melanoma Program

Presentations

- **Marcus Bosenberg, M.D, Ph.D.**, Professor of Dermatology, Pathology, and Immunobiology, Yale School of Medicine; Interim Director, Yale Center for Immuno-Oncology; Director, Center for Precision Cancer Modeling; Director, Yale SPORE in Skin Cancer; Co-Leader, Genetics, Genomics and Epigenetics, Yale Cancer Center
- **Roy Herbst, M.D, Ph.D.**, Ensign Professor of Medicine (Medical Oncology) and Professor of Pharmacology; Chief of Medical Oncology, Yale Cancer Center and Smilow Cancer Hospital; Associate Cancer Center Director for Translational Research, Yale Cancer Center
- **Aaron Ring, M.D, Ph.D.**, Assistant Professor of Immunobiology, Yale School of Medicine
- **Grace Chen, Ph.D.**, Assistant Professor of Immunobiology, Yale School of Medicine
- **Akiko Iwasaki, Ph.D.**, Waldemar Von Zedtwitz Professor of Immunobiology and Molecular, Cellular and Developmental Biology; Howard Hughes Medical Institute, Yale School of Medicine
- **Ira Mellman, Ph.D.**, Vice President, Cancer Immunology, Genentech; Professor of Biochemistry & Biophysics, UCSF

Discussion & Questions
Marcus Bosenberg, M.D, Ph.D.
Professor of Dermatology, Pathology, and Immunobiology, Yale School of Medicine;
Interim Director, Yale Center for Immuno-Oncology;
Director, Center for Precision Cancer Modeling;
Director, Yale SPORE in Skin Cancer;
Co-Leader, Genetics, Genomics and Epigenetics, Yale Cancer Center
• YCIO coordinates immuno-oncology efforts at Yale

• Leverages leading expertise in immunology and cancer

• Removes barriers and enables IO research at Yale
• State-of-the-art preclinical testing facility
• Focus on testing of IO agents
• Makes use of proprietary models created at Yale
• Development of Patient Derived Explant (PDE) models for evaluation of human IO agents
• SRAs with pharma companies
Roy Herbst, M.D, Ph.D.
Ensign Professor of Medicine (Medical Oncology) and Professor of Pharmacology; Chief of Medical Oncology, Yale Cancer Center and Smilow Cancer Hospital; Associate Cancer Center Director for Translational Research, Yale Cancer Center
YCC Disease Aligned Research Teams (DART)

DARTs promote translational research through scientific discovery, testing new discoveries in our clinics and, ultimately, turning new innovations into viable disease-specific therapeutics.

**Goals of the DARTs:**

1. To improve integration of our clinical and research programs
2. To increase the number of IITs that have a Yale translational research component
3. To build clinical/basic science teams to move toward team science and funding

**IMPACT**
- Improve clinical care
- Drive the field
  - Top Tier publications

**YCC DARTs**

- CI
- CPC
- DT
- GGE
- RR
- CSN
- CM

**SPORIES**

**Industry Alliance**
Transdisciplinary Collaboration & Coordination

SPORE Teams:

- **Skin**
  - Marcus Bosenberg, GGE
  - Harriet Kluger, DT

- **Lung Cancer**
  - Roy Herbst, DT
  - Lieping Chen, CI

- **Head and Neck**
  - Barbara Burtness, DT

- **Brain**
  - Murat Gunel, GGE
  - Antonio Omuro, DT

Renewed August 2019
Renewed August 2020
Funded September 2020
Submitted May 2020
Biomarker Analyses for PD-L1 Treatment

Mechanistic studies using pre and post biopsies

Adaptive Immune Response

- Three distinct patterns of nonresponse were observed
- Most patients who progressed failed to show up-regulation of PD-L1 or evidence of activated T cells
- These results provide evidence for the “inflamed tumor” hypothesis

IMpower110 Study Design

Chemotherapy-naive, PD-L1–selected patients with stage IV nsq or sq NSCLC

Stratification factors
• Sex
• ECOG PS
• PD-L1 IHC expression
• Histology

N = 572

**Arm A**
Atezolizumab 1200 mg q3w

**Arm B**
Nsq: cisplatin/carboplatin + pemetrexed
Ssq: cisplatin/carboplatin + gemcitabine
4 or 6 cycles

**Maintenance therapy (no crossover permitted)**

**PD or loss of clinical benefit**

**Survival follow-up**

**IMpower110: OS in PD-L1 High SP142 vs Dako 22C3**

**SP142 (TC3 or IC3-WT)**

<table>
<thead>
<tr>
<th></th>
<th>Atezo (n=107)</th>
<th>Chemo (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS</td>
<td>20.2</td>
<td>13.1</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.59 (0.40,0.89)</td>
<td></td>
</tr>
</tbody>
</table>

**22C3 BEP-WT (TPS ≥ 50%)**

<table>
<thead>
<tr>
<th></th>
<th>Atezo (n=134)</th>
<th>Chemo (n=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS</td>
<td>20.2</td>
<td>11.0</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.60 (0.41,0.86)</td>
<td></td>
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</tbody>
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**B**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients/ Total No. (%)</th>
<th>Median Progression-free Survival (mo)</th>
<th>Hazard Ratio for Disease Progression or Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any PD-L1 expression Could be evaluated for blood-based TMB</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>165/554 (29.8)</td>
<td>9.3</td>
<td>0.53 (0.36–0.79)</td>
</tr>
<tr>
<td>Yes</td>
<td>389/554 (70.2)</td>
<td>5.5</td>
<td>0.88 (0.70–1.11)</td>
</tr>
<tr>
<td>Blood-based TMB</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≥10</td>
<td>175/389 (45.0)</td>
<td>5.5</td>
<td>0.74 (0.53–1.05)</td>
</tr>
<tr>
<td>≥16</td>
<td>87/389 (22.4)</td>
<td>6.8</td>
<td>0.55 (0.33–0.92)</td>
</tr>
<tr>
<td>≥20</td>
<td>56/389 (14.4)</td>
<td>6.8</td>
<td>0.56 (0.30–1.06)</td>
</tr>
<tr>
<td>&lt;10</td>
<td>214/389 (55.0)</td>
<td>5.5</td>
<td>1.03 (0.76–1.39)</td>
</tr>
<tr>
<td>&lt;16</td>
<td>302/389 (77.6)</td>
<td>4.5</td>
<td>1.00 (0.78–1.29)</td>
</tr>
<tr>
<td>&lt;20</td>
<td>333/389 (85.6)</td>
<td>4.9</td>
<td>0.95 (0.74–1.21)</td>
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</table>
Roy Herbst, M.D., Ph.D.
Associate Cancer Center Director for Translational Research

Ed Kaftan, Ph.D.
Associate Director for Translational Research Administration

Meina Wang, Ph.D.
Senior Research Project Manager

Yang Zhou, Ph.D.
Program Manager

Philip Grover
Executive Administrative Coordinator

Lisa DeChello
Sr. Admin Assistant

Office of Translational Research Established 2011
Aaron Ring, M.D, Ph.D.
Assistant Professor of Immunobiology, Yale School of Medicine
Cytokines: The first immune-targeting drugs that could cure

High-Dose Recombinant Interleukin 2 Therapy for Patients With Metastatic Melanoma: Analysis of 270 Patients Treated Between 1985 and 1993

By Michael B. Atkins, Michael T. Lotze, Janice P. Dutcher, Richard I. Fisher, Geoffrey Weiss, Kim Margolin, Jeff Abrams, Mario Szol, David Parkinson, Michael Hawkins, Carolyn Paradise, Lori Kunkel, and Steven A. Rosenberg

Atkins et al., Cancer J Sci Am., 2000
Interleukin-18: Powerful in a test tube, but a dud in the clinic

A Phase 2, Randomized Study of SB-485232, rhIL-18, in Patients With Previously Untreated Metastatic Melanoma

Ahmad A. Tarhini, MD1, Michael Millward, MD2, Paul Mainwaring, MD3, Richard Kefford, MD4, Ted Logan, MD5, Anna Pavlick, MD6, Steven J. Kathman, MD7, Kevin H. Laubscher, MD8, Mohammed M. Dar, MD9, and John M. Kirkwood, MD1

“Among 63 subjects evaluable for response, [only] 1 achieved a partial response... Due to the low apparent level of clinical efficacy, the study was terminated at the end of stage 1.”

Tarhini et al., Cancer, 2009
Decoy-Resistant IL-18 (DR-18): Overcoming the IL-18 binding protein checkpoint in the tumor microenvironment

**WT IL-18**
- IL-18BP
- TIL
- Activated TIL

**DR-18**
- IL-18Rα

**Graph**
- Days post engraftment
- Survival (%)
- Tumor volume 50-100mm³
- MC38 Tumor cells 0.5x10⁶
- Tumor volume 0.32mg/kg IL-18/DR-18 (s.c.)
- Day 0, 7, 10, 14, 17, 21
- Saline (0/25)
- αPD1 (7/17)
- IL-18 (0/10)
- DR-18 (27/39)
- IL-18+αPD1 (4/10)
- DR-18+αPD1 (9/10)

**Article**
*IL-18BP is a secreted immune checkpoint and barrier to IL-18 immunotherapy*

Zhou et al., Nature 2020
Translating DR-18 into the clinic: Phase I trial of lead DR-18 variant ST-067 to begin in June 2021
Discovering natural cancer therapies within patients:
New technology detects endogenous therapeutic autoantibodies

The immune system is a rich source of natural biologic drug products, antibodies:

- Protective Disease-Modifying Abs
- Harmful Disease-Modifying Abs

➢ “Clinical trials of nature” can teach us about autoantibody responses that harm vs **protect** patients

Rapid Exoproteome Antigen Profiling (REAP): Ultra-high throughput discovery of autoantibody targets
Grace Chen, Ph.D.
Assistant Professor of Immunobiology, Yale School of Medicine
• What are the molecular mechanisms for maintaining the balance between the accurate recognition of self/non-self and preventing disease?

• How can we capitalize on this distinction to develop novel cancer therapeutics?
RNA Modifications Immunity


Akiko Iwasaki, Ph.D.
Waldemar Von Zedtwitz Professor of Immunobiology and Molecular, Cellular and Developmental Biology; Howard Hughes Medical Institute, Yale School of Medicine
**Immune Surveillance**

1. Antigen drains into draining lymph node via APCs or via flow and primes T cells

**T cell Trafficking/microenvironment**

2. T cells traffic into site of immune response. Passive (EPR) or active trafficking Chemokine gradient

**Effector function/BBB**

3. Cytotoxic killing/effector functions inside tumor/or other site.

**Checkpoint inhibitors**
Leveraging immune priming and effector mechanisms to improve immune checkpoint blockade therapies

**Immune Surveillance**
1. Antigen drains into draining lymph node via APCs or via flow and primes T cells

**LymphAxis**
VEGF-C to increase immune priming for GBM.

**ERVMap**
Endogenous retroviruses as tumor antigens

**CynAxis**
BBB opening to increase antibody (ICB) access to the GBM.

**T cell Trafficking/microenvironment**
2. T cells traffic into site of immune response. Passive (EPR) or active trafficking Chemokine gradient

**RIGImmune**
SLR to increase immune priming and possibly T cell recruitment

**Effector function/BBB**
3. Cytotoxic killing/effector functions inside tumor/or other site.

**Checkpoint inhibitors**

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1. Antigen drains into draining lymph node via APCs or via flow and primes T cells
Ira Mellman, Ph.D.
Vice President, Cancer Immunology, Genentech;
Professor of Biochemistry & Biophysics, UCSF
The immune response to cancer is a series of potential rate limiting steps: **The Cancer Immunity Cycle**

1. Release of cancer cell antigens (Cancer cell death)
2. Cancer antigen presentation (Dendritic cells/APCs)
3. Priming and activation (APCs and T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells, through the stroma, and into tumors (CTLs, endothelial cells, stromal cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (CTLs, cancer cells and immune cells)
Discussion
ATTEND

Novel Cancer Therapeutics & Delivery Systems
**Date:** Thursday, November 5th, 2020  
**Time:** 11:00 a.m – 12:30 p.m EST

Defining Mechanisms and Biomarkers of Sensitivity & Resistance to Anti-Cancer Treatments
**Date:** Wednesday, December 9th, 2020  
**Time:** 1:00 p.m-2:30 p.m EST

CONNECT

Please direct general questions, opportunities, and, information to:

Kathy Lynch  
University Director,  
Corporate Strategy & Engagement  
Kathleen.lynch@yale.edu

Or:

YaleNewHavenHealth  
Smilow Cancer Hospital

https://www.yalecancercenter.org/

https://ocr.yale.edu/
Thank you for participating!