THE COMPLEX CHALLENGES OF STRATIFYING PATIENTS FOR IMMUNOTHERAPY

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Chief Scientific Officer
Covance
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Disclosure

Employee of LabCorp/Covance. Will discuss non-approved drugs.
Topics

► Immuno-Oncology Overview
  • Therapeutic Modalities
  • Drug Development Needs
    – Combination Therapies
    – Evolving Trial Design(s)
    – Challenges
  • Importance of Biomarkers

► Biomarkers for Immunotherapy
  • Tissue-based biomarkers
    – PD-L1 Immunohistochemistry Assays
  • Genomic Biomarkers in Immuno-Oncology

► Summary
Multiple approaches to immunotherapy in cancer

- Immune Checkpoint Inhibition
  - PD-1/PD-L1

- Immune System Activators
  - OX-40

- Adoptive T Cell Transfer
  - CAR-T

- Cancer Vaccines

Marcela V. Maus et al. Blood 2014
Approval History for Cancer Immunotherapies

Generation 1
- Ipilimumab (Bristol-Myers Squibb)
- Sipuleucel-T (Dendreon, now Valeant Pharmaceuticals)

Generation 2
- Pembrolizumab (Merck)
- Blinatumomab (Amgen)
- Nivolumab (Bristol-Myers Squibb)
- T-vec (Amgen)

Generation 3
- Atezolizumab (Genentech/Roche)
- CAR-Ts (Novartis)
- Multiple therapies under development
- Durvalumab (AstraZeneca)


[Approved] [Under investigation]
Immuno-Oncology Drug Development

Key Immuno-Oncology Features

Animal and Cell Models
Mechanism of Action
Immuno-toxicology
Trial Experience
Preclinical
Safety
Clinical Monitoring
Investigator Quality
Trial Design & Execution
Competition vs Collaboration
Marketplace
Companion Diagnostics
Biomarkers
Health Economics
Alliance Management
Central Labs & Specialty Labs
Patient Data
Market Access
Current Challenges in Immuno-Oncology Drug Development Area

- Highly competitive landscape
  - Number of companies, approaches and molecules in development
- Availability of appropriate patients
  - Increasing number of trials, with demand for specific enrollment
- Which biomarker(s) should be considered
  - Appropriate Cell, Tissue, Genomic biomarkers
  - Consideration for use as companion or complementary diagnostic
- Incorporation of appropriate trial design and execution strategy
The Evolution of Oncology Clinical Trial Design

<table>
<thead>
<tr>
<th>Cytotoxic</th>
<th>Targeted</th>
<th>Immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td><strong>3 + 3 dose-escalation design</strong></td>
<td><strong>3 + 3 dose-escalation design with large expansion cohorts in selected populations</strong></td>
</tr>
<tr>
<td></td>
<td>Escalation</td>
<td>Escalation</td>
</tr>
<tr>
<td></td>
<td>Expansion</td>
<td>Expansion</td>
</tr>
<tr>
<td><strong>Drug approval</strong></td>
<td>Based on later phase 2 or 3 trials</td>
<td>Conditional of accelerated approval based on large molecularly selected expansion cohorts</td>
</tr>
<tr>
<td></td>
<td>P1</td>
<td>P1</td>
</tr>
<tr>
<td></td>
<td>P2</td>
<td><strong>Approval</strong></td>
</tr>
<tr>
<td></td>
<td>P3</td>
<td><strong>Approval</strong></td>
</tr>
<tr>
<td><strong>Drug development timeframe</strong></td>
<td>10 years</td>
<td>5-8 years</td>
</tr>
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</table>

Trial Design Considerations

• Success of targeted cancer therapies and immunotherapy
  • Focus on speed and efficiency of study/trial execution
• Trial design considerations
  • Platform trials
  • Umbrella or Basket trials
  • Rapid cohort expansions
• Considerations around breakthrough status and accelerated approval pathway
• Appropriate tools to assess of efficacy and toxicity
Checkpoint Inhibitors

- Multiple cellular receptors and molecules activate and/or inhibit the immune system.
- Agents that overcome the checkpoint inhibition reactivate the immune system against tumors.
- There are four approved drugs addressing checkpoint inhibition for melanoma, bladder cancer, renal cell cancers, head and neck cancers, cHL and NSCLC.

http://www.emdgroup.com/emd/innovation/research_activities/research_activities.html#1
PD-1/PD-L1 the Current Backbone for Immuno-Oncology

Co-stimulatory mAbs targeting:
- CD137
- OX40
- CD40
- GITR

Conventional agents inducing immunogenic cell death:
- Chemotherapy
- Radiotherapy
- Anti-angiogenics
- Targeted therapies

Other checkpoint inhibitory molecules:
- CTLA4
- LAG3
- TIM3
- BTLA
- TIGIT

Cancer vaccines considering individual neoantigens

Function modification of immunosuppressive enzymes such as:
- IDO1
- iNOS

Personalized Combinations Guided by Biomarkers

Treg cell targeting of inhibition

Adoptive cell therapy

Myeloid cell modulation

PD1 or PDL1 blockade
Complex Trial Design and Combination Therapy

Events and Milestones
- • Study assessments
  • Toxicity assessment
  • Toxicity management
  • Data entry
- • PD-L1 IHC based on fresh biopsy
- • Tumor assessment
  • 5 day window until randomization
  • Investigator assessment of response
- • Tumor size change < 20%
  - Continue checkpoint inhibitor
- • Tumor size change ≥ 20%
  - RANDOMIZE
    - Tumor size change < 20%
      - RANDOMIZE
        - Tumor size change ≥ 20%
          - Continue checkpoint inhibitor
- Vendor performance
- Site compliance
- Sample quality
- Sample tracking

Study Risks
- • Study compliance
  • Impact of site experience on:
    • Toxicity management
    • Treatment duration
- PD-L1 +
- Checkpoint inhibitor
- 8 week treatment cycle
- 8-week tumor assessment

Complex Trial Design and Combination Therapy
- Tumor type A, B, C, …, Z
- Indication, 1, 2, 3, …, N

- RANDOMIZE
  - Checkpoint inhibitor
  - Checkpoint inh + Combo partner A
  - Checkpoint inh + Combo partner B
  - Checkpoint inh + Combo partner C
  - Checkpoint inh + Combo partner D

Next iteration
- RANDOMIZE
  - Checkpoint inhibitor
  - Checkpoint inh + Combo partner C
  - Checkpoint inh + Combo partner D
Clinical Trials Involving PD-1/PD-L1 Based Immuno-Therapies
PD-L1 Biomarker Utilization

PD-L1 Testing Results by PD-L1 IHC Ab Clone
Biomarker Approaches for Immuno-Oncology

A wide variety of biomarkers have been associated with immune responsiveness and therefore a variety of platforms and assays are needed in the assessment and potential prediction of patient response to specific therapies.
Biomarker Assays in Immuno-Oncology

- **Cell Based Assays**
  - **Immuno-Assays**
    - Pro-inflammatory, cytokine and chemokine assays
  - **Flow Cytometry and Cell-Based assays**
    - NK cell activation, T-cell proliferation, intracellular signaling/phosphorylation, complement activation
    - Receptor occupancy, intracellular signaling

- **Tissue Based Assays**
  - Anatomic Pathology Immunohistochemistry
    - PD-1, TICs

- **Genomics Assays**
  - Mutational Burden, Neo-Antigens
  - Immune Response Gene Expression Profiling
  - Microsatellite Instability

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**Chemokine Panel**

- IL-8 (HA)
- Eotaxin-3
- IP-10
- MCP-1
- MCP-4
- MDC
- MIP-1β
- MIP-1α
- TARC

**ECL Signal**

- Conc [pg/mL]

**PD-1 Expression**

- [Viable CD45+]
- FL6 INT / FL3 INT

- B cells
- T cells

- CD45R-FL3
- CD3-APC
PD-L1 Expression and Response Rates

**PD-L1 Expression in NSCLC**

**Companion Diagnostic** and/or **Complementary Diagnostic** assays are in use providing clinical decision making information

**Level of PD-L1 expression-correlation with response**

Garon et al, NEJM 2015
### Summary of PD-L1 Assays

<table>
<thead>
<tr>
<th>Drug Developer</th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
<th>Durvalumab</th>
<th>Atezolizumab</th>
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<tbody>
<tr>
<td>MAb</td>
<td>Humanized IgG4</td>
<td>Humanized IgG4</td>
<td>Human Fc-modified IgG1</td>
<td>Human Fc-modified IgG1</td>
</tr>
<tr>
<td>Target</td>
<td>PD-1</td>
<td>PD-1</td>
<td>PD-L1</td>
<td>PD-L1</td>
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<tr>
<td>Approved Indications</td>
<td>Melanoma, NSCLC, HNSCC</td>
<td>Melanoma, NSCLC, RCC, cHL, H&amp;N</td>
<td>NA</td>
<td>Bladder and NSCLC</td>
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<tr>
<td>IHC Developer</td>
<td>Dako</td>
<td>Dako</td>
<td>Ventana</td>
<td>Ventana</td>
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<tr>
<td>AB Clone</td>
<td>22C3, mouse</td>
<td>28-8, rabbit</td>
<td>SP263, rabbit</td>
<td>SP142, rabbit</td>
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<tr>
<td>Expression</td>
<td>Tumor Cells (membrane) and Stroma</td>
<td>Tumor Cells (membrane)</td>
<td>Tumor Cells (membrane)</td>
<td>Tumor Cells, TICs</td>
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<tr>
<td>Scoring Cut-Off</td>
<td>≥1%, &gt;50% TCs in NSCLC</td>
<td>≥1% TCs in Melanoma and NSCLC</td>
<td>25% in NSCLC, SCCH&amp;N</td>
<td>Intensity (2+, 3+) and % in TCs and TICs</td>
</tr>
</tbody>
</table>

Adapted from, Hansen and Siu, JAMA Oncology 2016
Genomic Assays

- Mutational Analysis
  - Mutational Burden
  - Production of Neo-Antigens
  - Resistance Pathways
  - Genomic Instability
    - Microsatellite instability as a predictor of response to immuno-oncology therapies

- T-Cell Repertoire Analysis
  - T-cell Receptor (TCR) diversity and response to immuno-oncology therapy

- Gene Expression Profiling
  - Immune Function/Responsiveness Genes

- Monitoring Response
  - Role of liquid biopsy technologies
Mutational Burden in Cancers

Alexandrov et al., Nature 2013
Mutational Load and Neoantigens and Response to Ipilimumab

Snyder et al NEJM 2014
Microsatellite Instability (MSI) Status

POTENTIAL RESPONSE TO CHECKPOINT INHIBITION

<table>
<thead>
<tr>
<th>CANCER</th>
<th>% MSI +</th>
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<tbody>
<tr>
<td>Endometrial</td>
<td>22-33</td>
</tr>
<tr>
<td>Colon</td>
<td>~20</td>
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<tr>
<td>Cervical</td>
<td>8</td>
</tr>
<tr>
<td>Esophageal</td>
<td>7</td>
</tr>
<tr>
<td>Skin</td>
<td>0-2</td>
</tr>
<tr>
<td>Breast</td>
<td>0-2</td>
</tr>
</tbody>
</table>

Jonathan C. Dudley et al. CCR 2016;22:813-820
MMR and Response to Checkpoint Inhibition

RADIOGRAPHIC RESPONSE

Le et al, NEJM 2015
# MSI as a Tumor Agnostic Biomarker

<table>
<thead>
<tr>
<th>Study</th>
<th>Design and Patient Population</th>
<th>Number of patients</th>
<th>MSI-H/dMMR testing</th>
<th>Dose</th>
<th>Prior therapy</th>
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</thead>
<tbody>
<tr>
<td>KEYNOTE-016</td>
<td>prospective, investigator-initiated</td>
<td>28 CRC</td>
<td>local PCR or IHC</td>
<td>10 mg/kg every 2 weeks</td>
<td>CRC: ≥ 2 prior regimens, Non-CRC: ≥1 prior regimen</td>
</tr>
<tr>
<td>NCT01876511</td>
<td>6 sites</td>
<td>30 non-CRC</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>KEYNOTE-164</td>
<td>prospective international multicenter</td>
<td>61</td>
<td>local PCR or IHC</td>
<td>200 mg every 3 weeks</td>
<td>Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb</td>
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<tr>
<td>NCT02460198</td>
<td>CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>KEYNOTE-012</td>
<td>retrospectively identified patients with PD-L1-positive</td>
<td>6</td>
<td>central PCR</td>
<td>10 mg/kg every 2 weeks</td>
<td>≥1 prior regimen</td>
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<tr>
<td>NCT01848834</td>
<td>gastric, bladder, or triple-negative breast cancer</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>KEYNOTE-028</td>
<td>retrospectively identified patients with PD-L1-positive</td>
<td>5</td>
<td>central PCR</td>
<td>10 mg/kg every 2 weeks</td>
<td>≥1 prior regimen</td>
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<tr>
<td>NCT02054806</td>
<td>esophageal, biliary, breast, endometrial, or CRC</td>
<td></td>
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<tr>
<td>KEYNOTE-158</td>
<td>prospective international multicenter enrollment of</td>
<td>19</td>
<td>local PCR or IHC</td>
<td>200 mg every 3 weeks</td>
<td>≥1 prior regimen</td>
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<tr>
<td>NCT02628067</td>
<td>patients with MSI-H/dMMR non-CRC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>retrospectively identified patients who were enrolled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>in specific rare tumor non-CRC cohorts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>149</td>
<td></td>
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</tr>
</tbody>
</table>

CRC = colorectal cancer  
PCR = polymerase chain reaction  
IHC = immunohistochemistry
Pan-Cancer Immune Profiling Panel
Liquid Biopsy for Treatment Monitoring

CASE STUDY

- 74 year-old male diagnosed with Squamous Cell Carcinoma of skin to Lymph Node
- Treatment: Pembrolizumab
- Patient showed widespread genome instability at baseline
- cfDNA data show loss of genomic stability over time
- Confirmed that the patient was showing a clinical response

Ikeda et al, Genomic Medicine, 2016
Acquired Resistance to Immunotherapy

- Genomic alterations associated with acquired resistance to checkpoint inhibitors in melanoma
  - Interferon-receptor-associated Janus Kinase (Jak1 and Jak2)
  - β-2-microglobulin

- Genomic alterations in the neoantigen landscape in NSCLC and H&N cancers
  - Deletions of chromosomal regions containing the alterations

Zartesky et al, NEJM 2016
Anagonostou et al, Cancer Discovery, 2017
Potential Approach for Immunotherapy

Dijkstra et al JAMA Oncology 2016


Summary

Immuno-Oncology trials require experience and expertise across all phases of drug development

A variety of potential biomarker assays relevant for assessment of efficacy of immuno-oncology therapies

- Cell, Tissue, Genomics biomarker assays

PD-L1 expression associated with response in some tumor types

- Companion and Complimentary diagnostic assays for NSCLC and melanoma
- Different PD-L1 assays in development and/or use
  - Different MAbs, assay platforms, scoring criteria and cut-offs, utility for different indications
  - Harmonization of assay formats needed to address analytical performance variability
  - Current situation presents a variety of challenges for development and commercialization

Genomic Biomarkers of Response and Potential Resistance