Research Considerations for New Therapies
CAR T-Cell, Check Point Inhibitors, and Beyond

What are Research Considerations for New Therapies – CAR T-Cell, Check Point Inhibitors, & Beyond?

Disclosures

• As a government employee, I have no ongoing financial relationships to disclose
**Immunotherapy targets**

- Activating receptors
- Inhibitory receptors
- Total stimulation

**Immuno-oncology development landscape**

- Multiple drug classes across all stages of development
- Multiple trials of novel combinations with immunotherapies

**Accelerating cancer drug development**

- Immunotherapies moving rapidly from lab to clinic
- Thousands of cancer patients treated on global clinical trials

**Example timeline: immune checkpoint inhibitor**

- FDA approvals
  - 2015
  - 2016
  - 2017
  - 2018

* * *
**FDA-approved immune checkpoint inhibitors**

<table>
<thead>
<tr>
<th>Initial US Approval</th>
<th>Agent</th>
<th>Tumor Types</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>ipilimumab (Yervoy)</td>
<td>Melanoma</td>
</tr>
<tr>
<td>2014</td>
<td>pembrolizumab (Keytruda)</td>
<td>Melanoma, Non-small cell lung cancer, Head &amp; neck squamous cell cancer, Classical Hodgkin lymphoma, Urothelial carcinoma, Microsatellite instability-high/mismatch repair deficient cancers</td>
</tr>
<tr>
<td>2014</td>
<td>nivolumab (Opdivo)</td>
<td>Melanoma, Non-small cell lung cancer, Renal cell carcinoma, Head &amp; neck squamous cell cancer, Urothelial carcinoma, Microsatellite instability-high/mismatch repair deficient colorectal cancer</td>
</tr>
<tr>
<td>2017</td>
<td>avelumab (Bavencio)</td>
<td>Merkel cell carcinoma, Urothelial carcinoma, Non-small cell lung cancer, Non-small cell lung cancer, Non-small cell lung cancer</td>
</tr>
</tbody>
</table>

**Tissue agnostic drug approval of immunotherapy**

- 2017 approval of pembrolizumab for microsatellite instability-high/mismatch repair deficient cancers
- First time FDA approved a cancer treatment based on common biomarker rather than the location of tumor

**Immune-mediated adverse events**

- Pseudoprogression and immune-related responses

- Incidence of approximately 4% across solid tumors
- Delayed clinical responses with premature classification as progressive disease by standard RECIST criteria
- Initial increase in tumor lesion size, then decrease in tumor size
- Development of new lesions
- Led to development of novel immune response criteria

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*Lee, et al. NEJM 2017*

*Flaherty, Le, and Lemery, ASCO Educational Book 2017*

*FDA Center for Drug Evaluation and Research, Advancing Health Through Innovation: New Drug Therapy Approvals 2017*
Chimeric Antigen Receptor (CAR) T cell therapies

- Gene modified T cells show promise for cancer therapy
- Products are complex with many subcomponents
- Toxicity remains concerning
- Risk mitigation
  - Risk Evaluation and Mitigation Strategies (REMS)
  - Post-marketing requirement: Long-term follow up studies
- Opportunities for continued scientific investigation

Vatsan, Bross, Liu, Therien, De Haan, Lu, Hehn, Niland, Hasan, and Puri, JCO 2015

FDA-approved CAR T cell therapies

<table>
<thead>
<tr>
<th>Initial U.S. Approval</th>
<th>Chimeric antigen receptor (CAR) T cells</th>
<th>Currently approved indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>Tisagenlecleucel (Kymriah)</td>
<td>• Patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia refractory or in second or later relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy</td>
</tr>
<tr>
<td>2017</td>
<td>Axicabtagene ciloleucel (Yescarta)</td>
<td>• Adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy</td>
</tr>
</tbody>
</table>

Key Takeaways

- FDA actively engages stakeholders for development of cancer treatments such as immune checkpoint blockade and CAR T-cells
- Immunotherapies are an important drug class with potential prolonged responses but often times lower objective response rates
- Immunotherapies are associated with unique adverse event profiles
- Changing landscape of complex oncology drugs and combinations

Brudno and Kochenderfer, Blood 2016
FDA Oncology Resources

- List of recent Hematology/Oncology Approvals
- Medical product labels and other approval information: Drugs@FDA
- Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.) for recent oncology drug approvals
- Oncology Center of Excellence Twitter: @FDAOncology
- Oncology Center of Excellence Website: www.fda.gov/ocel

Acknowledgments

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- Richard Pazdur MD
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- Najat Bouchkouj MD
- Kristin Goldberg
- Ke Liu MD
- Poornima Sharma MD

What are research considerations for new therapies - CAR T-Cell, check point inhibitors, and beyond?

Carlos R. Bachier, MD
Program Director
HCT Program
Sarah Cannon
Agenda

- Overview of components needed for effective management of patients on IEC trials
- Research operation infrastructure
- Nursing considerations
- Site qualification
- Workflow
- Regulatory oversight

DEVELOPMENT OF AN ORGANIZATIONAL STRUCTURE

Committee Goals:
- Ensure safety, consistency and quality for our patients
- Demonstrate network capabilities and competency
- Improve patient outcomes
- Share processes learned and developed practices.

IECT Research Program Meeting
IEC Research Staffing Models

- **Research Roles**
  - **Clinical Research Coordinator** – study/sponsor point of contact, prescreen, facilitator, logistics coordination, more complex data entry, investigator communication, source document organization, staff training.
  - **Data Coordinator** – majority of data entry, query resolution, source clarification.
  - **Treating Investigator** – consenting, eligibility documentation and review, admission and drug orders, daily inpatient visits, AE and Con Med assessments, sponsor communication.

- **Other Roles**
  - **Clinical Nurse** – eligibility documentation and review, admission and drug orders, daily inpatient visits, AE and Con Med assessments.
  - **Laboratory Technician/Phlebotomist** – draw lab kits, process central labs, pack and ship per IATA guidelines.
  - **Pharmacist** – receive study drug (N/A for CAR T), track study drug per research SOPs and protocol.
  - **Apheresis and Cellular Therapy** – product procurement, handling, packaging, shipping, and receiving. Documentation per protocol.

IEC Site Qualification
IECT OPERATIONS TOOLKIT

<table>
<thead>
<tr>
<th>Competencies &amp; Privileges</th>
<th>SOPs &amp; Resource Documents</th>
<th>Education &amp; Training</th>
<th>Finance &amp; Contracting</th>
</tr>
</thead>
<tbody>
<tr>
<td>• RN</td>
<td>• All FACT-required SOPs</td>
<td>• HealthStream IECT Education module</td>
<td>• Vendor Qualifications</td>
</tr>
<tr>
<td>• Apheresis</td>
<td>• Prep for vendor-required SOP management</td>
<td>• Consulting Physician Training slide deck</td>
<td>• Payer/Vendor contracting</td>
</tr>
<tr>
<td>• CTL Tech</td>
<td>• Pre-site selection checklist</td>
<td>• Data Coordinator Training</td>
<td>• Coding &amp; Billing Updates</td>
</tr>
<tr>
<td>• Research RN</td>
<td>• CRS Grading Tool</td>
<td>• Patient Education &amp; Wallet Cards</td>
<td></td>
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<tr>
<td>• Clinical Pharmacist</td>
<td>• Patient Consent form</td>
<td>• Nurse neuro assessment training</td>
<td></td>
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<tr>
<td>• Physician</td>
<td>• CAR T-Cell Readiness checklist</td>
<td>• Mock collection &amp; Infusion case study</td>
<td></td>
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<tr>
<td>• APP</td>
<td>• CARTOX 10 documentation tool</td>
<td></td>
<td></td>
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<tr>
<td>• Physician privileges</td>
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</tbody>
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SCBCN DEVELOPED TWO CAR T-CELL THERAPY NURSING EDUCATION MODULES

• Car T-Cell Therapy: A New Frontier
• CAR T-Cell Therapy: Recognition and Management of Toxicities
• Expert Clinical Advisory panel functioned as consultants & reviewers
• Free CNE hours provided
• Web-based, administered via HealthStream LMS
• Interactive
• Millennial learner-focused
• Designed to be updated as technology advances

ASCO Research Community Forum
2018 Annual Meeting

IEC Budget Considerations

✓ Research Procedures
  • Apheresis (and associated equipment/materials)
  • Product handling (by site/facility personnel)
  • Inpatient observation (as required by protocol)
  • Assessments required by protocol to monitor subject
    • Beyond those that are performed per routine care
✓ Research Personnel
  • Clinical Research Coordinator
  • Data Coordinator
  • Research Nurse
  • Principal Investigator
  • Pharmacist

ASCO Research Community Forum
Annual Meeting
IEC Regulatory Oversight—Foundation for Accreditation of Cellular Therapy (FACT)

Why Standards for Immune Effector Cells?

- FACT-accredited transplant programs
  - Participation in immune effector cell trials
  - Desire to apply FACT requirements to these new services
- Drug manufacturers
  - Investment in controlled, safe clinical trials
  - Need for continued assurance of proper handling and use of products after licensure
- Regulators
  - Responsibility for approving only safe and effective products for licensure
  - Interest in field's ability to handle toxicities
- Payers
  - Anticipation of drug licensure ➔ requests for reimbursement
  - Expectation of good outcomes for covered services

Patient Safety, Outcomes, and Access

Key Takeaways

- Immune Effector Cell Research requires significant resources and oversight similar to phase I trials
- Important aspects for successful management of IEC trials include
  - Development of an organizational structure
  - Staff training and education (both research and non-research related)
  - Research operational capabilities
  - Development of IEC specific budgets
  - Compliance with regulatory oversight (FDA and FACT)
- Clinical trials in IEC are on the rise in numbers and complexity

Discussion
Immunotherapy References

- ASCO Guideline: Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitor Therapy
- List of recent Hematology/Oncology Approvals
- Medical product labels and other approval information: Drugs@FDA
- Oncology Center of Excellence Twitter: @FDAMC
- Oncology Center of Excellence Website: www.fda.gov/ceo
- FAQs for Inspecting Immune Effector Cells
- Inspector Bulletin: Immune Effector Cells
- Immune Effector Cell webpage: publications referencing FACT, Educational recordings
- Standards and Accreditation Manuals: free download; print copies for purchase