

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

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# 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)

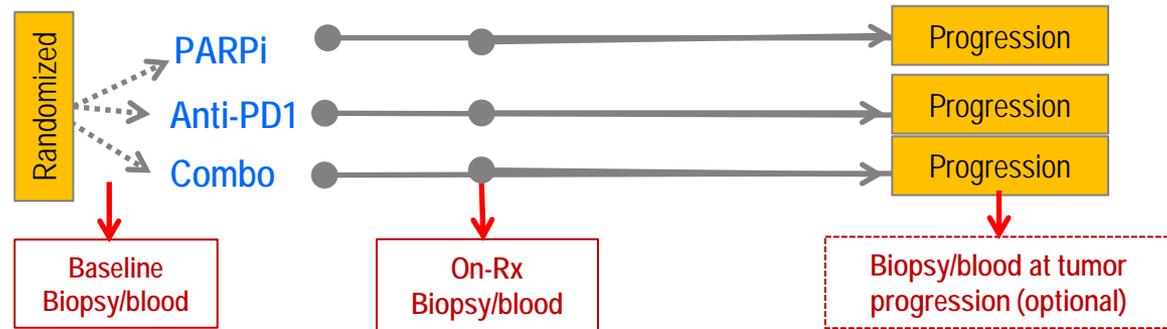
<b>Checkpoint inhibitors of T cells</b> Anti-CTLA-4 (ipilimumab, tremelimumab) Anti-PD-1 (nivolumab, pembrolizumab) Anti-PD-L1 (durvalumab, atezolizumab) <b>Cytokine:</b> IL-15; IL-12	<b>Vaccines</b> CDX1401 (against NY-ESO-1) PSA PROSTVAC/TRICOM, CEA/TRICOM/PANVAC, gp100, HPV, RAS, P53, MART and others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

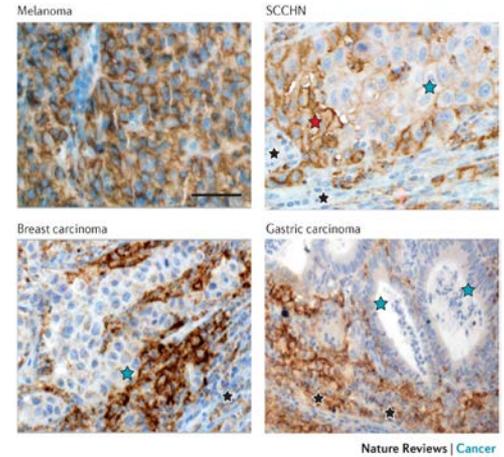
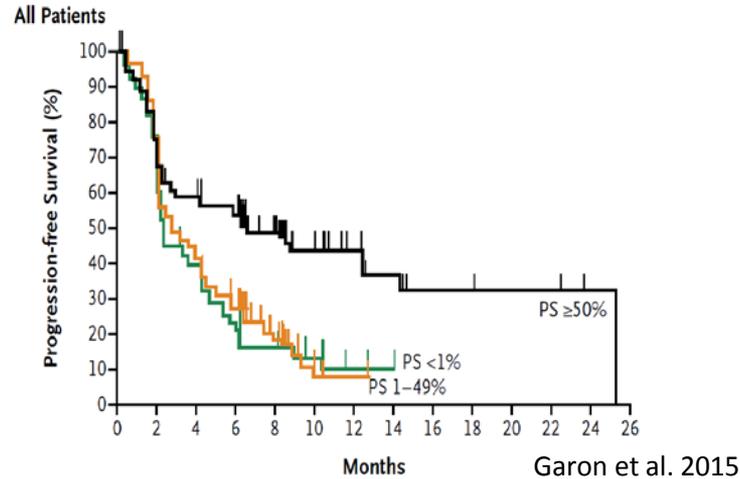


- Primary clinical endpoint – comparison of the Objective Response Rates
- Biomarker endpoints – monitor immunomodulation using standardized assays:
  - Baseline - tumor/immune profiles to predict response/benefit and toxicity
  - On-treatment - impact of various agents on reprogramming tumor and tumor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



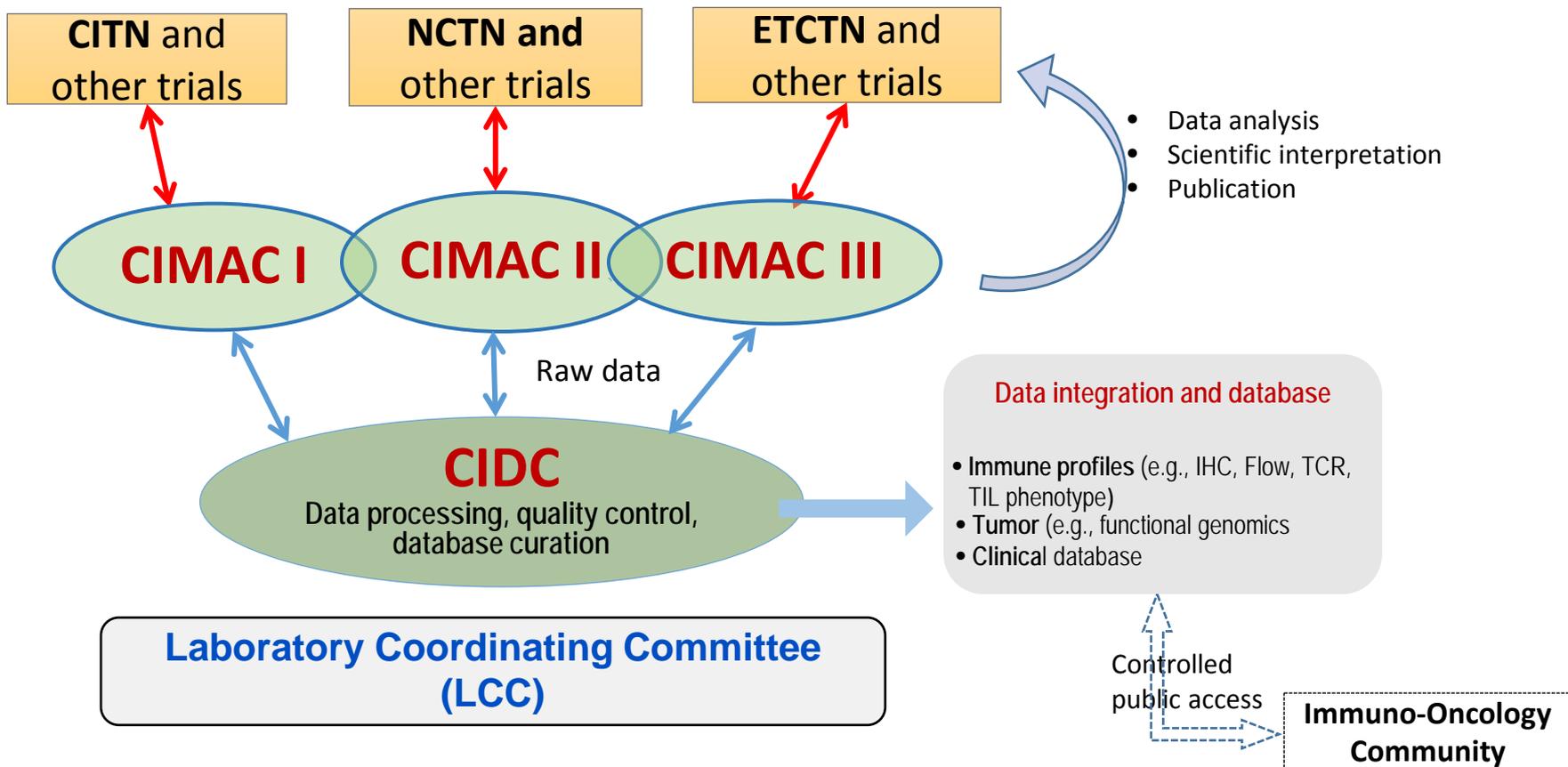
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## Assays standardized with different methods make it difficult to compare results across studies (and can hinder progress)

- 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>
• 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>
• 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