New York City September 23, 2017
Brian Brewer
Cancer Research Institute

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GI Cancers Alliance  
Imerman Angels  
Immunotherapy Foundation  
Let Life Happen  
Melanoma Research Foundation  
National Ovarian Cancer Coalition  
NYU Langone Health  
Patient Empowerment Network
Our Guest Faculty

Scientific Experts

Leena Gandhi, M.D., Ph.D.
NYU Perlmutter Cancer Center

Michael Postow, M.D.
Memorial Sloan Kettering Cancer Center

Robert Vonderheide, M.D., D.Phil.
UPenn Abramson Cancer Center

Dmitriy Zamarin, M.D., Ph.D.
Memorial Sloan Kettering Cancer Center

Patient Experts

Janie Ferling
Melanoma

Kristin Kleinhofer
Leukemia

Philip Prichard
Kidney Cancer

Johanna Sedman
Prostate Cancer (caregiver)
## Schedule of Events

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:00am</td>
<td>Registration and networking</td>
</tr>
<tr>
<td>10:00am</td>
<td>Program commences</td>
</tr>
<tr>
<td>10:15am</td>
<td><strong>Welcome</strong>&lt;br&gt;By: Brian Brewer</td>
</tr>
<tr>
<td></td>
<td><strong>Introduction to the Cancer Research Institute</strong>&lt;br&gt;By: Jill O'Donnell-Tormey, Ph.D.</td>
</tr>
<tr>
<td>10:15am</td>
<td><strong>Hear from the experts</strong>&lt;br&gt;Learn the basics of immunotherapy&lt;br&gt;Leena Gandhi, M.D., Ph.D.</td>
</tr>
<tr>
<td></td>
<td>Latest research update panel&lt;br&gt;Moderator&lt;br&gt;Leena Gandhi, M.D., Ph.D.</td>
</tr>
<tr>
<td></td>
<td>Panelists&lt;br&gt;Michael Postow, M.D.&lt;br&gt;Robert Vonderheide, M.D., D.Phil.&lt;br&gt;Dmitriy Zamarin, M.D., Ph.D.</td>
</tr>
<tr>
<td>11:30am</td>
<td><strong>Patient perspective</strong>&lt;br&gt;Hear from a melanoma survivor&lt;br&gt;Janie Ferling</td>
</tr>
<tr>
<td>12:00pm</td>
<td>Lunch and networking</td>
</tr>
<tr>
<td>1:00pm</td>
<td><strong>Demystifying clinical trials</strong>&lt;br&gt;Learn about clinical trials and panel discussion&lt;br&gt;Moderator: Brian Brewer</td>
</tr>
<tr>
<td></td>
<td>Panelists&lt;br&gt;Kristin Kleinhofer&lt;br&gt;Philip Prichard&lt;br&gt;Johanna Sedman</td>
</tr>
<tr>
<td>2:00pm</td>
<td>Refreshment break</td>
</tr>
<tr>
<td>2:15pm</td>
<td><strong>Breakout sessions</strong>&lt;br&gt;Your choice of moderated discussion with our experts or a general networking session&lt;br&gt;Breast / Pancreatic Cancer&lt;br&gt;By: Robert Vonderheide, M.D., D.Phil.&lt;br&gt;Melanoma&lt;br&gt;By: Michael Postow, M.D.&lt;br&gt;Gynecologic Cancers&lt;br&gt;By: Dmitriy Zamarin, M.D., Ph.D.&lt;br&gt;General Immunotherapy &amp; Networking&lt;br&gt;By: Leena Gandhi, M.D., Ph.D.</td>
</tr>
<tr>
<td>3:15pm</td>
<td>Program closes</td>
</tr>
<tr>
<td>9:00am - 4:00pm</td>
<td><strong>Clinical trial navigator appointments</strong>&lt;br&gt;Appointments will be available all day. If you didn’t pre-register, check with the registration desk.</td>
</tr>
</tbody>
</table>
Jill O’Donnell-Tormey, Ph.D.
Cancer Research Institute

Introducing CRI
IMMUNOTHERAPY BASICS

Leena Gandhi M.D. Ph.D.
Director of Thoracic Medical Oncology
Associate Professor of Medicine, NYU Perlmutter Cancer Center
Immune Recognition of Cancer

T cell

Cancer cell

Cytolytic T Lymphocyte (CTL)

TCR

CD8

Class I MHC (HLA A, B) + peptide

Processing

Tumor Cell
Two general strategies to promote the immune system to destroy cancer

• Boost the offense ("Active immunotherapy")
  – Increase the number and function of T cells capable of recognizing and attacking tumor cells
  – Stimulate T cell activation
  – Cytokines (IL-12), vaccines

• Block the defense ("Passive immunotherapy")
  – Interfere with inhibitory pathways in the tumor site that resist T cell attack
  – Block T cell inhibition
  – PD-1 inhibitors, CTLA4 inhibitors
Immunotherapy and the Tail of the Curve: IL-12

![Survival Curve Figure]

Fig 2.—Survival of patients with metastatic melanoma and renal cell cancer treated with high-dose bolus interleukin 2, as assessed in June 1993.

Vaccines have been disappointing in cancer therapy

PREVENTION
• Vaccine to hepatitis B in humans to prevent liver carcinoma
• Vaccination to HPV prevents cervical cancer

TREATMENT
• Many trials, few successes
Signals that regulate T cell activation

Signal 1
- Ag recognition (TCR-pMHC)
- Signal sensitivity (CD4/CD8)

Signal 2
- Tcon
  - Costimulation/coinhibition
  - Activation
  - Differentiation
- Treg
  - Development (CD28)
  - Suppressive activity (CTLA-4)

Signal 3
- Tcon
  - Maximum activation
  - Effector function
  - Exhaustion
- Treg
  - Decreased T\textsubscript{FR} activity
  - pTreg induction

Impact on Teff vs. Treg
- Anti-CTLA-4
- Anti-PD-1
- Anti-PD-L1

Impact on intratumoral depletion
- Derepression

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Cancer Immunology Research: Perspective from a Master of Immunology

TARGETED THERAPIES HIT THE ONCOGENIC “DRIVERS”

- EGFR inhibitor
- ALK/ROS inhibitor
- BRAF inhibitor
- MET inhibitor

Carboplatin + Pemetrexed

Slide courtesy of D. Barbie
PD1 or PD-L1 targeted drugs

Slide courtesy of David Barbie
In addition to having activity in multiple cancer types, PD-1 inhibitors overall have less side effects than traditional chemotherapies.
Anti-PD-1/L1 Immunotherapy in Cancer: Works for some, not all

WHO BENEFITS IN LUNG CANCER:

• Smokers
• Those with higher “mutational load” (burden of genetic changes)
• Those with high levels of PD-L1
PD-L1
IMMUNOHISTOCHEMICAL STAINING

Staining intensity: 0+ PD-L1 = 0% positive
Staining intensity: 1+ PD-L1 = 2% positive
Staining intensity: 2+ PD-L1 = 100% positive
Staining intensity: 3+ PD-L1 = 100% positive
T cell-infiltrated tumors contain MULTIPLE inhibitory pathways

- Multiple “defense” pathways are co-opted in tumors once T cells enter
- Suggests the notion that blocking two together might be superior
Nivolumab/Ipilimumab vs. nivolumab in Non-Small Cell Lung Cancer (NSCLC): PD-L1 expression

Figure 3: Objective responses across tumour PD-L1 expression levels. Combination data based on a Feb 18, 2016, database lock; monotherapy data based on a March 12, 2015, database lock. This trial was not randomised across combination and monotherapy cohorts.

Hellman M et al., Lancet Oncology Jan 2017
Nivolumab Plus Ipilimumab in First-line NSCLC: Treatment-related Adverse Effects

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total Patients With an Event, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo 3 Q2W + Ipi 1 Q12W (n = 38)</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5</td>
</tr>
<tr>
<td>Hepatic</td>
<td>37</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
</tr>
<tr>
<td>Renal</td>
<td>5</td>
</tr>
<tr>
<td>Skin</td>
<td>5</td>
</tr>
<tr>
<td>Nivo 3 Q2W + Ipi 1 Q6W (n = 39)</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>15</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>5</td>
</tr>
<tr>
<td>Hepatic</td>
<td>8</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3</td>
</tr>
<tr>
<td>Renal</td>
<td>3</td>
</tr>
<tr>
<td>Skin</td>
<td>3</td>
</tr>
<tr>
<td>Nivo 3 Q2W (n = 52)</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>14</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>2</td>
</tr>
<tr>
<td>Hepatic</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4</td>
</tr>
<tr>
<td>Renal</td>
<td>4</td>
</tr>
<tr>
<td>Skin</td>
<td>21</td>
</tr>
</tbody>
</table>

- All treatment-related pulmonary events were pneumonitis
- Grade 1–2 hypersensitivity/infusion reaction occurred in 5% and 6% of patients in the nivo 3 Q2W + Ipi 1 Q12W and monotherapy groups, respectively

Combination data based on a February 2016 database lock; monotherapy data based on a March 2015 database lock
Select AEs are those with potential immunologic etiology that require frequent monitoring/intervention

Hellman MD et al., ASCO 2016
T-Cell Response: Second Signal to Accelerate or Brake

Activating Signals
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory Signals
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

T-Cell Stimulation

T-Cell Inhibition

Other strategies to boost inflammation can include:
- Chemotherapy
- Radiation
- Surgery
- Vaccines
BOOSTING THE POTENTIAL FOR IMMUNE RESPONSE WITH COMBINATION THERAPIES

Hypothetical slide illustrating a scientific concept that is beyond data available so far. These charts are not intended to predict what may actually be observed in clinical studies.

T cell adoptive transfer

- T cells are isolated from tumor site or blood
- Expanded in laboratory
- Can be engineered to recognize new targets
- T cells are reintroduced back to the patient, usually with other agents

Yee C. 2009 ASCO Educational Book
Adoptive “CAR” T cell therapy

- Isolate patient’s peripheral blood T cells
- Lentivirus transduced with “CAR” (chimeric antigen receptor)
- CAR – anti-CD19 antibody fragment fused to intracellular domains of potent T cell signaling subunits
- Re-infuse “CAR”-modified T cells into patient
- Successful for treating children with B cell malignancies
CAR T cells win FDA approval 2017

• 1<sup>st</sup> CAR T cell therapy approved for acute lymphoblastic leukemia in children and young adults on August 31, 2017

• 1<sup>st</sup> “living drug” approval

• More to come.....
Useful resources about cancer immunotherapy

https://www.cancerresearch.org/patients/what-is-immunotherapy

https://www.pennmedicine.org/cancer/navigating-cancer-care/treatment-types/immunotherapy

https://www.mskcc.org/immunotherapy-msk

https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy.html
Panel Discussion

LATEST RESEARCH UPDATE
### Scientific Panel

**Moderator**

Leena Gandhi, M.D., Ph.D.

**Panel**

Michael Postow, M.D.
Melanoma

Robert Vonderheide, M.D., D.Phil.
Pancreatic & Breast Cancer

Dmitriy Zamarin, M.D., Ph.D.
Gynecologic Cancer
Janie Ferling
Melanoma Survivor

PATIENT PERSPECTIVE
LUNCH AND NETWORKING
Brian Brewer
Cancer Research Institute

DEMYSTIFYING CLINICAL TRIALS
What Are Clinical Trials?

- Research studies that involve people
- Designed to answer specific questions about new and existing treatments
- Aim to improve treatments and the quality of life for people with disease
Getting from Discovery to Approval

Drug Discovery
- Pre-Disclosure: 3 - 6 years
- ~5,000-10,000 Compounds

Preclinical
- Preclinical: 250

Clinical Trials
- Phase 1: 6 - 7 years
- Phase 2: 100-500 Volunteers
- Phase 3: 1,000-5,000 Volunteers
- FDA Review: 0.5 - 2 years

FDA Approval
- Scale-Up to Mfg.: Indefinite
- Post-Marketing Surveillance: Indefinite

Source: AppliedClinicalTrials.com
What Are Clinical Trial Phases?

Phase 1

Is the treatment safe?

Purpose:
- First study in humans
- Find best dose, delivery method, and schedule
- Monitor for side effects
- Determine safety

Number of people: 20-100

Phase 2

Does it work?

Purpose:
- Look for effect on specific type(s) of cancer
- Continue monitoring for side effects and safety

Number of people: 100-500

Phase 3

Does it work better?

Purpose:
- Compare new treatment (or new use of a treatment) with current standard treatment
- Determine risk vs. benefit

Number of people: 1,000-5k+

# Pros and Cons of Clinical Trials

<table>
<thead>
<tr>
<th>Potential Advantages</th>
<th>Potential Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to best possible care</td>
<td>Unknown side effects or risks</td>
</tr>
<tr>
<td>Receiving new drugs before they’re widely available</td>
<td>Unknown benefits—drugs may not work as intended</td>
</tr>
<tr>
<td>Close monitoring by medical team</td>
<td>Not all patients may benefit</td>
</tr>
<tr>
<td>Chance to play active role in healthcare and research</td>
<td>Frequent tests and clinic visits</td>
</tr>
<tr>
<td>Help future generations</td>
<td>Possible need to travel to trial sites</td>
</tr>
</tbody>
</table>

Questions to Ask Before Volunteering

- Why is this trial being done?
- Why is it believed that the treatment being studied may be better than the standard treatment?
- What are my other options (standard treatments, other trials)?
- How did patients do in any previous studies of this treatment?
- How will the doctor know if treatment is working?
- How long will the trial last?
Questions to Ask Before Volunteering

- Can I continue to receive this treatment after the trial ends?
- What kinds of procedures or tests are involved?
- What impact will the trial have on my daily life?
- Will I have to travel for treatment? Will I be compensated?
- How often will I need to travel to receive treatment?
- Will I be hospitalized as part of the trial?
- What costs (if any) will be my responsibility to pay?

Getting into a Clinical Trial Isn’t Always a Given

Trials are designed to ask specific questions, and must adhere strictly to entry criteria to ensure data is accurate and meaningful.

This also helps ensure patients who could be made worse by treatment are not exposed to the risk.

Common criteria include:

- cancer type or stage
- treatment history
- genetic factors
- age
- medical history
- current health status
I might only get placebo ("sugar pill") instead of treatment.

Fact: Placebos are rarely used and never given in the absence of some form of treatment.
Clinical Trials: Myth versus Fact

Trials are only for people who have run out of treatment options (a “last resort”).

Fact: Clinical trials are designed for people with cancer of all types and stages.

Clinical Trials: Myth versus Fact

I need to travel to a large hospital or cancer center to participate in a clinical trial.

Fact: Trials take place at local hospitals, cancer centers, and doctors’ offices in all parts of the country, in both urban and rural areas.

My health insurance doesn’t cover the cost of care in a clinical trial.

Fact: Doctor visits, hospital stays, and certain testing procedures may be covered by insurance. Research costs are typically covered by the trial sponsor.
Clinical Trials: Myth versus Fact

Signing a consent form “locks” me into staying in a trial.

Fact: You are free to change your mind for any reason about participating in a trial anytime before or during a trial.

Clinical Trials: Myth versus Fact

I will be made to feel like a “guinea pig” experiment.

Fact: The overwhelming majority of trial participants say they were treated with dignity and respect, and report having had a positive experience in a trial.

Clinical trials aren’t safe.

Fact: Safeguards including an Institutional Review Board, Data and Safety Monitoring Board, and an ongoing informed consent process ensure patients’ rights and safety are protected.

**A Word About Informed Consent**

Informed consent = having all the facts before and during a trial

- Study purpose
- Length of time of the study
- Predictable risks
- Possible benefits
- Expectations
- Patient’s rights

- Treatment alternatives
- Patient health monitoring
- Safeguards in place
- How to withdraw from study

Be bold in asking for details. It’s YOUR treatment plan.
How Can I Find a Clinical Trial?

- Ask your doctor
- Ask another doctor if necessary...
- Contact a patient advocacy organization
  - Seek assistance from a clinical trial navigator, if offered
  - CRI Clinical Trial Finder: 1 (855) 216-0127
- Search online
  - https://www.cancerresearch.org/patients/clinical-trials
  - https://clinicaltrials.gov/
Panel Discussion

IMMUNOTHERAPY CLINICAL TRIALS
Patient Panel

Moderator
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Panel
Kristin Kleinhofer
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Prostate Cancer (caregiver)
BREAKOUT SESSIONS
Breakout Rooms

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General Immunotherapy
Leena Gandhi, M.D., Ph.D.

Riverside Park
Central Park I and II
Union Square Park
Gotham Ballroom (Here)
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