NCI Strategy and Current landscape of Clinical Immunotherapy Trials

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Disclosure Slide:

- Nothing to disclose
Innovative Imaging Techniques Are Essential for Further Development of I-O drugs

- Immunotherapy has shown remarkable activity in a variety of cancers, but only a minority of patients receive benefit
- Strategies to optimize patients’ outcomes may rely on:
  - Use of biomarkers (including imaging) to characterize the tumor/immune interface at the cellular and molecular levels
  - Rational combination therapies to overcome intrinsic or acquired resistance

- Categories of imaging that may help to inform immunotherapy:
  - Prognostic: Pre-existing features that inform about the likelihood of benefit or adverse events from various therapies, including the risk of hyperprogression
  - Predictive: Early Surrogates Indicating Response or Failure of Response to Therapy
    - (e.g. PET scan in patients with Hodgkin Lymphoma)
  - Pharmacodynamic: Imaging for dose selection and sequencing of therapies
    - (e.g. novel strategies for visualizing CD8 cells on imaging)
  - Correlative/Surrogate: Evaluating tumor progression versus pseudoprogression
<table>
<thead>
<tr>
<th>Category of Biomarker</th>
<th>Definition</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prognostic</td>
<td>Evaluates overall outcome regardless of intervention</td>
<td>Immunoscore, neut/lymph ratio</td>
</tr>
<tr>
<td>Predictive</td>
<td>Evaluates the likelihood of response to treatment</td>
<td>PD-L1 expression, baseline MDSC</td>
</tr>
<tr>
<td>Pharmacodynamic</td>
<td>Measures drug effect on the target</td>
<td>TCR Sequencing, CD8 TIL</td>
</tr>
<tr>
<td>Pharmacokinetic</td>
<td>Measures drug distribution, metabolism, and excretion</td>
<td>Persistence of CAR-T Cells</td>
</tr>
<tr>
<td>Correlative or surrogate endpoint</td>
<td>Acts as a substitute for clinically meaningful endpoint</td>
<td>Progression-Free Survival, as measured by RECIST</td>
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</table>
Pseudoprogression: a Unique Problem for Immunotherapy

- Tumor-infiltrating lymphocytes (TILs) are a necessary pre-condition for initiating a response
- Immunotherapy involves a systems approach to tumor cell killing
- There is an inherent dynamism to the tumor microenvironment and the interplay of immune cells within the TME
- Imaging modalities such as standard PET or CT imaging scans may not be granular enough to differentiate between growth in tumor or infiltration by immune cells
- If therapy is halted at an early stage, patients may fail to experience a benefit that would have otherwise occurred if therapy had continued
- Conversely, clinicians waiting to determine if a progression event is a true event, they may:
  - Continue a therapy that is providing no benefit to a patient
  - Avoid steroids or other anti-inflammatory agents
  - Delay switching to other potential therapeutic options
Hyperprogression

- Posited as an event in which the addition of an immuno-oncology agent leads to accelerated disease progression by an as yet undetermined mechanism
- Definitions vary
Patient Level vs. Trial Level Issues

- There can be different needs at the patient level versus the emergent issues at a trial level
  - Patient Level: What to do with a patient in clinic with a new lesion?
    - irRC was first designed as a decision-making tool
  - Trial Level: What is the purpose of a new set of criteria?
    - RECIST, iRECIST, response rate, etc. are not necessarily proxies for patient benefit
    - New criteria must be compared in massive data collection exercises and compared to older, more established criteria to determine if they can serve as a surrogate for overall survival, improvement in QoL, or other measures of patient benefit
    - On a trial, experimental and control arms must be measured by same criteria
Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok, Axel Hoos, Steven O'Day, Jeffrey S. Weber, Omid Hamid, Celeste Lebbé, Michele Malo, Michael Binder, Oliver Bohnsack, Geoffrey Nichol, Rachel Humphrey, and F. Stephen Hodi

DOI: 10.1158/1078-0432.CCR-09-1624 Published December 2009

Abstract

**Purpose:** Immunotherapeutic agents produce antitumor effects by inducing cancer-specific immune responses or by modifying native immune processes. Resulting clinical response patterns extend beyond those of cytotoxic agents and can manifest after an initial increase in tumor burden or the appearance of new lesions (progressive disease). Response Evaluation Criteria in Solid Tumors or WHO criteria, designed to detect early effects of cytotoxic agents, may not provide a complete assessment of immunotherapeutic agents. Novel criteria for the evaluation of antitumor responses with immunotherapeutic agents are required.

**Experimental Design:** The phase II clinical trial program with ipilimumab, an antibody that blocks CTL antigen-4, represents the most comprehensive data set available to date for an immunotherapeutic agent. Novel immune therapy response criteria proposed, based on the shared
Immune-Modified Response Evaluation Criteria In Solid Tumors (imRECIST): Refining Guidelines to Assess the Clinical Benefit of Cancer Immunotherapy

F. Stephen Hodi, Marcus Ballinger, Benjamin Lyons, Jean-Charles Soria, Mizuki Nishino, Josep Tabernero, Thomas Powles, David Smith, Axel Hoos, Chris McKenna, Ulrich Beyer, Ina Rhee, Gregg Fine, Nathan Winslow, Daniel S. Chen, and Jedd D. Wolchok

ABSTRACT

Purpose
Treating solid tumors with cancer immunotherapy (CIT) can result in unconventional responses and overall survival (OS) benefits that are not adequately captured by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1. We describe immune-modified RECIST (imRECIST) criteria, designed to better capture CIT responses.

Patients and Methods
Atezolizumab data from clinical trials in non-small-cell lung cancer, metastatic urothelial carcinoma,
The landscape of anti-PD1/PDL1 mAb clinical trials in 2017 and 2020. As of September 2020, 4,400 clinical trials are in the current landscape, nearly tripling since in September 2017. Other PDx includes any anti-PD1/L1 mAbs without FDA approvals.

Main targets assessed in combination with anti-PD1/L1 mAbs. The graph shows the number of combination trials starting each year since 2011. The main 20 targets assessed in combination are shown in descending order according to the number of trials started in 2020. *Only data from the first three quarters of 2020 were used to generate the analysis.

CTEP IO Agents (selected) –

- **Anti-PD-1/L1**: Nivolumab, Pembrolizumab, Durvalumab, Atezolizumab
- **Anti-CTLA-4**: Ipilimumab, Tremelimumab
- **Other T Cell Modulators**: LAG3, Anti-CD27 mAb (CellDex), Anti-CCR4 mAb, IDO (INCB0243360), FLT3 ligand
- **Non-T-cell targeted**: CD47
- **T-cell engaging bispecific**: CD19 BiTE (Blinatumomab)

**Cytokines:**
- IL-15
- IL-12
- IL-7

**Oncolytic virus:**
- T-VEC

**Adoptive cell therapy**
- GD-2 CAR T

**IMIDs**
- Lenalidomide
- Pomalidomide

- **Non-immunotherapy agents** are potential partners in IO combinations
  - PI3K (alpha, beta, gamma) inhibitors
  - MEK, RAF inhibitors
  - VEGF (TKIs, mAb) inhibitors
  - Epigenetics (HDAC, EZH, BET, DMT)
  - PARP inhibitors and other DDR inhibitors
  - CDK4/6 inhibitors
  - Antibody drug conjugates (HER2, mesothelin, CD30)
  - Chemotherapy
  - Radiotherapy, including novel radiopharmaceuticals
  - B-cell targeting: Ibrutinib, PI3K

- **Cytokines:**
  - IL-15
  - IL-12
  - IL-7

- **Oncolytic virus:**
  - T-VEC

- **Adoptive cell therapy**
  - GD-2 CAR T

- **IMIDs**
  - Lenalidomide
  - Pomalidomide
CTEP trials for anti-PD1/L1 in numbers - activated in 2015-2020

- **128 trials** (31 already closed to accrual)
  - 33 phase III (4 completed accrual)
  - 40 randomized phase 2 (out of 66 phase 2 trials)

- **Actual accrual**: ~8000

- **Publications (2015-2018)**: 27 publications

- **Trial Networks**
  - 47 from ETCTN
  - 5 from CITN
  - COG/PED-CITN
  - NCTN

![Diagram showing distribution of trials by drug](image)
Overall Scope of CTEP Phase 1-2 trials with anti-PD-1/PD-L1

**Special patient populations**
- Solid organ transplant
- Organ dysfunction (AIM-Nivo)
- HIV
- Rare tumors/clinical settings
  - 52 rare tumor cohorts (DART)
  - Meningioma
  - ASPS
  - Angiosarcoma
- AML post allotransplant
- Post ATC therapy
- Unique molecule subsets? - TFE/Translocation RCC (Nivo +/-axitinib)

**Pediatric IO**
- Nivo Ipi
- High TMB
- GD2 CAR T Cell Therapies
- CD47 plus Ch14.19

**Novel approaches**
- Cell therapy (GD2 CART)
- Neoantigen vaccine

**Neoadjuvant trials**
- Chemo CPI (TNBC)
- ChemoRT + CPI (Rectal platform trial)
- RCC

**Biomarker-driven**
- Immune modulation by chemotherapy (10292)

**Novel combinations**
(most trials randomized)
- Ipilimumab (multiple)*
- IL-7 (Bladder; GBM) *
- IL15, IL12, IL7
- CD27 (NHL) *; + CCR4 (DLBCL)*
- PARPi (TNBC, Ovarian, Pancreatic, Lung) *
- VEGF TKI (endometrial, Lung, RCC, GBM) *
- Cabo (neuroendocrine; GU; thyroid ca)
- BV (melanoma) *
- PI3K (alpha, beta, delta) *
- MEKi (Biliary Ca, NSCLC) *
- ADC (mesothelin, HER-2) *
- HDAC I (Ovarian) *
- Other Epigenetics (HDAC, EZH2, BET …)
- Chemo (SCLC, bladder) *
- RT (MCC, NSCLC, meningioma, rectal) *
- New radiopharmaceuticals

* Randomized trials
iRECIST

- Developed by the RECIST working group
- Main goal is to obtain data to help standardize and validate the application of immune response criteria
- Relatively conservative approach, with only minor modifications to RECIST 1.1
- If a patient is determined to have RECIST Progressive Disease (PD) but is at a later timepoint found to have tumor shrinkage, the new nadir is determined from that point
  - Initial progression timepoint is redefined as “iUPD” or immune unconfirmed progressive disease
What didn’t change from RECIST 1.1 to iRECIST?

<table>
<thead>
<tr>
<th>RECIST 1.1</th>
<th>iRECIST</th>
</tr>
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<tbody>
<tr>
<td>Definition of measurable lesions</td>
<td>No change</td>
</tr>
<tr>
<td>Definition of target vs. non-target</td>
<td>No change</td>
</tr>
<tr>
<td>Measurement of nodal lesions</td>
<td>No change</td>
</tr>
<tr>
<td>CR, PR, SD, duration, confirmation of CR/PR</td>
<td>No change</td>
</tr>
</tbody>
</table>
An Ideal Design for 2 Active Agents
Theory for regression and growth

\[ f(t) = e^{(g \cdot t)} + e^{(-d \cdot t)} - 1 \]

Where \( f \) = tumor measurement in \( t \) days
\( d \) = regression rate constant; \( g \) = growth rate constant
The value of data sharing

- Large public datasets of medical data
  - Enable exploratory data analysis and modeling
  - Avoid duplication of data acquisition
  - Enable collaborative research
  - Compare different data methods with the same data
  - Make better design for future clinical studies
- Leverage the skills of lower resource individuals
The Cancer Imaging Archive

- Open access de-identified imaging data
- Covers most modalities (CT/MR/PET/RT)
- Wide variety of cancers + phantoms
- Patient populations vary from a few to >26,000 (NLST)
- Many have associated meta-data
  - Demographics/outcomes/therapy
  - Pathology histology imaging
- Radiologist expert and automated computational analyses (segmentations, features)
- ‘Omics via TCGA, CPTAC, and GEO

http://www.cancerimagingarchive.net
Conclusions

- Focus must be on utilizing tools, such as iRECIST or other imaging modalities to evaluate for patient benefit, and also for comparisons to other criteria.
- There should be a distinction between patient-level and trial-level surrogacy, and they should not be confused.
- Collection of additional data and the provision of greater access to researchers can allow for evaluations of a variety of competing criteria.
- Further evaluation of pseudoprogression may be improved with biopsy-driven, translational research efforts to help better characterize these phenomena in close collaboration with radiological colleagues.
- Imaging datasets should be made public (through efforts such as the TCIA) to help advance the field of radiomics – if clinically annotated images are provided, the field can rapidly advance.