

**Cancer Immune Monitoring and Analysis Centers (CIMACs) (U24)**  
**&**  
**Cancer Immunologic Data Commons (CIDC) (U24)**

Magdalena Thurin, Ph.D., CDP  
Helen Chen, M.D., CTEP

Min Song, Ph.D., Howard Streicher, M.D., Elad Sharon, M.D., M.P.H.,  
James Zwiebel, M.D., Barbara Conley, M.D., Lisa McShane, Ph.D, and  
Jeff Abrams, M.D.

# Cancer Immunotherapy Monitoring Network

## Objectives:

- To support high-quality correlative studies in NCI-sponsored early phase (Phase I and Phase II) clinical trials to improve the treatment outcome
- To use the early phase studies as a proving ground for clinically-informative biomarkers which can be validated in late phase clinical trials

## Summary of the DCTD Cancer Immunotherapy Workshop

NCI Shady Grove, January 14-15, 2016

Helen Chen, M.D. CTEP, on Behalf of DCTD

A 1.5-day meeting with thought leaders in the field to discuss ...

- Opportunities and gaps in cancer immunology/immunotherapy
- What NCI should do to facilitate further development

# Speakers and invited guests

## Extramural scientists

- James Allison, MD Anderson
- Ira Mellman, Genentech
- Karolina Palucka, Jackson Lab
- Elizabeth Jaffee, Hopkins
- Mario Sznol, Yale
- Padmanee Sharma, MD Anderson
- Mac Cheever, Fred Hutchinson

## Biomarker/informatics experts:

- Kurt Schalper, Yale
- Elaine Mardis, Wash University
- Lisa Butterfield, Pittsburg
- Anna Wu, UCLA
- Atul Butte, UCSF
- Stanley Hamilton, MD Anderson
- Diagnostic: Adaptive, NanoString, Nodality, Immudex

## Industry:

- Merck, Incyte, AstraZeneca/MedImmune

## NCI Intramural Scientists

- Steven Rosenberg, NCI
- Nickolas Restifo, NCI
- Jay Berzofsky
- Remy Bosselut
- Stephen Hewitt

## NCI Extramural Scientists, DCTD

- J Doroshow, J Abrams, T Hecht
- CTEP: H Chen, H Streicher, E Sharon, J Zwiebel, M Song
- Cancer Diagnosis Program: M Thurin
- Biologics Resource Branch: S Creekmore, A Welch
- Radiation Research Program: M Ahmed
- Biometric Research Program: R Simon

## NCI Division of Cancer Biology:

- C Marks, S McCarthy, K Howcroft, D Singer

# What Should NCI Do?

## Specific Recommendations:

### Basic science

- Animal Models
- Tumor Microenvironment

### Clinical Research

- ✓ “Translation” rich clinical trials
- ✓ Biomarkers for Immuno-Oncology (I-O)
- ✓ Searchable OncoImmune Database
- Clinical trials for Adoptive Cell Therapy

# Biomarkers are critical to further development of I-O drugs

- Immunotherapy has shown remarkable activities in a variety of cancers. However, only a minority of patients receive benefit.
- Strategies to optimize patients' outcomes will rely on:
  - Use of biomarkers to characterize the tumor/immune interphase at the cellular and molecular levels
  - Rational combination therapies to overcome intrinsic or acquired resistance
- **Categories of biomarkers to inform immunotherapy:**
  - Predictive biomarkers that inform about the likelihood of benefit or toxicities from therapies
  - Mechanism-based resistance biomarkers that are potentially actionable
  - Biomarkers for designing rational combination strategies
  - Biomarkers for monitoring treatment response and recurrence
  - Pharmacodynamic biomarkers for dose selection and sequencing of therapies

# NCI clinical trial networks are ideally positioned to address clinical and biomarker questions for immunotherapy

*Between 2010 –August 2016*

- **95 immunotherapy trials were activated in the DCTD Clinical Trial Networks**  
(NCTN, ETCTN, CITN, ABTC and PBTC)\*
- **> 20 agents are under CRADA** (Collaborative Research and Development Agreement)

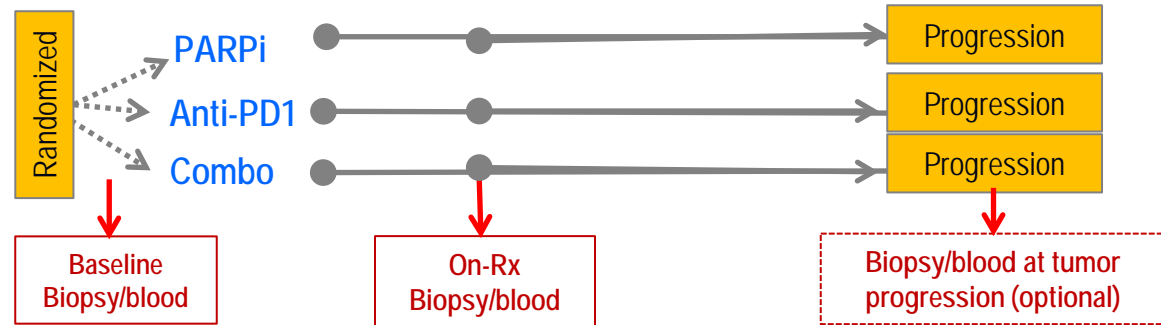
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| <b>Checkpoint inhibitors of T cells</b><br>Anti-CTLA-4 (ipilimumab, tremelimumab)<br>Anti-PD-1 (nivolumab, pembrolizumab)<br>Anti-PD-L1 (durvalumab, atezolizumab)<br><b>Cytokine:</b> IL-15; IL-12 | <b>Vaccines</b><br>CDX1401 (against NY-ESO-1)<br>PSA PROSTVAC/TRICOM,<br>CEA/TRICOM/PANVAC, gp100, HPV,<br>RAS, P53, MART and others<br><b>Oncolytic virus:</b> T-VEC | <b>T-cell engaging bispecific Ab</b><br>CD19 BiTE (Blinatumomab)<br><b>Other modulators:</b><br>IDO (INCB0243360); FLT3 ligand<br>Lenalidomide, Pomalidomide:<br>Anti-CD27 mAb, Anti-CCR4 mAB |
|---|---|---|

- **Clinical studies include:**
  - Phase 3 trials in metastatic and adjuvant settings (melanoma, bladder, lung) – 9 trials
  - Randomized phase 2 for novel combinations and high priority indications – 14 trials
  - Signal-seeking trials in rare tumors, pediatric malignancies and HIV+ patients
  - Pilot studies for biological endpoints (metastatic or neoadjuvant settings)

\* **Most randomized trials have mandatory collection of baseline tissues/blood**

\* **Many Phase 1-2 trials mandate on-treatment biopsies**

An example of an early clinical trial for immunotherapy conducted in ETCTN



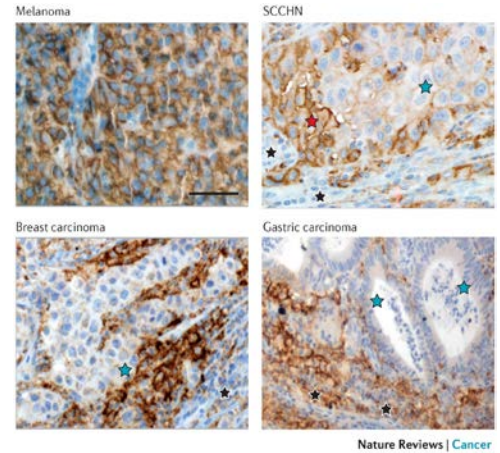
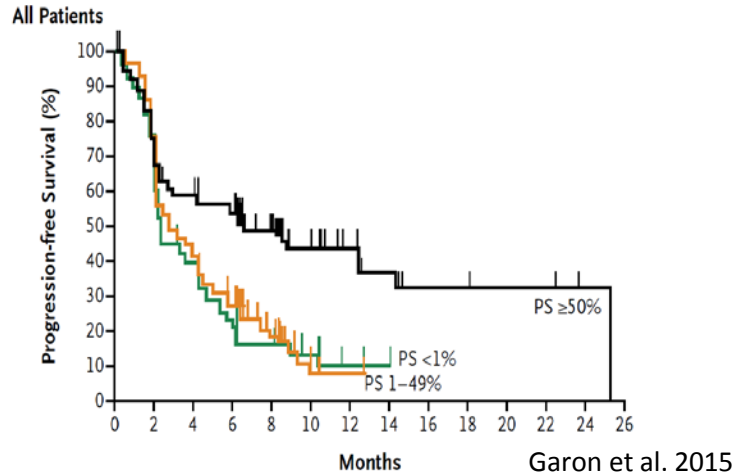
- Primary clinical endpoint – comparison of the Objective Response Rates
- Biomarker endpoints – monitor immunomodulation using standardized assays:
  - Baseline - tumor/immune profiles to predict response/benefit and toxicity
  - On-treatment - impact of various agents on reprogramming tumor and tumor microenvironment
  - At progression – knowledge based resistance mechanism evaluation



## A variety of assays and platforms are required to address the biomarker questions

- **However**
  - The most potentially informative assays are not always available to all trials
  - Often, in NCI Network trials, there is no designated funding for biomarker studies (need to apply for grant funding which is difficult to coordinate with clinical timelines)
  - Different labs often have different assays, platforms, SOPs, or scoring methods
  - No existing system for data deposit and integrated analysis across trials

Predictive relevance of PD-L1: Expression level of the PD-L1 is associated with the higher likelihood of clinical benefit in NSCLC patients treated with pembrolizumab



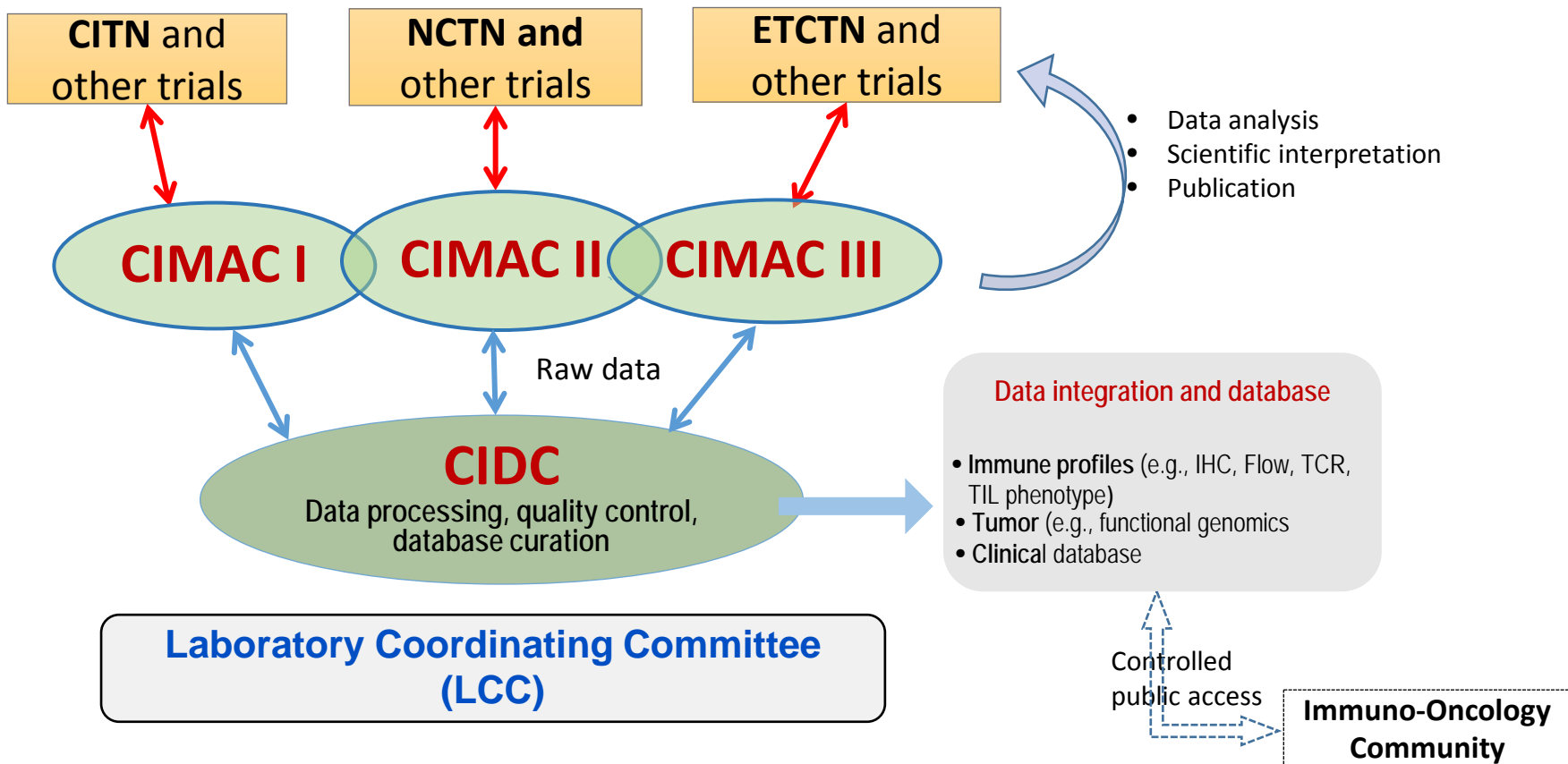
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## Assays standardized with different methods make it difficult to compare results across studies (and can hinder progress)

- Different PD-L1 specific antibody clones produce different results
- Different staining protocols and platforms
- Different assessment methods (Tumor cells, TILs, or both)
- Different scoring methods (% staining, H-score)
- **Cannot compare treatments or easily build upon the results**

|                  | 5JHU        | Merck                | BMS                 | Roche  | AZ              |
|------------------|-------------|----------------------|---------------------|--|-----------------|
| mAb              | 5H1         | 22-C3 (DAKO pharmDx) | 28-8 (DAKO pharmDx) | SP142 (Ventana)                                    | SP263 (Ventana) |
| Platform         | Manual      | Link 48 autostainer  | Link 48 autostainer | BenchMark ULTRA                                    | BenchMark ULTRA |
| Scoring criteria | Tumor cells | Tumor cells          | Tumor cells         | Tumor cells and/or tumor infiltrating immune cells | Tumor cells     |
| Positive cutoff  | ≥5%         | ≥50%                 | ≥1%                 | ≥5%  | ≥25%            |

# Cancer Immune Monitoring and Analysis Centers (CIMACs) and Cancer Immunologic Data Commons (CIDC) Network



## CIMACs – General Role

### Cancer Immune Monitoring and Analysis Centers – Up to 3 awards:

Conduct correlative studies and provide immunoprofiling analyses for specimens from:

- **Phase 1-2 clinical trials** conducted within DCTD-supported Networks/Consortia (NCTN, ETCTN, CITN, PBTC, and ABTC)
- **NCI-supported clinical trials from outside** the established Networks/Consortia (grant mechanisms such as R01, P01, P30 Cancer Centers, P50 SPOREs)

## CIMACs – Specific Functions

- **Multidisciplinary expertise** (immunology, oncology, pathology, molecular biology, assay development)
- **Access to high-quality, well-annotated specimens** from immunotherapy trials
- **Consistent analytically-validated** biomarker assay platforms across trials for retrospective and prospective analyses
- **Study design support and CLIA-certified testing**
- **Computational biology and biostatistics** resources for high-throughput data analysis; specific projects require specific statistical tools and approaches.

## Examples of well established assays for monitoring responses to immunotherapy

- **Tumor genomics:** Whole Exome Sequencing (WES), Targeted gene sequencing, RNA-seq (e.g., mutational load, neoantigen signature)
- **Tumor subtyping:** nCounter Analysis System for Gene Expression profiling/pathway activation etc., microsatellite instability (MSI),
- **T-cell number and function:** T-cell receptor (TCR) V region usage, Peptide-MHC Tetramers, Intracellular Cytokines by Multiparameter FACS, Cytokine mRNA Levels by Real-Time Quantitative RT-PCR, nCounter Immune Gene Expression Profiling Panel
- **Tumor histopathology:** Multicolor IHC, multiplexed immunofluorescence (IF), (e.g., CD3/CD8 Immunoscore, other T cells, M $\Phi$ , DC, MDSC, NK, tumor antigens, PD-L1)
- **Blood/Serum:** Fluorescence activated Cell Sorting (FACS), Mass Cytometry (CyTOF) (e.g., Immunophenotyping, Intracellular cytokines), TCR sequencing for lymphocyte clonality, ELISpot (e.g., T cell functional assay for intracellular IFN $\gamma$ /granzyme B), cell free DNA (cfDNA), Multiplex Enzyme-Linked Immunosorbent Assay (ELISA) (e.g., Cytokine panels)

## Cancer Immunologic Data Commons (CIDC)

- **Single site** – responsible for data quality and harmonization across CIMACs
- **Bioinformatics Function:**
  - Collaboration with the CIMACs to facilitate standardization of the data and fostering best practices among the CIMACs and their clinical collaborators
  - Systematic collection and integration of molecular data across IO trials
  - Establishing and managing database to host the tumor/immune profiling data
  - Sharing the data with other investigators to promote secondary data analyses
  - Collaboration with other data centers (e.g., Genomics Data Commons), whenever possible



## CIDC - Administrative Function and Laboratory Coordinating Committee (LCC)

- **Administrative Function:**
  - Establishment and maintenance of an internal website for the network
  - Dissemination of the information about the resources available within the CIMACs laboratory network to the broader immunotherapy community
  - Administration of proposals/requests from outside the primary partnerships for supports from the CIMACs
- **Laboratory Coordinating Committee (LCC)** - a scientific committee that will be responsible for:
  - Strategic planning and prioritization of scientific questions regarding optimization of resources for correlative studies
  - Prioritization of requests for CIMAC services from outside the NCI Clinical Trials Networks
  - LCC will include representatives of the CIMACs, CIDC and the NCI

# Network's Annual Budget

## CIMACs U24

|                           |              |
|---------------------------|--------------|
| • Laboratory Centers*     | \$3,200K     |
| • Scientific Staff        | \$950K       |
| • Network meetings/travel | <u>\$50K</u> |
| <br>                      |              |
| • Direct Costs            | \$4,200K     |
| • Total Costs             | \$6,500K     |

## CIDC U24

|                           |              |
|---------------------------|--------------|
| • Scientific Leadership   | \$350K       |
| • Bioinformatics Analysis | \$150K       |
| • Computers/Data Servers  | \$120K       |
| • Database Systems Access | \$20K        |
| • Network meeting/travel  | <u>\$10K</u> |
| <br>                      |              |
| • Direct Costs            | \$650K       |
| • Total Costs             | \$1,000K     |

\*Expected: 360 patients/year  
(at \$8,000/patient)

- Back up Slides

# Network Opportunities

## *How individual clinical investigators might work with CIMACs*

- Clinical Investigators will propose clinical trial concepts (with associated biomarker studies) to CTEP/NCI through the current review mechanisms
  - If decision is made to utilize the CIMAC lab network, the designated CIMAC for the trial network will:
    - Determine collaboratively which assays should be performed by CIMAC
    - Assist clinical trial team to refine the statistical design and hypothesis
    - Analyze data in collaboration with clinical trial team (e.g., study statistician) for scientific interpretation
  - Biomarker plans can be accomplished through one of the following mechanisms:
    - Work independently of CIMAC (e.g. PI to secure own funding and diagnostic capacity)
    - Use CIMAC for all biomarker studies related to the trial
    - Use CIMAC for some of the platforms (e.g. WES and neoantigen algorithm)
- \*Submission of biomarker data to central database is required for all NCI supported trials when the data center becomes available