The NCI CIMAC-CIDC Network: Opportunities for SWOG Investigators

SWOG Spring Group Meeting, April 25th, 2019
San Francisco, CA, USA

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Professor and Chair, Department of Translational Molecular Pathology, Division of Pathology & Laboratory Medicine
Translational Research Director, Khalifa Institute for Personalized Cancer Therapy (IPCT)
The University of Texas MD Anderson Cancer Center, Houston, TX.
Disclosures

- **Advisory Board:** Genentech/Roche, Bristol-Myers Squibb, Astra Zeneca/Medimmune, Pfizer, HTG Molecular, Asuragen, Merck, GlaxoSmithKline, Guardant Health and MSD.

- **Speaker:** Medscape, MSD, Genentech/Roche, Pfizer

- **Research support:** Genentech, Oncoplex, HTG Molecular, DepArray, Merck, Bristol-Myers Squibb, Medimmune, Adaptive, Adaptimmune, EMD Serono, Pfizer, Takeda, Amgen, Karus, Johnson & Johnson, Bayer, Iovance, 4D, Novartis, and Akoya.
Presentation Outline

- Biomarker development for immunotherapy: *from discovery to clinical utilization*
- Cancer Immune Monitoring and Analysis Centers (CIMAC) & Cancer Immunologic Data Commons (CIDC): *Goals and Description*
- CIMAC-CIDC Assays: *Tier 1 and Tier 2*
- CIMAC Trials and SWOG Collaborations
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Developing Markers for Immunotherapy

Phenotype markers

- PD-L1 IHC
- TILs
- Th1/IFN-γ
- Serum IL-8
- T-cell prolif & MDSCs
- IPRES/Serpinb9
- Microbiome

Genomic markers

- MSI
- Mutational burden
- DNA FISH
- TCRβ clonality

References:

- Topalian et al., 2012, NEJM
- Herbst et al., 2014, Nature
- Garon et al., 2015, NEJM
- Weber et al., 2015 Lancet
- Taube et al., 2014 CCR
- Tumeh et al., 2014, Nature
- Le et al., 2015, NEJM
- Seiwert et al., 2015, ASCO
- Prat et al., 2017, Can Res
- Ayers et al., 2017, JCI
- Sannamed et al., 2017, Ann Oncol
- Carleton et al., 2018 ASCO
- Kitano et al., 2014, CIR
- Huang et al., 2017, Nature
- Sharma et al., 2018, AACR
- Hugo et al., 2016, Cell
- Pan et al., 2018, Science
- Vetizou et al., 2015, Science
- Sivan et al., 2015, Science
- Gopalakrishnan et al., 2018, Science
- Le et al., 2015, NEJM
- Overman et al., 2017, JCO
- Snyder et al., 2014, NEJM
- Van Allen et al., 2015, Science
- Rizvi et al., 2015, Science
- Hugo et al., 2016, Cell
- Zaretzky et al., 2016, NEJM
- Gao et al., 2016, Cell
- Gettinger et al., 2017, Can Discovery
- Pan et al., 2018, Science
- Miao et al., 2018, Science
- Ansell et al., 2014, NEJM
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Slide Courtesy of Dr. Kurt Schalper, Yale Cancer Center
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*Slide Courtesy of Dr. Kurt Schalper, Yale Cancer Center*
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Clinical standard (LDT)

*Slide Courtesy of Dr. Kurt Schalper, Yale Cancer Center*
Multiscale and Dynamic Atlas of Immune Changes

Comprehensive
- Organ imaging (MRI, CT scan)
- Tissue mapping (MIBI, VECTRA, histology)
- Cellular mapping (CyTOF, scRNAseq, MIBI)
- Molecular mapping (WES, TCRseq, scRNAseq, neoantigens, MIBI, CyTOF)
- Data analysis
- Data sharing

Longitudinal
- On-treatment
- Relapse

Patient-centric
- Post

Modified from slide courtesy Sacha Gnjatic, Mount Sinai, New York, CIMAC
What is the patient's overall inflammatory state/immune competence?

Luminex serum cytokines

What is the immune state of the tumor?

ATACseq

RNA Seq

Modified from slide courtesy Holden Maecker, Stanford University CIMAC
# Developing Markers for Immunotherapy

<table>
<thead>
<tr>
<th>Category</th>
<th>Assay</th>
<th>Specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune cells characterization</strong></td>
<td>Immunohistochemistry (image analysis)</td>
<td>Tissue</td>
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<tr>
<td></td>
<td>Immunofluorescence (multiplex; image analysis)</td>
<td>Tissue</td>
</tr>
<tr>
<td></td>
<td>Flow cytometry and CyTOF (panels)</td>
<td>Tissue and blood</td>
</tr>
<tr>
<td></td>
<td>Codex, MIBI and CyTOF Imaging (IMC) (panels)</td>
<td>Tissue</td>
</tr>
<tr>
<td><strong>Functional assessments</strong></td>
<td>Flow cytometry detection of T cell activation</td>
<td>Tissue and blood</td>
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<td></td>
<td>ELISPOT</td>
<td>Blood</td>
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<td></td>
<td>Neo-antigen prediction (from WES and RNA-seq)</td>
<td>Tissue</td>
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<tr>
<td></td>
<td>TCR and BCR sequencing</td>
<td>Tissue and blood</td>
</tr>
<tr>
<td><strong>Host factors</strong></td>
<td>Cytokine analyses (MSD, Luminex, ELISA)</td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td>Microbiome (16S deep sequencing)</td>
<td>Stool (others)</td>
</tr>
<tr>
<td><strong>Tumor and malignant cells genomics</strong></td>
<td>Next generation sequencing (WES, RNA-seq, targeted)</td>
<td>Tissue</td>
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<tr>
<td></td>
<td>Low-input gene expression signatures (Nanostring, HTG-Edge Seq, Affymetrix arrays)</td>
<td>Tissue (FFPE)</td>
</tr>
<tr>
<td></td>
<td>Liquid biopsy (cfDNA, exosomes, CTC)</td>
<td>Blood</td>
</tr>
</tbody>
</table>

*MD Anderson CIMAC*

C. Bernatchez, G. Al-Atrash, C. Haymaker, I. Wistuba
Biomarker Discovery Strategy
Immunotherapy Trials/APOLLO Platform MD Anderson Cancer Center

Prospective Studies

Enrollment

Pre-treatment tumor biopsy

Toxicity

Blood (→)
- Plasma (cfDNA), cytokines
- PMBCs (germline DNA)
- Flow cytometry (2 panels)
- Functional T cells assays
- TCR sequencing

Stools (→) Microbiome
- (→) No tumor biopsy (skin, colon, etc.)
  - Blood
  - Fluids (BAL)
  - Skin microbiome

Treatment

During treatment tumor biopsy (e.g. 4-6wks)

Biopsy (→)
- Histology
- IHC
- mIF
- mRNA (Nanostring, HTG Edge-Seq)
- TBD
- Flow cytometry (TILs)
- RNA-seq
- DNA (WES, targeted, TCR/B)

Progression

Tumor biopsy at progression

B. Sanchez –Espiridion et al, MD Anderson Cancer Center CIMAC

Pre-tox

Post-tox

Tox-resolution

Pre-treatment tumor biopsy

During treatment tumor biopsy (e.g. 4-6wks)

Tumor biopsy at progression

Blood (→)
- Plasma (cfDNA), cytokines
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B. Sanchez –Espiridion et al, MD Anderson Cancer Center CIMAC
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• Biomarker development for immunotherapy: from discovery to clinical utilization

• Cancer Immune Monitoring and Analysis Centers (CIMAC) & Cancer Immunologic Data Commons (CIDC): Goals and Description

• CIMAC-CIDC Assays: Tier 1 and Tier 2

• CIMAC and SWOG: Protocols and Process
The Era of Immuno-Oncology

- **Dilemma**: Many agents targeting the immune system and specific genetic alterations in tumor cells are in clinical trials or approved for treatment but it remains unclear why the majority of patients with cancer do not respond.

- **Proposed Solution**: Development and implementation of state-of-the-art standard assays for immuno-monitoring of clinical trials across NIH/NCI sponsored studies to study mechanism of sensitivity and resistance.
Cancer Immune Monitoring and Analysis Centers (CIMACs) & Cancer Immunologic Data Commons (CIDC)

Laboratory Coordinating Committee (LCC)

NCTN (SWOG, ECOG-ACRIN) → NCTN (NRG, Alliance) → ABTC → ETCTN → CITN → COG; Ped-CITN; PBTC

LCC determines CIMAC assignments based on: assays required; CIMAC workload; established CIMAC-trial relationships

CIMAC 1 (MD Anderson Cancer Center) → CIMAC 2 (Icahn School of Medicine) → CIMAC 3 (Dana Farber Cancer Institute) → CIMAC 4 (Stanford University)

Cancer Immunologic Data Commons (CIDC) (Dana Farber Cancer Institute)

MD Anderson Cancer Center (Ignacio Wistuba, Gheath Al-Atrash, Chantale Bernatchez) → Mount Sinai (Icahn School of Medicine, Sacha Gnjatic) → Dana-Farber Cancer Institute (Catherine Wu, F. Stephen Hodi) → Stanford Cancer Institute (Holden Maecker, Sean Bendall)
CIMAC–CIDC Immuno-Oncology Biomarker Network

- Each CIMAC is a multidisciplinary team (assays, statistical/computational experts, translational scientists, clinicians).
- Each CIMAC will be aligned with Clinical Trial Networks and Consortia-Collaborate in scientific planning, tissue accession, data analysis, and publication.
- A given CIMAC may perform all or specific assays for each study, depending on resource prioritization and expertise.
- Utilization of the CIMACs-CIDC resource is voluntary, but the studies will require collaboration with the CIMACs investigators and approval from the CTEP.
- The CIMACs will cover comprehensive profiling for approximately 500 patient/specimens per year (MDACC: 125 patients per year)
CIMAC & CIDC Laboratory Coordination Committee (LCC) and Working Groups (WGs)

Laboratory Coordinating Committee (LCC)

Chair: Ignacio Wistuba
Co-chairs: Catherine Wu, Holden Maecker, Sacha Gnjatic, Shirley Liu

Clinical Trials Coordination
Specimen Tracking
Assays and Platforms
Bioinformatics and Statistics
Software and Database

- Genomics WG
- IHC/IF WG
- CyTOF WG
- Nanostring WG
- Microbiome WG
- TCR-Seq WG

WG Chair:
F. Steven Hodi, Gheath Al-Atrash
Ignacio Wistuba
Holden Maecker
Shirley Liu
Ethan Cerami

NCI Lead and PMs:
Helen Chen
Melissa Bowman
David Patton
Irina Lubensky
Radim Moravec
Cathy Rowe
Magdalena Thurin
Min Song, Stephen Hewitt
Chris Karlovich, Biswajit Das
Sylvie Janssens
Yingdong Zhao
Laura Yee
Lisa McShane
Joyce Yu

David Patton
Joyce Yu

NATIONAL CANCER INSTITUTE
Cancer Immunologic Data Commons (CIDC)

*Ethan Cerami, PhD, and Shirley Liu, PhD*

*Danna Farber Cancer Center*

**CIDC is Responsible for:**

- Developing Meta-Data Standards
- Creating a Centralized Data Warehouse of all data
- Developing and running bioinformatics pipelines
- Enabling data access and data visualization
- Ensuring that all data is protected and meets federal data security requirements.

**Current Status:**

- Core Cloud Platform developed and deployed.
- Core data model developed.
- Federal security audit in place and continuing (must be completed before ingestion of data).
- Process in place for onboarding all new CIMAC assays.
- Multiple pipelines completed or in development (WES, RNA-seq, etc.).
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• CIMAC and SWOG: *Protocols and Process*
## Tier 1 assays
(recommended for most trials)

- Whole Exome Sequencing (WES)
- RNA-seq
- IHC singleplex
  - PD-L1 FDA approved assay
- IHC/IF multiplex
- CyTOF
- Olink
- Nanostring IO panel

## Tier 2 assays
(trial-dependent)

- Microbiome
- TCR repertoire
- Single-cell-seq
- ctDNA-seq
- MIBI
- ATAC-seq
- scRNA-TCR

**Other Assays:**
ELISA, B cell response, T cell functional assays (ELISPOT, multimers)

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A prospective CIMAC Umbrella Protocol for collections and processing of specimens has been developed.

*Slide Courtesy of Holden Maecker, PhD, Stanford University CIMAC*
CIMAC & CIDC Assays
Tier 1 Assays - Validation and Harmonization

- Assay validation at each CIMAC
- Assay harmonization among CIMACs
**CIMAC & CIDC Assays**

Multiplex Immunofluorescence – 7-9 markers/panel

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**Opal™ - TSA System for Multiplex Polaris IF**

**Vectra/Polaris™ (Perkin Elmer)**

**InForm™ (Perkin Elmer)**

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**MD Anderson CIMAC mIF Panels**

<table>
<thead>
<tr>
<th>Panel 1</th>
<th>Panel 2</th>
<th>Panel 3</th>
<th>Panel 4</th>
<th>Panel 5</th>
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</thead>
<tbody>
<tr>
<td>TILs &amp; PD-L1/PD1</td>
<td>Immune Checkpoints</td>
<td>Myeloid Cells</td>
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<tr>
<td>PD-L1</td>
<td>CD3</td>
<td>PD-L1</td>
<td>LAG-3</td>
<td>CD11b</td>
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<td>PD-1</td>
<td>CD8</td>
<td>IDO-1</td>
<td>TIM-3</td>
<td>CD14</td>
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<tr>
<td>CD3</td>
<td>Granzyme B</td>
<td>B7-H3</td>
<td>ICOS</td>
<td>CD33</td>
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<td>CD8</td>
<td>CD45Ro</td>
<td>B7-H4</td>
<td>OX-40</td>
<td>CD66b</td>
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<td>CD68</td>
<td>FOXP3</td>
<td>Vista</td>
<td>CD3</td>
<td>CD68</td>
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<tr>
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<td>CD3</td>
<td>CD20</td>
<td>CD163</td>
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<tr>
<td>AE1/AE3</td>
<td>AE1/AE3</td>
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CIMAC & CIDC Assays
CyTOF Tissue and Blood - Initial Panel Design

<table>
<thead>
<tr>
<th>CyTOF Panel</th>
<th>Target</th>
<th>Clone</th>
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</thead>
<tbody>
<tr>
<td>Target</td>
<td>CD19</td>
<td>HIB19</td>
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<tr>
<td>CD45RA</td>
<td>CD45RA</td>
<td>HI100</td>
</tr>
<tr>
<td>CD4</td>
<td>CD4</td>
<td>RPA-T4</td>
</tr>
<tr>
<td>CD8a</td>
<td>CD8a</td>
<td>RPA-T8</td>
</tr>
<tr>
<td>CD16</td>
<td>CD16</td>
<td>3G8</td>
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<tr>
<td>CD1c</td>
<td>CD1c</td>
<td>L161</td>
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<tr>
<td>CD123</td>
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<td>6H6</td>
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<td>CD66b</td>
<td>CD66b</td>
<td>G10F5</td>
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<td>CD27</td>
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<td>O323</td>
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<td>CD14</td>
<td>CD14</td>
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<tr>
<td>CD38</td>
<td>CD38</td>
<td>HB-7</td>
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<tr>
<td>HLADR</td>
<td>HLADR</td>
<td>L243</td>
</tr>
</tbody>
</table>

- Panel for study monitoring includes intracellular markers such as FoxP3 and Ki67
- Panel has open channels for flexibility of additional markers to assess specific hypothesis/targets
CIMAC & CIDC Assays
O-Link Multiplex Targeted Soluble Protein Analytes

O-Link Soluble Proteomic Analysis

Example in 3 MM patients treated with CAR T cells

Analye serum at various time points with 92 soluble analyte multiplex panel probing immuno-oncology proteins such as cytokines, chemokines, and soluble checkpoint molecules using O-Link’s platform with oligo extensions.

Mt. Sinai HIMC is the first approved O-Link service provider in US.

Slide Courtesy of Sacha Gnajtic, PhD, Mt. Sinai, New York City, CIMAC
CIMAC & CIDC Clinical Trials

- Each CIMAC has 4-6 trials for collaboration.

- Correlatively the network has 700 patients by 2019, 1,700 projected accrual by 2023.

*Slide Courtesy of Helen Chen, MD, NCI (CIMAC-CIDC Network)*
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Identification of Trials/Samples and CIMAC/CIDC Intake Process

- Type of trials: completed, ongoing or new.
- Type of specimens: tissue (fresh/FFPE), blood and fluids; all banked and processed by NCI Group Banks Committee (e.g., SWOG bank)
- Comprehensive analysis is preferred, but “hybrid” approach is acceptable (e.g. SWOG Lung MAP and DART trials)
- Trials list provided by NCI/CTEP, but CIMAC can work directly with investigators on new concepts
- **Data analysis will be done in collaboration with trial investigators, including statisticians and translational medicine teams**
- Data integration will be performed at CIDC
CIMAC Review Approval Process

1. **CIMAC Intake form** (prepared in collaboration with SWOG investigators)
2. Review/approval by CIMAC Clinical Trial Working Group and Laboratory Coordination Committee (LCC)
3. Approval by SWOG clinical trial group (with participation of SWOG Translational Committee)
4. Approval by CTEP
5. Sample transfer from SWOG biobank to CIMAC
CIMAC SWOG Trials – Lung MAP S1400I

- **S1400I**: A Phase III Randomized Study of Nivolumab plus Ipilimumab versus Nivolumab for previously-treated patients with Stage IV squamous cell lung cancer and no matching biomarker

- **Primary Objective**: Overall survival

- **Secondary Objective(s)**: Define biomarkers that are associated with innate and acquired resistance

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**Study Chair**: Vassiliki A. Papadimitrakopoulou, MD  
**Sub-study Chairs**: Scott N. Gettinger, MD, Lyudmila A. Bazhenova, MD

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**Total accrual**:  
- 350 patients to be accrued over 27-36 months

**Tissue Collection**:  
- Baseline and progression among responders  
- FFPE Block or 12 unstained unstained 4-5 micron sections.

**Blood Collection**:  
- Pre-screening, Screening or Pre-study Weeks 3, 7, 9.  
- First progression after study treatment  
- 8-10 ml EDTA tube blood for plasma and buffy coats

**CIMAC Tier 1 Assays**:  
- Tissue: PD-L1 IHC, WES, RNA-seq, mIF  
- Blood: O-link
CIMAC SWOG Trials – DART Trial

**DART**: Dual Anti-CTLA-4 & Anti-PD-1 blockade in Rare Tumors

**Primary Objective**: To evaluate the overall response rate (ORR) in patients with advanced rare cancers treated with ipilimumab plus nivolumab combination therapy.

**Study Chairs**: Sandip Patel, MD, Young Chae, MD, Razelle Kurzrock, MD

### DART Rare Tumors List

<table>
<thead>
<tr>
<th>Rare cancers included in DART</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transitional cell carcinoma other than renal pelvis urethral or bladder</td>
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<tr>
<td>Cell tumor of the tonsils and extra nodal tumors</td>
</tr>
<tr>
<td>Seminoma and testicular sex cord cancer</td>
</tr>
<tr>
<td>Non seminomatous tumor</td>
</tr>
<tr>
<td>Teratoma with malignant transformation</td>
</tr>
<tr>
<td>Epithelial tumors of penis - squamous adenocarcinomas and carcinomas with variants of penis</td>
</tr>
<tr>
<td>Squamous cell carcinoma variants of the peritoneal GI tract</td>
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<tr>
<td>Spindle cell type of kidney, pelvis and ureter</td>
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<tr>
<td>Adenocarcinomas with variants of GI tract (excluding prostate cancer)</td>
</tr>
<tr>
<td>Endometrioid malignant tumors</td>
</tr>
<tr>
<td>Adenocarcinomas of pancreas and digestive tract</td>
</tr>
<tr>
<td>Neuroendocrine carcinomas including carcinoma of the lung and other sites of other sites</td>
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<tr>
<td>Placental carcinoma, malignant</td>
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<tr>
<td>Paragangliomas</td>
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<tr>
<td>Gastrointestinal - pyloric gland, thyroid gland parathyroid gland adrenal cortex</td>
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<tr>
<td>Dermoid tumors</td>
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<tr>
<td>Perihilar or chest tumors and IHH related tumors</td>
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<tr>
<td>Malignant germ cell tumors</td>
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<tr>
<td>Carcinomas</td>
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<tr>
<td>Adrenal cortical tumors</td>
</tr>
<tr>
<td>Tumor of unknown primary</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

### Accrual:
- **DART Activated**: 1/13/17
- **First Patient Treated**: 1/30/17

### As of 9/1/18:
- 809 sites approved to enroll through CTSU
- Total enrollment: 525 patients
- 37 Cohorts originally
- 53 cohorts in amendment 5

### CIMAC Tier 1 Assays:
- **Tissue**: PD-L1 IHC, WES, RNA-seq/Nanostring panel, mIF
- **Blood**: CyTOF panel, O-link panel