Immuno-Oncology Drug Development Workshop

October 13 & 14, 2016

Hyatt Regency on Capitol Hill

Washington, DC
Day 2 Introduction

Suzanne Topalian, MD
Workshop Co-Chair
Regulatory Pathways for Approval
Considerations for Alternate Endpoints

Maitreyee Hazarika, M.D.
Office of Hematology and Oncology Products, Office of New Drugs, Center for Drug Evaluation and Research, FDA

FDA-AACR Immuno-Oncology Drug Development Workshop
October 13-14, 2016
Disclosures

• No financial relationships to disclose

• Will not discuss off-label use of approved products
Requirements for FDA Approval

• Substantial evidence of effectiveness in adequate and well-controlled studies with acceptable safety

• FDA examines evidence in context of the disease, line of therapy, available therapy, study design, endpoints, and magnitude of evidence

• Ability to generate product labeling that:
  – Defines appropriate patient population for whom the drug is indicated
  – Provides adequate information to enable safe and effective use

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Regulatory Pathways for Approval

• Regular Approval
  – Approval based on demonstration of direct clinical benefit or effect on an established surrogate

• Accelerated Approval
  – Intent to treat serious or life-threatening illnesses
  – Approval based on a surrogate or intermediate endpoint reasonably likely to predict clinical benefit
  – Provides meaningful therapeutic benefit over available therapy
  – Requires confirmatory clinical studies to verify and/or describe actual clinical benefit
FDA Expedited Programs: Goals

• Address an unmet medical need in the treatment of a serious or life-threatening condition

• Facilitate and expedite development and review of promising new drugs

• Ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies’ benefits justify their risks

• Allow for earlier attention to investigational agents that have promise in treating such conditions, including earlier consultation with FDA
FDA Expedited Programs

- **Fast Track**
- **Breakthrough Therapy**
- **Priority Review**
- **Accelerated Approval**

### Phases:

- **Non-Clinical**
  - IND Submission
- **Early Clinical**
  - Dose Exploration / Preliminary Activity
- **Registration Trial(s)**
  - SPA*
  - Efficacy and Safety Data
- **NDA/BLA Submission**
  - FDA Review

*Special Protocol Assessment

*Slide from Paul Kluetz, MD*
Codevelopment of Two or More Investigational Drugs

- Combination intended to treat a serious disease or condition
- Compelling biological rationale for use of combination
- Contribution of individual agents to the treatment effect of the agents used in combination
- Safety evaluation for potential increased risks
- Early and frequent interaction with FDA to facilitate development
Considerations of Endpoints Supporting Past Approvals

Overall Survival (OS)

– Direct evidence of clinical benefit
– Randomized controlled studies
– Superiority or non-inferiority
– Larger studies
– Long follow-up
– May be confounded by cross-over and subsequent therapy
Tumor-assessment Endpoints

Objective Response Rate (ORR), Progression-free Survival (PFS), Disease-free Survival, Relapse-Free Survival, Time to Tumor Progression*

- Surrogate for clinical benefit
  - Accelerated or regular approval depends on magnitude of effect, effect duration, disease setting, and risk-benefit to available therapy
- Adjuvant setting after definitive surgery or radiotherapy
- Single-arm or randomized controlled studies
- Smaller sample size
- Blinded external review (or audit)
- Clinical significance: benefit vs. risk

* Based on RECIST criteria

www.fda.gov
Endpoints Based on Symptom Assessment

Patient Reported Outcomes (PRO)

- Quality of life, physical functioning, tumor related symptoms, and symptomatic adverse events
- Patient perspective of direct clinical benefit
- Randomized blinded studies
- Fit for purpose tool for measurement
- Missing or incomplete data
- Interpretation: clinical significance of small changes
Approval of an Application

• 21 CFR 314.105(c)

FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the statutory standards for safety and effectiveness.

• FDA applies flexibility regarding the evidence required to support approval to address particular challenges posed by each disease.
Innovative Endpoints

• Pathologic complete response
  – pertuzumab in neoadjuvant breast cancer

• Spleen volume reduction and patient reported outcomes (total symptom score)
  – ruxolitinib in myelofibrosis

• Red blood cell transfusion independence
  – lenalidomide in MDS

• Major cytogenetic / hematologic response
  – imatinib, nilotinib in CML
Melanoma

- **Ipilimumab (anti-CTLA4) vs. gp100**
  - ORR: 10.9% vs. 1.5%; median duration of response not reached in either arm
  - OS: HR 0.66 (95% CI: 0.51, 0.87); median OS 10 vs. 6 months

Ipilimumab Kaplan-Meier (K-M) curves for OS
Melanoma

- Targeted (BRAF inhibitor or BRAF+MEK inhibitor) therapy

Vemurafenib K-M OS

Dabrafenib K-M PFS

Dabrafenib + Trametinib K-M OS

(Vemurafenib USPI)

(Dabrafenib USPI)

(Dabrafenib USPI)
Melanoma

- Nivolumab and pembrolizumab (anti-PD1) K-M curves for PFS
Immuno-oncology Drugs Considerations

- Low ORR with prolonged duration of response
- Small differences in median PFS
- Delayed separation of PFS and OS K-M curves
- Median OS may obscure long-term benefits in minority of patients
- Late plateau of survival curves likely represent long-term responders who remain progression free for years
Immuno-oncology Study Design Challenges

- Measures of clinical benefit with innovative endpoints
- Identify surrogate endpoints for OS
- Characterize clinical benefit with alternate analyses
- Improve on the tail of the survival curves
- Expedite approval: enrichment designs, reduced sample size with biomarkers, adaptive trials
Acknowledgements

- Marc Theoret, MD
- Paul Kluetz, MD
- Patricia Keegan, MD
- Amy McKee, MD
- Kirsten Goldberg, MA
- Richard Pazdur, MD
References & Resources

- Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. 2007
- Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination. 2013
Challenges in Interpreting Results Based on Traditional Endpoints

Rajeshwari Sridhara, Ph.D.
Director, Division of Biometrics V

FDA-AACR Immuno-oncology Workshop 2016
Disclosures

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• This presentation reflects the views of the author and should not be construed to represent FDA’s views or policies
Traditional Endpoints

• Objective Response Rate based on RECIST criteria
• Progression-Free Survival – Time from randomization to disease progression (based on RECIST criteria) or death whichever occurs first
• Overall survival – Time from randomization to death
• Patient reported outcome (PRO) – improvement or time to deterioration
Effect of Therapeutic Interventions

Cytotoxic/targeted therapy → Tumor Response → Overall Survival

Beneficial or Harmful Effects
Not Measured by Tumor Size Changes
Effect of Immuno-oncology Product

Immuno-therapy → Immune Response → Tumor Response → Overall Survival

Beneficial or Harmful Effects
Not Measured by Tumor Size Changes
Effect of Immuno-oncology Product

Immuno-therapy → Immune Response → Tumor Response → Overall Survival

Beneficial or Harmful Effects
Not Measured by Tumor Size Changes

Other Biomarkers?
Regulatory Considerations

• “…Evidence consisting of adequate and well-controlled investigations, including clinical investigations, by qualified scientific experts, that proves the drug will have the effect claimed by its labeling…” (Section 505(d) FD&C Act of 1962 as amended)

• Single study – consistency among different endpoints
Trial Design

• Single arm trials (analysis) – patient population generally more refractory; difficult to attribute safety concerns. Long-term safety unknown as survival is generally short; Approval pathway – accelerated generally based on ORR

• Randomized clinical trials – Optimal dose? optimal length of follow-up (based on interim results)?; optimal length of treatment – treat till disease progression? Approval pathway – can be accelerated or regular
## Approved Products – Advanced Melanoma

<table>
<thead>
<tr>
<th>Product</th>
<th>ORR</th>
<th>PFS HR</th>
<th>OS HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipi+gp100 vs. gp100</td>
<td>5.7% vs. 1.5%</td>
<td>0.81</td>
<td>0.68</td>
</tr>
<tr>
<td>Pembro</td>
<td>24%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pembro vs. Ipi</td>
<td>34% vs. 12%</td>
<td>0.58</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>33% vs. 12%</td>
<td>0.58</td>
<td>0.69</td>
</tr>
<tr>
<td>Pembro vs. Chemo</td>
<td>21% vs. 4%</td>
<td>0.57</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>25% vs. 4%</td>
<td>0.50</td>
<td>-</td>
</tr>
<tr>
<td>Nivo</td>
<td>32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivo+Ipi</td>
<td>60% vs. 11%</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Nivo+Ipi , Nivo vs. Ipi</td>
<td>50% vs. 14%</td>
<td>0.42</td>
<td></td>
</tr>
<tr>
<td></td>
<td>40% vs. 14%</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Nivo vs. Dacarb</td>
<td>34% vs. 9%</td>
<td>0.43</td>
<td>0.42</td>
</tr>
</tbody>
</table>
## Approved Products – Advanced NSCLC

<table>
<thead>
<tr>
<th>Product</th>
<th>ORR</th>
<th>PFS HR</th>
<th>OS HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivo</td>
<td>15%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nivo vs. docetaxel (Sqam)</td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>Nivo vs. docetaxel (non-squam)</td>
<td>19% vs. 12%</td>
<td>0.92</td>
<td>0.73</td>
</tr>
<tr>
<td>Pembro (PDL1&gt;50%)</td>
<td>41%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Approved Products in Other Diseases

Renal Cell Carcinoma
• Nivo vs. Everolimus: ORR 21.5% vs. 3.9%; OS HR = 0.73

Classical Hodgkin Lymphoma
• Nivo: ORR 65%

Head and Neck Cancer
• Pembro: ORR 16%

Urothelial Carcinoma
• Atezo: 14.8%; (PD-L1 < 5% : 9.5%, PD-L1 > 5% : 26%)

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Endpoints

• Metastatic melanoma
  – Ipi – OS ↑, ORR ↑ and PFS (non-proportionality)
  – Pembro - OS ↑, ORR ↑ and PFS (non-proportionality)
  – Nivo - OS ↑, ORR ↑ and PFS (non-proportionality)

• Metastatic NSCLC
  – Pembro - ORR possibly ↑
  – Nivo - OS ↑, ORR ↑ and PFS non-proportionality

• Metastatic RCC
  – Nivo - OS ↑, ORR ↑ and PFS non-proportionality

• PRO disease dependent and has not been evaluated rigorously.
  No long term experience with IM products
Association Between ORR, PFS and OS

Individual level association

• Patient-level responder analysis performed to compare PFS and OS between responders and non-responders, irrespective of treatment assignment using the pooled dataset of anti PD-1 products
  – Hazard ratios of PFS and OS estimated from Cox model stratified by study
  – Kaplan-Meier estimates of PFS and OS by response status

• Spearman rank correlation for PFS vs. OS
Association between ORR, PFS and OS

Trial level association

• Treatment effect estimates
  – ORR: odds ratio from logistic regression model
  – PFS: hazard ratio (HR) from Cox regression model
  – OS: HR from Cox regression model

• Weighted linear regression model performed on original and also log-transformed effects
  – weights equal to number of patients
  – $R_{trial}^2$ used to quantify the proportion of variance explained by the regression
## Results (Mushti, ASA Biopharm workshop 2016)

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Endpoint</th>
<th>Secondary endpoint</th>
<th>N</th>
<th>OS HR</th>
<th>PFS HR</th>
<th>ORR Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study-1</td>
<td>PFS (IRC), OS</td>
<td>ORR (IRC)</td>
<td>359</td>
<td>0.898</td>
<td>0.595</td>
<td>5.4190</td>
</tr>
<tr>
<td>Study-2</td>
<td>PFS (IRC), OS</td>
<td>ORR (IRC)</td>
<td>360</td>
<td>0.815</td>
<td>0.529</td>
<td>7.2833</td>
</tr>
<tr>
<td>Study-3</td>
<td>OS, PFS (IRC)</td>
<td>ORR (IRC)</td>
<td>557</td>
<td>0.618</td>
<td>0.551</td>
<td>3.3367</td>
</tr>
<tr>
<td>Study-4</td>
<td>OS, PFS (IRC)</td>
<td>ORR (IRC)</td>
<td>555</td>
<td>0.563</td>
<td>0.582</td>
<td>3.1270</td>
</tr>
<tr>
<td>Study-5</td>
<td>OS, PFS (IRC)</td>
<td>ORR (IRC)</td>
<td>687</td>
<td>0.732</td>
<td>0.869</td>
<td>1.6951</td>
</tr>
<tr>
<td>Study-6</td>
<td>OS, PFS (IRC)</td>
<td>ORR (IRC)</td>
<td>689</td>
<td>0.631</td>
<td>0.788</td>
<td>1.6940</td>
</tr>
<tr>
<td>Study-7</td>
<td>PFS (IRC)</td>
<td>OS, ORR (IRC)</td>
<td>305</td>
<td>0.614</td>
<td>0.499</td>
<td>2.0320</td>
</tr>
<tr>
<td>Study-8</td>
<td>OS</td>
<td>ORR, PFS (INV)</td>
<td>272</td>
<td>0.590</td>
<td>0.630</td>
<td>2.6042</td>
</tr>
<tr>
<td>Study-9</td>
<td>OS</td>
<td>ORR, PFS (INV)</td>
<td>821</td>
<td>0.758</td>
<td>0.873</td>
<td>5.9323</td>
</tr>
<tr>
<td>Study-10</td>
<td>ORR (IRC), OS</td>
<td>PFS (IRC)</td>
<td>182</td>
<td>0.864</td>
<td>0.736</td>
<td>4.9762</td>
</tr>
<tr>
<td>Study-11</td>
<td>OS</td>
<td>ORR, PFS(INV)</td>
<td>582</td>
<td>0.750</td>
<td>0.909</td>
<td>1.6742</td>
</tr>
<tr>
<td>Study-12</td>
<td>OS</td>
<td>ORR INV, PFS (INV)</td>
<td>418</td>
<td>0.418</td>
<td>0.432</td>
<td>4.1149</td>
</tr>
<tr>
<td>Study-13</td>
<td>PFS(INV), OS</td>
<td>ORR (INV)</td>
<td>631</td>
<td>0.708</td>
<td>0.572</td>
<td>3.2949</td>
</tr>
<tr>
<td>Study-14</td>
<td>PFS(INV), OS</td>
<td>ORR (INV)</td>
<td>629</td>
<td>0.702</td>
<td>0.432</td>
<td>5.7838</td>
</tr>
<tr>
<td>Study-15</td>
<td>ORR (INV)</td>
<td>PFS (INV)</td>
<td>142</td>
<td>0.792</td>
<td>0.396</td>
<td>13.5655</td>
</tr>
<tr>
<td>Study-16</td>
<td>OS</td>
<td>PFS (INV), ORR (INV)</td>
<td>361</td>
<td>0.691</td>
<td>0.882</td>
<td>2.5055</td>
</tr>
</tbody>
</table>

www.fda.gov
Trial-level association results: PFS vs. OS

# Trials: 12
# Patients: 6435

\[ R_{trial}^2 = 0.1141 \]

\[ R_{trial}^2 (\text{log – transformed}) = 0.1395 \]

Mushti, ASA Biopharm workshop 2016
Trial-level association results:

**ORR vs. OS**

\[ R^2_{\text{trial}} = 0.131 \]

\[ R^2_{\text{trial}} \text{ (excluding outlier)} = 0.2357 \]

Mushti, ASA Biopharm workshop 2016
Patient-level Responder analysis results for OS

- Responders were associated with better OS compared with non-responders (HR= 0.129, 95% CI: 0.11, 0.15)

Response rates:
- Treatment group: 32%
- Control: 12.7%

Mushti, ASA Biopharm workshop 2016
Patient-level Responder analysis results for PFS

- Responders were associated with better PFS compared with non-responders (HR= 0.118, 95% CI: 0.11, 0.13)

Response rates:
- Treatment group: 32%
- Control: 12.7%

Mushti, ASA Biopharm workshop 2016
Nivolumab 2\textsuperscript{nd} line non squamous mNSCLC: PFS analysis – \textit{Pseudo Progression}?

![Graph showing PFS analysis for Nivolumab and Docetaxel treatments.](graph.png)
Examples of Non-proportionality: Nivolumab, CA209067 Trial - PFS
Examples of Non-proportionality: Pembrolizumab, P002 Trial – PFS
Biomarker

- PD-L1 expression > 50% restricted indication - Pembro for NSCLC with companion diagnostic
- PD-L1 expression 1%, 5%, 10%? Nivo for non-squamous NSCLC—indication not restricted, complementary diagnostic
- PD-L1 expression >1%? Nivo for metastatic melanoma – indication not restricted, complementary diagnostic
- No standard assay or threshold
- Other biomarkers?
- **Unanswered:** Is there a subgroup of patients who contribute to the plateau at the end of the survival curve
Challenges

• Going forward: what should be the primary endpoint?
  – PFS – is the RECIST progression criteria accurate for IO products; in most cases proportional hazard assumption does not hold – alternate analysis methods needed to accurately summarize the late separation of curves
  – ORR inconsistent
  – What other intermediate endpoints can be used?

• Length of follow-up
  – Toxicities different from chemotherapy
  – Beyond treatment follow-up

• Future trial designs in combination with another IO product or with other targeted and cytotoxic therapies? Endpoint, Toxicity, follow-up, length of treatment?
Summary

• Current knowledge is limited
• Need for exploration of intermediate endpoints other than ORR and PFS
• Need for standardization in biomarker measurement assays
• Identification of potential subgroup with long-term benefit
• Alternative ways in which data can be summarized – address non-proportionality
• Critical consideration on duration of treatment and length of follow-up necessary
• Innovative trial designs including master protocols, enrichment and adaptive designs could be considered, if network infrastructure and resources are available to implement such designs
Session IIIa
Endpoints for I-O Products: Considerations for Unique Efficacy Based on Unique Biology of Checkpoint Inhibitors

Moderator: Renzo Canetta, MD

Speakers:
Lawrence Schwartz, MD
Sumithra Mandrekar, PhD
Axel Hoos, PhD
Nicholas Latimer, PhD
FDA-AACR Immuno-Oncology Drug development Workshop

Traditional Endpoints
Introduction: An Historical Perspective

Renzo Canetta, MD
Washington, DC, October 13-14, 2016
Conflict of Interest

- I have been employed for a long time by Bristol-Myers Squibb (BMY).

- As such, I hold stocks in BMY and in two of its spin-off companies:
  - Mead Johnson Nutritionals (MJN)
  - Zimmer Biomet Holdings (ZBH)
US Approved Immunologic and Immuno-Oncologic Agents

The Last Century

1986: BCG live
1986: interferon a2A
1989: interferon a2B
1992: aldesleukin

This Century

2010: sipuleucel-T
2011: ipilimumab
2014: pembrolizumab
2014: nivolumab
2015: atezolizumab
2016: talimogene

1986: BCG live
1986: interferon a2A
1989: interferon a2B
1992: aldesleukin
2010: sipuleucel-T
2011: ipilimumab
2014: pembrolizumab
2014: nivolumab
2015: atezolizumab
2016: talimogene
## Durable Objective Response Rate Approvals

<table>
<thead>
<tr>
<th>YEAR</th>
<th>COMPOUND</th>
<th>INDICATION</th>
<th>CR+PR %</th>
<th>DURATION (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>interferon a2A</td>
<td>hairy cell leukemia</td>
<td>61</td>
<td>NA</td>
</tr>
<tr>
<td>1988</td>
<td>interferon a2A</td>
<td>HIV+ Kaposi’s sarcoma</td>
<td>7-45</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>interferon a2B</td>
<td>HIV+ Kaposi’s sarcoma</td>
<td>30</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>BCG live</td>
<td>bladder (in situ)</td>
<td>76</td>
<td>48 mos.</td>
</tr>
<tr>
<td>1992</td>
<td>aldesleukin</td>
<td>renal cell</td>
<td>15</td>
<td>54 mos.</td>
</tr>
<tr>
<td>1998</td>
<td>&quot;</td>
<td>melanoma</td>
<td>16</td>
<td>9 mos. #</td>
</tr>
<tr>
<td>2014</td>
<td>pembrolizumab</td>
<td>melanoma (2L) **</td>
<td>24</td>
<td>median n.r.</td>
</tr>
<tr>
<td></td>
<td>nivolumab</td>
<td>melanoma (2L) **</td>
<td>32</td>
<td>87% &gt; 6 mos.</td>
</tr>
<tr>
<td>2015</td>
<td>pembrolizumab</td>
<td>lung nsc PD-L1+ *</td>
<td>41</td>
<td>84% &gt; 6 mos.</td>
</tr>
<tr>
<td></td>
<td>ipi+nivo combo</td>
<td>melanoma (1L) *</td>
<td>60</td>
<td>79% &gt; 6 mos.</td>
</tr>
<tr>
<td></td>
<td>talimogene</td>
<td>local melanoma</td>
<td>16</td>
<td>100% &gt; 6 mos.</td>
</tr>
<tr>
<td>2016</td>
<td>pembrolizumab</td>
<td>head &amp; neck *</td>
<td>16</td>
<td>82% &gt; 6 mos.</td>
</tr>
<tr>
<td></td>
<td>nivolumab</td>
<td>Hodgkin’s disease *</td>
<td>65</td>
<td>8.7 mos.</td>
</tr>
<tr>
<td></td>
<td>atezolizumab</td>
<td>bladder *</td>
<td>15</td>
<td>12.7 mos.</td>
</tr>
</tbody>
</table>

* Accelerated approval  ** Accelerated approval converted to full approval later  
#  59+ months for CRs
# Progression-Free (PFS) and Disease-Free (DFS) Survival Approvals

<table>
<thead>
<tr>
<th>YEAR</th>
<th>COMPOUND</th>
<th>INDICATION</th>
<th>RESULTS (median,months)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986</td>
<td>interferon a2B</td>
<td>hairy cell leukemia</td>
<td>DFS = n.r. vs 6.8</td>
<td>NA</td>
</tr>
<tr>
<td>1989</td>
<td>BCG live</td>
<td>bladder (Ta/T1)</td>
<td>2-yr DFS = 57% vs 45%</td>
<td>NA</td>
</tr>
<tr>
<td>1995</td>
<td>interferon a2B</td>
<td>adj.melanoma</td>
<td>DFS = 20.5 vs 11.8</td>
<td>NA</td>
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<tr>
<td>1997</td>
<td>interferon a2B</td>
<td>follicular NHL</td>
<td>PFS = 34.8 vs 18</td>
<td>NA</td>
</tr>
<tr>
<td>2015</td>
<td>ipilimumab</td>
<td>adj.melanoma</td>
<td>DFS = 26 vs 17</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>pembrolizumab</td>
<td>melanoma (2L)</td>
<td>PFS = 2.9 vs 2.7</td>
<td>0.57/0.50</td>
</tr>
<tr>
<td></td>
<td>nivolumab</td>
<td>melanoma BRAF+ (1L)*</td>
<td>PFS = 6.9 vs 2.9</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>ipi+nivo combo</td>
<td>melanoma (1L)*</td>
<td>PFS = 11.5 vs 2.9</td>
<td>0.42</td>
</tr>
</tbody>
</table>

* Accelerated approval
# Overall Survival (OS) Approvals

<table>
<thead>
<tr>
<th>YEAR</th>
<th>COMPOUND</th>
<th>INDICATION</th>
<th>RESULTS (median, months)</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>interferon a2A</td>
<td>CML (Phila+)</td>
<td>69 vs 55</td>
<td>NA</td>
</tr>
<tr>
<td>2010</td>
<td>sipuleucel-T</td>
<td>prostate</td>
<td>25.8 vs 21.7</td>
<td>0.775</td>
</tr>
<tr>
<td>2011</td>
<td>ipilimumab</td>
<td>melanoma</td>
<td>10 vs 6</td>
<td>0.66</td>
</tr>
<tr>
<td>2015</td>
<td>pembrolizumab</td>
<td>melanoma (1L)</td>
<td>n.r. vs n.r.</td>
<td>0.69-0.63</td>
</tr>
<tr>
<td></td>
<td>nivolumab</td>
<td>melanoma BRAF- (1L)</td>
<td>n.r. vs 10.8</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>“</td>
<td>lung squamous</td>
<td>9.2 vs 6.0</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>“</td>
<td>lung non-squamous</td>
<td>12.2 vs 9.4</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>“</td>
<td>renal cell</td>
<td>25.0 vs 19.6</td>
<td>0.73</td>
</tr>
</tbody>
</table>
# Traditional Endpoints Concordance (or not) for Compounds Approved on OS

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>INDICATION</th>
<th>PFS (median, months)</th>
<th>CR+PR (%)</th>
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</thead>
<tbody>
<tr>
<td>interferon a2A</td>
<td>CML (Phila+)</td>
<td>69 vs 46 (HR NA)</td>
<td>60 vs 70</td>
</tr>
<tr>
<td>sipuleucel-T</td>
<td>prostate</td>
<td>NA (HR 0.95)</td>
<td>NA</td>
</tr>
<tr>
<td>ipilimumab</td>
<td>melanoma</td>
<td>2.86 vs 2.76 (HR 0.64)*</td>
<td>10.9 vs 1.5</td>
</tr>
<tr>
<td>pembrolizumab</td>
<td>melanoma (1L)</td>
<td>4.1/5.5 vs 2.8 (HR 0.58)</td>
<td>33/34 vs 12</td>
</tr>
<tr>
<td>nivolumab</td>
<td>melanoma BRAF- (1L)</td>
<td>5.1 vs 2.2 (HR 0.43)</td>
<td>34 vs 9</td>
</tr>
<tr>
<td>&quot;</td>
<td>lung squamous</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>&quot;</td>
<td>lung non-squamous</td>
<td>2.3 vs 3.9 (HR 0.92)</td>
<td>56 vs 36</td>
</tr>
<tr>
<td>&quot;</td>
<td>renal cell</td>
<td>NA</td>
<td>21.5 vs 3.9</td>
</tr>
</tbody>
</table>

* In FDA BLA clinical review, not in label
Questions

• Are there unique challenges in objective response rates (ORR) and duration assessment?
• Are there unique challenges in time-to-event analyses such as disease-free survival (DFS) and progression-free survival (PFS)?
• Is overall survival (OS) still an attainable endpoint?
• Any special considerations for combinations?
Tumor measurement based endpoints: Lessons learned from the RECIST database experience

Sumithra J. Mandrekar
Mayo Clinic

FDA-AACR Public Workshop
Immuno-Oncology Drug Development
October 13-14, 2016
Collaborators

• Vassar College
  – Ming-Wen An (Co-PI)

• Mayo Clinic
  – Dan Sargent
  – Axel Grothey
  – Jeff Meyers

• EORTC
  – Jan Bogaerts

• Summer students
  Xinxin Dong, and Yu Han
Challenges and Successes

Response rate and RECIST based time-to-event endpoints
Successes

• Response is relatively simple to determine and understand for clinical trial decision making

• Response Rate is similarly simple for patients to understand
Challenges

• Data Quality
  – Missing measurements
  – Inconsistently measured lesions
  – Conflicting measurements for same lesion at same time point
  – Measurements based on clinical examination only

• Response Rate
  – Does not capture cytostatic activity
  – Categorizes otherwise inherently continuous measurements leading to a potential loss of information

• Continuous metrics
  – Handling progression due to new lesions
LANGRECIST Database

Breast Cancer

NSCLC

Colorectal Cancer

Total number of patients from 13 trials: 3 tumor types

Excluded
All measurements from clinical evaluations
No measurements

An et al. (JNCI 2015)
Mandrekar et al. (JCO 2014)
Total number of patients from 13 trials: 3 tumor types

Excluded
All measurements from clinical evaluations
No measurements
Have at least one measurement from imaging assessments
Excluded
No baseline measurements
No post-baseline measurements
Conflicting responses or measurements at same assessment time
Non-conflicting baseline and post-baseline measurements

Breast Cancer

<table>
<thead>
<tr>
<th>2328</th>
<th>521</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>297</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1510</th>
<th>13</th>
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<tbody>
<tr>
<td></td>
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<td>193</td>
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<table>
<thead>
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<th>13</th>
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<tbody>
<tr>
<td></td>
<td>13</td>
</tr>
</tbody>
</table>

NSCLC

<table>
<thead>
<tr>
<th>8062</th>
<th>13</th>
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<tr>
<td></td>
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</table>

<table>
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<tr>
<td></td>
<td>300</td>
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<tr>
<td></td>
<td>79</td>
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</table>

Colorectal Cancer

<table>
<thead>
<tr>
<th>1353</th>
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<td></td>
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<table>
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<td></td>
<td>92</td>
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<tr>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

| 1237 | 1237 |

RECIST Database
RECIST Database

Total number of patients from 13 trials: 3 tumor types

Breast Cancer

2328

521

297

1510

13

53

193

1251

32

1219

NSCLC

4381

13

933

3435

13

300

79

3043

10

3033

Colorectal Cancer

1353

2

16

1335

0

92

6

1237

9

1228

Excluded
All measurements from clinical evaluations

Excluded
No measurements

Have at least one measurement from imaging assessments

Excluded
No baseline measurements

Conflicting responses or measurements at same assessment time

Non-conflicting baseline and post-baseline measurements

Excluded
No lesions measured consistently across all assessments

Final analysis set
Timing of Assessments
Timing of Assessments

• More frequent measurements
  – (+) more real-time monitoring about tumor activity
  – (−) Not according to clinical care and thus subject to missing measurements
<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Protocol assessment week</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Breast</td>
<td>0 6 12 18</td>
</tr>
<tr>
<td>Study 2</td>
<td>Breast</td>
<td>0 6 12 18</td>
</tr>
<tr>
<td>Study 3</td>
<td>Breast</td>
<td>0 6 12 18 24</td>
</tr>
<tr>
<td>Study 4</td>
<td>Breast</td>
<td>0 6 12 21</td>
</tr>
<tr>
<td>Study 5</td>
<td>Breast</td>
<td>0 9 18 24</td>
</tr>
<tr>
<td>Study 6</td>
<td>Breast</td>
<td>0 3 6 9 12 15 18 21 24</td>
</tr>
<tr>
<td>Study 7</td>
<td>Breast</td>
<td>0 9 15 21</td>
</tr>
<tr>
<td>Study 8</td>
<td>Colon</td>
<td>0 6 12 18 24</td>
</tr>
<tr>
<td>Study 9</td>
<td>Colon</td>
<td>0 7 14 21</td>
</tr>
<tr>
<td>Study 10</td>
<td>NSCLC</td>
<td>0 6 12 18</td>
</tr>
<tr>
<td>Study 11</td>
<td>NSCLC</td>
<td>0 6 12 18</td>
</tr>
<tr>
<td>Study 12</td>
<td>NSCLC</td>
<td>0 3 6 12 18</td>
</tr>
<tr>
<td>Study 13</td>
<td>NSCLC</td>
<td>0 3 6 12 18</td>
</tr>
</tbody>
</table>
Assessment Window

• Based on expected assessment times

• Sliding expected window:
  – If observed assessment time was within the +/- 2 week window, next expected was recalculated based on observed
  – Example: If current expected was 4 weeks and next expected was at 8 weeks, but current observed was at 6 weeks, then the next *adjusted expected* would be at 10 weeks instead of 8.
Assessment Window

Reasons for not being within the window (Not Perfect):

• Going off treatment early for reasons other than progression or death

• Missing an assessment followed by progression or off-treatment (without assessment)
RESULTS
Alternative cutpoints and continuous metrics no better than RECIST response
Categorical Metrics

• Dichotomous Tumor Response (DiTR)
  – PD/SD vs. PR/CR (response vs. others)

• Disease Control Rate (DCR)
  – PD vs. SD/PR/CR (progression vs. others)

• Trichotomous Tumor Response (TriTR)
  – PD vs. SD vs. PR/CR
KM Curves for OS across metrics at 12 and 24 weeks landmark time points

Mandrekar et al. (JCO 2014)

A: Breast
B: NSCLC
C: Colorectal
C-indices across datasets, metrics, and time points

A: Breast  
B: NSCLC  
C: Colorectal

Mandrekar et al. (JCO 2014)
Continuous Metrics

• Absolute change in tumor size
  – Between 0 and 6 weeks, and
  – Between 6 and 12 weeks

• Percent change in tumor size
  – Between 0 and 6 weeks, and
  – Between 6 and 12 weeks
C-indices across continuous metrics, datasets

An et al. (JNCI 2015)
Summary

• **Metrics (TriTR, DiTR, DCR), continuous metrics**
  – Similar predictive performance (c-index)
  – Similar calibration (prediction-errors)
  – Similar PPV/NPV (positive/negative phase II yielding a positive/negative phase III)
  – Absolute and relative change in TM based metrics are no better than RECIST based TR as phase II endpoints

• **Time points (12- or 24-weeks)**
  – Overlapping CIs, comparable performance

• **Disease**
  – Breast performed poorly compared to Colon and NSCLC
Pseudo-progression, and treatment beyond progression
Pseudo-progression

• Different cutoffs for PD and PR considered:
  – PD: increase in 10%, 15% and 20% from baseline
  – PR: 10% to 50% in 5% increments
    • pair (30%, 20%) corresponds to the RECIST categorization

• No change in predictive ability

• RECIST cutpoints demonstrated similar predictive ability as the alternate cutpoints
Overall Survival with the TriTR metric

RECIST cut points

A: Breast
B: NSCLC
C: Colorectal

Mandrekar et al. (JCO 2014)
Treatment beyond disease progression

• Data unavailable in RECIST data warehouse
Long Term Survivors
Long term survivors: Illustration

Overall Survival Probability

<table>
<thead>
<tr>
<th>Months from Study Entry</th>
<th>Overall Survival Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>24</td>
<td>1.0</td>
</tr>
<tr>
<td>36</td>
<td>1.0</td>
</tr>
<tr>
<td>48</td>
<td>1.0</td>
</tr>
<tr>
<td>60</td>
<td>1.0</td>
</tr>
<tr>
<td>72</td>
<td>1.0</td>
</tr>
<tr>
<td>84</td>
<td>0.97</td>
</tr>
<tr>
<td>96</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Arm A
- N = 123
- Events = 26
- Median = Not Reached
- p-value = 0.28

Arm B
- N = 109
- Events = 15
- Median = Not Reached
Mixture Cure Model

- Assumes population is a mixture of individuals
  - Those who may experience the event of interest
  - Those who will never experience the event of interest and are cured
  - Each modeled separately

- Estimate the cure rate of a treatment
  - Uses a logit link function (logistic regression)

- Estimate the survival rate of uncured patients
  - Uses the proportional hazards model
**Mixture Cure Model**

- \( T = \text{failure time of interest} \)

- \( 1 - \pi(z) = \text{probability of a patient being cured given vector of covariates } z \)

- \( S(t|x) = \text{survival probability of uncured patients given vector of covariates } x \)

\[
S_{pop}(t|x, z) = \pi(z)S(t|x) + 1 - \pi(z)
\]

\[\text{latency} \quad \text{incidence}\]
### Mixture Cure Model Example

#### Cure Probability Model

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Z value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>-0.28</td>
<td>0.31</td>
<td>-0.91</td>
<td>0.37</td>
</tr>
<tr>
<td>Arm, B vs. A</td>
<td>-1.49</td>
<td>0.46</td>
<td>-3.21</td>
<td>0.001</td>
</tr>
</tbody>
</table>

#### Failure Time Distribution Model

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. Error</th>
<th>Z value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm, B vs. A</td>
<td>2.15</td>
<td>0.52</td>
<td>4.16</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Cure Fraction = \( 1 - \pi(z) = 1 - \frac{\exp(bz)}{1 + \exp(bz)} \)

- Arm A = \( 1 - \frac{\exp(-0.28)}{1 + \exp(-0.28)} = 0.57 \)
- Arm B = \( 1 - \frac{\exp(-0.28 - 1.49)}{1 + \exp(-0.28 - 1.49)} = 0.85 \)
Kaplan-Meier Plot for Overall Survival and Predicted Curves from Mixture Cure Model

Arm A, Fitted Curve from Mixture Cure Model in Black
Arm B, Fitted Curve from Mixture Cure Model in Black

Survival Probability

Months from Study Entry
Acknowledgements

• RECIST steering committee
• Supported in part by NIH grant, CA167326-01

• Amy S. Ruppert: Cure Model Slides
• Ming-Wen An and Jeffrey Meyers: RECIST slides
Thank you

mandrekar.sumithra@mayo.edu
Immunotherapy Clinical Endpoints

Challenges & Opportunities

Axel Hoos, MD, PhD
Senior Vice President, Oncology R&D, GSK
Co-Chair, CIC
Objectives

- Hypotheses from clinical observations with IO agents
- Clinical endpoint challenges
- Improving clinical endpoints
- Ultimate goals
Cancer Immunotherapy

- Mechanism of Action:
  - Indirect: Targeting the immune system, not the tumor
  - Immune response is dynamic and complex

- Consequences:
  - No direct anti-tumor effects
  - Delayed clinical effects: activation of immune mechanisms before clinical activity
Interactions between Immune System and Tumor

Schreiber R., Science 2011
Clinical Observations from Ipilimumab: Driving Hypotheses
Anti-CTLA-4 (Ipilimumab): Conventional Response

O’Regan, KN, et al. AJR 2011
Anti-CTLA-4 (Ipilimumab): Delayed Response

Week 12
Increase in tumor burden (mWHO PD)

Week 16
Responding

Week 72
Durable & ongoing response without signs of IRAEs

Hoos et al., J Natl Cancer Inst, 2010
Anti-CTLA-4 (Ipilimumab): Delayed Response

O’Regan, KN, et al. AJR 2011
Anti-CTLA-4 (Ipilimumab): Stable Disease

O’Regan, KN, et al. AJR 2011
Anti-CTLA-4 (Ipilimumab): Response with New Lesion

O’Regan, KN, et al. AJR 2011
Ipilimumab (anti-CTLA-4): Clinical Patterns of Response

A

B

C

E

Ipilimumab: Association of OS with Patterns of Response

Pembrolizumab: Association of OS with Patterns of Response (n = 594; 16% irR)

Wolchok et al., ASCO 2014
ORR - OS Relationship: Ipilimumab in Metastatic Melanoma

**Ipilimumab Alone**

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>DCR</th>
<th>Survival Rate at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11%</td>
<td>29%</td>
<td>24%</td>
</tr>
</tbody>
</table>

*Hodi et al., New Engl. J. Med. 2010*
PFS – OS Relationship: Nivolumab vs. Dacarbazine

OS HR 0.42

PFS HR 0.43

PFS - OS Relationship: Sipuleucel-T

No PFS benefit
OS HR 0.77

HR 0.77 (0.61-0.98), p=0.04

Kantoff et al., New Engl. J. Med. 2010
Hypotheses

- Unusual response patterns and delayed effects reflect the underlying biology of immune intervention.
- Novel patterns of response or stable disease represent clinical benefit because they are associated with better survival.
- Conventional chemotherapy-derived response or PFS assessment (RECIST, WHO) does not account for all benefit patterns and therefore underestimates clinical benefit. This may vary between types of immunotherapies.
- Evaluation of time-to-event endpoints can be impacted by delayed clinical effects (non-proportional hazards) and may require modified statistics.
ORR & PFS: Clinical (Trial) Challenges

- Conventional ORR and PFS underestimate IO drug effects
  - Potential for premature discontinuation of a new therapy
  - Potential for clinical trial failure if conventional effects are insufficient to meet study objectives
- Premature treatment discontinuation due to conventional PD
- Sequencing of therapies difficult due to potential ongoing effects of the prior agent before “true” PD
Improving clinical endpoints
ORR, PFS and OS
History: Improving Endpoints for IO Drugs

Clinical observations of unconventional “mixed” responses

Delayed Separation of KM Curves

irResponse Criteria

1995 - - - - - - 2005

2010

Versions of irRC:

irRECIST
iRECIST
imRECIST
irLugano (LYRIC)

1995 - - - 2005

2010

2015 2016

Increasing Data Availability

Ipilimumab

Tremelimumab

Pembrolizumab (Nivolumab)
Atezolizumab
Durvalumab

Hoos et al., JIT 2007
Wolchok et al., CCR 2009
Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria

Jedd D. Wolchok,1 Axel Hoos,2 Steven O'Day,3 Jeffrey S. Weber,4 Omid Hamid,3 Celeste Lebbé,5 Michele Maio,6 Michael Binder,7 Oliver Bohnsack,8 Geoffrey Nichol,9 Rachel Humphrey,2 and F. Stephen Hodi10

- Confirmation of PD
- Measurement of new lesions
- Total tumor burden including new lesions
- Treatment post initial PD
- Support new endpoints
  - irORR
  - irDCR
  - irPFS

Wolchok et al., Clin Cancer Res 2009
Advances of irRC utility between 2009 and 2015

- Transferability of irRC concepts between WHO and RECIST
- Application of irRC to diseases beyond melanoma
- Inclusion of irRC concepts into regulatory guidances of FDA and EMA
- Expansion of irRC beyond the initial implementation (further adaptation)
- Demonstration of an irRC class effect across several immunotherapies
### Beyond irResponse Criteria

<table>
<thead>
<tr>
<th>Concept</th>
<th>irRC</th>
<th>irRECIST</th>
<th>iRECIST</th>
<th>imRECIST</th>
<th>irLugano (LYRIC)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Originator</strong></td>
<td>CIC BMS</td>
<td>DFCI</td>
<td>RECIST Working Group</td>
<td>Genentech</td>
<td>Lymphoma Foundation &amp; CIC</td>
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<tr>
<td>Confirmation of PD or “Unconfirmed PD”</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Measurement of new lesions</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Total tumor burden includes new lesions</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Response beyond confirmed PD</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Treatment post initial PD</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>Supports new ORR and PFS endpoints</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>
CBER, FDA Guidance:
Therapeutic Cancer Vaccines

Guidance for Industry

Clinical Considerations for Therapeutic Cancer Vaccines

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the Federal Register notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5650 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD)(HFM-46), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, by calling 1-800-835-4709 or 301-827-1800, or email: ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm.

For questions on the context of this guidance, contact OCOD at the phone numbers listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologic Evaluation and Research
September 2008

- Delayed separation of K-M curves
- New response kinetics
- Treatment beyond progression
- Immune response measurements
- Randomized Phase 2 trials
EMA Guidance: Anti-cancer Drug Development

- Section on cancer immunotherapy
- Delayed effect
- Relative role of response
- Treatment beyond progression
- Randomized Phase 2 trials
Initial ipilimumab observations are reproduced in several other IO development programs and represent a class effect.

Novel endpoints reflect the biology of immunotherapies and more accurately capture clinical effects than standard endpoints.

There is a correlation between the proposed new endpoints and overall survival suggesting surrogacy.

Prospective use for exploratory and pivotal studies may be considered.
Increasingly Improving Survival with Immunotherapy

Control
Conventional Therapy
Immunotherapy (e.g. anti-CTLA-4)
Future Regimens
Survival Metastatic Melanoma: Phase 1 Ipilimumab + Nivolumab

Wolchok et al. ASCO 2013 #9012
### OS: Challenges and Solutions

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-proportional hazards</td>
<td>▪ New statistical models</td>
</tr>
<tr>
<td></td>
<td>▪ Overpowering of studies</td>
</tr>
<tr>
<td></td>
<td>▪ Sensitivity analyses</td>
</tr>
<tr>
<td>Increased duration of trials with continuously improving survival</td>
<td>▪ Earlier survival read-outs</td>
</tr>
<tr>
<td></td>
<td>(eg Milestone survival)</td>
</tr>
<tr>
<td></td>
<td>▪ Alternative PFS endpoints (eg irPFS)</td>
</tr>
<tr>
<td>Diluting effect of other survival influencing therapies post progression</td>
<td>▪ Earlier survival read-outs</td>
</tr>
<tr>
<td></td>
<td>(eg Milestone survival)</td>
</tr>
<tr>
<td></td>
<td>▪ Alternative PFS endpoints (eg irPFS)</td>
</tr>
<tr>
<td>Potential need for cross-over design if comparing increasingly effective therapies</td>
<td>▪ Alternative PFS endpoints (eg irPFS)</td>
</tr>
</tbody>
</table>
Ultimate Goals

- Better “Tools” – immunotherapy adapted endpoints
- Harmonize new criteria for a uniform approach
- Reflect biology in patients
- Accurately capture benefit
- Enable future trials in a context of substantially extended survival
Thank you !
Estimating survival benefit in the presence of non-proportional and complex hazard functions

FDA-AACR Workshop: “Immuno-Oncology Drug Development”
Day 2 – October 14, 2016

Dr Nicholas Latimer, Senior Research Fellow, NIHR Post-doctoral Fellow, University of Sheffield, Sheffield, UK
Plan

1. Standard survival analysis
2. Parametric survival analysis
3. Immuno-Oncology
   – What are the challenges?
   – What are the solutions?
4. Conclusions
Plan

1. Standard survival analysis
2. Parametric survival analysis
3. Immuno-Oncology
   – What are the challenges?
   – What are the solutions?
4. Conclusions
Survival analysis

- The analysis of time-to-event data from a specified time origin (e.g. randomisation) until the occurrence of a particular event or endpoint (e.g. disease progression, death)

- Commonly used in evaluating effectiveness of healthcare interventions

- Results are often summarised using
  - Kaplan-Meier curves
  - Median survival
  - Hazard Ratios
Kaplan-Meier curves

- The Kaplan-Meier estimates the probability of “surviving” until time $T$
- We can use them to estimate medians and means
- And can use a log-rank test to compare curves statistically
Cox PH models

- If we want to quantify the treatment effect we can use a Cox proportional hazards regression model.
- These produce hazard ratios (HR) which compare hazard rates between treatment groups.

⇒ The Cox model makes the proportional hazards assumption – the baseline hazard rate can change over time, but the hazard ratio cannot.
Issues with standard non-parametric survival analysis

- Log-rank tests and HRs from Cox models are reliant on the proportional hazards assumption
  - If this assumption does not hold, these analyses are not useful

- What we really want to know is the survival benefit of the new treatment
  - The truest estimate of this is the mean survival benefit – for resource allocation decisions means are more useful than medians
Issues with standard non-parametric survival analysis

- In the presence of heavy censoring, within-trial analyses may not be very informative.
- Mean survival estimates from the Kaplan-Meier curve are downwardly biased ("restricted").
Issues with standard non-parametric survival analysis

So...

→ If we want to estimate the mean survival benefit for the entire disease population we need to extrapolate from the trial data

→ There is a role for parametric survival analysis

→ This is commonly done for economic evaluation in health technology assessment (Latimer et al. 2013; Davies et al. 2012)
Plan

1. Standard survival analysis
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   – What are the challenges?
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Parametric survival models

- Parametric survival models use the assumption that the survival data follows an underlying probability distribution

- Hence survival can be predicted beyond the end of the trial

- Several parametric survival models exist, eg:
  - Exponential
  - Weibull
  - Gompertz
  - Log-logistic
  - Log normal
  - Generalised Gamma

- The key is to pick the most appropriate model
Parametric models

Exponential
- Simplest model
- Hazard is constant over time

Weibull
- 2 parameters
- Hazard can increase or decrease monotonically

Gompertz
- 2 parameters
- Hazard can increase or decrease monotonically

Log-logistic
- 2 parameters
- Hazard may increase and then decrease

Log normal
- 2 parameters
- Hazard may increase and then decrease

Generalised Gamma
- 3 parameters
- More flexible, includes exponential, Weibull, log normal as special cases

*Note: here, we are talking about the hazard rate, not the HR!
Parametric survival models

- Parametric survival models can be fitted assuming a proportional treatment effect.

- As for Cox models, this will not be appropriate if there is not a proportional treatment effect.

- Or, they can be fitted without assuming a proportional effect – e.g. by fitting models independently to each treatment group.
Parametric models

Different models give significantly differing curves

Model choice is critical

Must use a model that reflects the observed and expected hazards
Plan

1. Standard survival analysis
2. Parametric survival analysis
3. Immuno-Oncology
   – What are the challenges?
   – What are the solutions?
4. Conclusions
Survival modelling – in any disease area – is rarely straightforward

- Proportional hazards assumption often may not hold
- Often there is limited long-term survival data
- Hazard functions may not follow standard parametric distributions

Nevertheless, immuno-oncology appears to be characterised by certain features which have implications for survival modelling...
Immuno-oncology – challenges

1. Immuno drugs may not exhibit a proportional treatment effect

2. Immuno drugs may be associated with a delayed effect, long-term survivors and therefore complex hazard functions
Problem: Non-PH effects

1. Immuno drugs may not exhibit a proportional treatment effect
   ➔ PH assumption is not valid
   ➔ Cox models and log-rank tests may not be appropriate
   ➔ Parametric models that assume PH may not be appropriate

Figure adapted from Chen, 2013
Solutions: Non-PH effects

- Cox models can incorporate time-dependent treatment effects
  - But we no longer get a single, simple HR
  - But shouldn’t we be more interested in mean survival anyway? – hence non-parametric analysis is not that useful

- Parametric models can be fitted independently to each treatment arm
  - Don’t need to assume PH
  - May get a better estimate of the survival gain
Problem: Complex hazards

2. Immuno drugs may be associated with a delayed effect, long-term survivors and therefore complex hazard functions

→ Standard parametric models may not provide a good fit to the observed (or expected) hazard & survival functions

→ So survival estimates may be poor
Solutions: Complex hazards

Flexible parametric models

- Flexible parametric models use restricted cubic splines to estimate the shape of the log-cumulative hazard function.

- FPMs can accurately reflect complex hazard functions, with turning points (Royston and Parmar, 2002; Rutherford, Crowther and Lambert, 2015)…
Solutions: Complex hazards

Parametric cure models

- Sometimes it might appear that a % of patients have been “cured”
- Parametric cure models can be used to estimate the cure fraction, modelling ‘cured’ and ‘uncured’ with different distributions (Chen, 2015)

Parametric mixture models

- Sometimes it might appear that there are 2 (or more) distinct groups within the population, who have different survival distributions
- Parametric mixture models can be used to model with two (or more) distinct distributions (Lambert, 2007)
Solutions: Complex hazards

FPMs, cure and mixture models

- The FPM extrapolates beyond the data using only the final segment of the curve. This may or may not be appropriate for achieving accurate projections.

- Cure/mixture models may have a preferred biological basis as they do not involve segmenting the survival curve, but...
  - Can we prove that an assumption of a cure is reasonable?
  - Can we estimate the cure fraction based on short-term trial data?
  - Can we justify an assumption of two (or more) distinct groups?
  - Still need to select appropriate parametric models.
Plan

1. Standard survival analysis
2. Parametric survival analysis
3. Immuno-Oncology
   – What are the challenges?
   – What are the solutions?
4. Conclusions
Conclusions

- Immuno-Oncology *may* present “non-standard” issues for survival analysis
  - HRs and log-rank tests of Kaplan-Meier curves may not be useful
  - Standard parametric models may not fit

- We may need models that allow time-dependent treatment effects, or model survival curves independently

- FPMs, cure models and mixture models offer potential solutions
  - But each requires careful justification
  - As always, demonstrating the validity of extrapolated portions of survival curves is critical
References

• Latimer NR. Survival analysis for economic evaluations alongside clinical trials – extrapolation with patient-level data: Inconsistencies, limitations and a practical guide. Medical Decision Making 2013;33;6:743-54


• Lambert P. Modeling of the cure fraction in survival studies. The Stata Journal 2007 ;7;3:351-375


• Chen T. Predicting analysis times in randomized clinical trials with cancer immunotherapy. BMC Medical Research Methodology 2016;16;12
Session IIIa Panel Discussion
Endpoints for I-O Products: Considerations for Unique Efficacy Based on Unique Biology of Checkpoint Inhibitors

Moderator: Renzo Canetta, MD

Speakers:
Lawrence Schwartz, MD
Sumithra Mandrekar, PhD
Axel Hoos, PhD
Nicholas Latimer, PhD

Panelist:
Shenghui Tang, PhD
Session IIIb
Use of Alternate Efficacy Endpoints with I-O Products

Moderator: Marc Theoret, MD

Speakers:
Sirisha Mushti, PhD
Xin (Cindy) Gao, PhD
Antoni Ribas, MD, PhD
Jan Bogaerts, PhD
Daniel S. Chen, MD, PhD
Keaven Anderson, PhD
Tai-Tsang Chen, PhD
How we assess benefit from IO agents
DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Antoni Ribas, MD, PhD

DISCLOSURES
Amgen, Genentech, Merck, Novartis:
Consultant – Honoraria to UCLA

Acteris, Advaxis, Compugen, CytomX, Five Prime, Kite Pharma:
Scientific Advisory Board – Stock
Very long term responses with CTLA4 blockade

Dr Ed, 39 years old in 2004, metastatic melanoma to the liver, adrenal gland and bone, told he had months left to live.

Hi Toni, I would like that you improve my hazard ratio for survival by 0.68
Very long term responses with CTLA4 blockade

Dr Ed, 39 years old in 2004, metastatic melanoma to the liver, adrenal gland and bone, told he had months left to live.

Hi Toni, I would like to see my two daughters grow and go to college.
Very long term responses with CTLA4 blockade

Dr Ed, 39 years old in 2004, metastatic melanoma to the liver, adrenal gland and bone, told he had months left to live.

Forbes, Oct 2007

Top of Rangitoto volcano, Auckland, New Zealand, Nov 2015.
What IO benefit analysis captures living to take your children to college?

- ORR
- PFS
- OS
- Durable response rate
What IO benefit analysis captures living to take your children to college?

- ORR
- PFS
- OS
- Durable response rate
OPTiM: Phase 3 trial of talimogene laherparepvec (T-VEC) vs sc GM-CSF for unresected stage IIIB/C and IV melanoma

Primary Endpoint: Durable Response Rate per EAC

<table>
<thead>
<tr>
<th>ITT Set</th>
<th>GM-CSF (N=141)</th>
<th>T-VEC (N= 295)</th>
<th>Unadjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Durable Response Rate</td>
<td>2.1%</td>
<td>16.3%</td>
<td>8.9</td>
</tr>
</tbody>
</table>

95% CI: (2.7, 29.2)
P < 0.0001

143 patients (33%) in the ITT set met the criteria to be reviewed by the EAC (ie, had best response per investigator of CR or PR or on therapy for ≥ 9 months)

Andtbacka et al. JCO 2013
PFS and OS are more likely to be positive when benefitting very little all patients than when benefitting a lot (maybe curing) a subset of patients.

Which treatment would you rather respond to?

- **PFS**
  - HR++++
  - HR++
  - OR-

- **OS**
  - HR++
  - HR++
  - OR+++

- **DRR**
  - OR+++
  - OR+++
  - OR+++
Conclusions

• The main benefit of IO agents is inducing very long lasting responses in patients with metastatic cancer

• ORR, PFS and OS may not always capture this benefit, and may depend on the type of benefit in the control arm
  – PFS and OS usually favor a small benefit in a lot of patients than a life-changing benefit in a subset of patients

• DRR:
  – Captures the intended benefit of IO agents
  – Independent of the performance of the control arm
  – Independent of other post-progression therapies
Milestones for Survival: Overall Survival versus Earlier Endpoints

Jan Bogaerts, PhD
EORTC, Brussels
Conflicts

• No conflicts
• EORTC works with most major pharma companies and receives grants in various forms of cooperation to run studies
• Permanent member of the EMA SAG
Overview

• Some comments coming from our work on (i)RECIST
• Lack of gold standard for earlier endpoints
• Thoughts about how survival data can be interpreted
(i)RECIST

• Current status of RECIST:
  – Busy writing up the analysis of the targeted agents warehouse analysis
  – In writing: RECIST recommendations for how to use it in immunology setting: L. Seymour coordinates
  – This will be discussed at EORTC-NCI-AACR Molecular Targets and Cancer Therapeutics Symposium, Munich (end of the year)
• Contrast between PD per RECIST and the decision to stop treatment
• RECIST is a method to standardize and reach some degree of comparability across studies
  – Should it always define end of treatment?
• A ‘paradox by construction’:
• When RECIST PD is reached, the data flow stops, making it impossible to look into many interesting questions (no data)
Intermediate endpoints

• There is no gold standard for what constitutes ‘response’ or ‘progression’ (IMO)
• There will always be some degree of convention
• We can reach high degrees of correlation with OS, if not surrogacy in the Prentice sense
Any dichotomisation will show separation

Also in the work by S. Mandrekar et al (no ‘better’ split)

Temptation to maximize RR

Thanks to S. Litiere
### Table 4. Best Overall Response for Patients Alive at Least 5 Years

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Ipilimumab + Dacarbazine (n = 40)</th>
<th>Placebo + Dacarbazine (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Complete response</td>
<td>3</td>
<td>7.5</td>
</tr>
<tr>
<td>Partial response</td>
<td>17</td>
<td>42.5</td>
</tr>
<tr>
<td>Stable disease</td>
<td>11</td>
<td>27.5</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7</td>
<td>17.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Objective response rate</td>
<td></td>
<td>50</td>
</tr>
</tbody>
</table>
For immunotherapy

• While OS outcomes dominate, we should prepare and come to better goal setting
  – What is an acceptable “delay” or waiting time for patients to stay on treatment in ‘apparent PD’

• Definition of progression should not take a form that recognizes any level of activity
  – This question will come back if OS is not significant, while PFS is
Do we need to change stat methods?

Diverging hazards
Late separation of the curve
50% of patients:
- bad prognosis group
- no effect at all (overlapping curves)

50% of patients:
- better prognosis group
- huge effect
The ‘mix’ of those two

This is a ‘caricature’, but deserves reminding
Many mechanisms can lead to this

- Late drug effect
  - We know this is at work
- Unidentified factor
- Too broad population
- Non-compliance
- Short term effect that is not maintained
- ...

![Graph showing Arm 1 and Arm 2 with a downward trend over time.](image)
Thank you
Non-Classical Response Patterns, Immune-Modified RECIST and Immune-Modified PFS: Potential Optimization of Radiographic Endpoints for Immunotherapies

Ballinger M, Lyons B, Winslow N, Fine G, Chen DS

Dan Chen, M.D. Ph.D.
Vice President, Global Head of Cancer Immunotherapy Development
Genentech/Roche

FDA-AACR Immuno-Oncology Drug Development
October 14, 2016
a complex set of tumor, host and environmental factors govern strength, and timing of anti-cancer immune responses

Chen and Mellman. *Immunity* 2013

Chen and Mellman. *Publication pending* 2016

Non-Classical Responses after Radiographic PD

Atezolizumab monotherapy

Baseline | Week 6 | Week 12 | Week 18 | Week 46
--- | --- | --- | --- | ---

Neck mass

Week 15

DFCI (Hodi)

Sosman et al. SMR Meeting 2013

Infiltrating lymphocytes

Necrotic melanoma

Ipilimumab monotherapy

Screening | 12 wk | 72 wk
--- | --- | ---

Atezolizumab (*TECENTRIQ*): Anti-PDL1 mAb

Ipilimumab (*YERVOY*): Anti-CTLA mAb

Wolchok et al., 2009

Non-Classical Responses: Reversion to SD or PR
Atezolizumab Monotherapy from Phase I study

Atezolizumab monotherapy: RCC
RECIST: PD; irRC: PD

Atezolizumab monotherapy: NSCLC
RECIST: SD; irRC: SD

Atezolizumab monotherapy: NSCLC
RECIST: SD; irRC: SD

Atezolizumab monotherapy: RCC
RECIST: PR; irRC: PR
Tumor burden can decrease in patients treated beyond RECIST 1.1 PD

Atezolizumab treated NSCLC patients (POPLAR study)

Best change in target lesions from RECIST 1.1 PD for patients continuing atezolizumab beyond PD (investigator assessed)
Patterns of Non-Classical Response

"Spikes"

"Blip" or "Oscillating"
Patterns of Non-Classical Response

- Non Target Progression
- New Lesion

“Spikes”

“Non-target lesion PD”

“New Lesion”

“Blip” or “Oscillating”

Measurable Tumor Burden

Patterns of Response with Atezolizumab: 
*First PD in Target Lesions that later reverts to non-PD*

**POPLAR (2L/3L NSCLC)**
Sum of longest diameter

**IMvigor 210 (2L+ mUC)**
Sum of longest diameter

---

**POPLAR: Randomized P2 study of Atezolizumab monotherapy in 2/3L NSCLC**
**IMvigor210: Atezolizumab P2 study in mUC (bladder cancer)**

Patterns of Response with Atezolizumab: 
*PD due to NL or NTL only*

**POPLAR (2L/3L NSCLC)**
Sum of longest diameter

**IMvigor 210 (2L+ mUC)**
Sum of longest diameter

POPLAR: Randomized P2 study of Atezolizumab monotherapy in 2/3L NSCLC
IMvigor210: Atezolizumab P2 study in mUC (bladder cancer)

## Frequency of Atypical Response Patterns with Atezolizumab

<table>
<thead>
<tr>
<th>Pattern</th>
<th>#1 (Target Lesions Revert)</th>
<th>#2 (Non-target/New)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>First PD due to target lesions progression that reverts to non-PD after further tumor scans</td>
<td>Non-Target or new Lesion PD without Target Lesion PD</td>
</tr>
<tr>
<td>Pattern addressed by imRECIST v1.0</td>
<td>Yes, PFS event may be negated by subsequent non-PD</td>
<td>Yes</td>
</tr>
<tr>
<td>Frequency in POPLAR (2L/3L NSCLC)</td>
<td>8/144 (5.6%)</td>
<td>36/144 (25%)</td>
</tr>
<tr>
<td>Frequency in IMvigor 210 (2L+ mUC)</td>
<td>13/310 (4.2%)</td>
<td>71/310 (22.9%)</td>
</tr>
</tbody>
</table>

Data cutoff: Dec 1, 2015

Immune-modified Response Criteria aim to Capture Benefit that is Not Captured by RECISTv1.1

- **irRC** (immune-related response criteria): derived from WHO; designed to better account for ipilimumab non-classical response patterns
- **Immune-modified RECIST (imRECIST)**: derived from RECIST 1.1 using irRC principles
  - Includes definitions for imPFS analysis

<table>
<thead>
<tr>
<th>Tumor burden</th>
<th>RECIST 1.1</th>
<th>irRC (Wolchok et al., 2009)</th>
<th>IM-RECIST (GNE/Roche)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unidimensional</td>
<td>• Unidimensional</td>
<td>• Bidimensional per WHO</td>
<td>Unidimensional per RECIST 1.1</td>
</tr>
<tr>
<td>Up to 5 target lesions/2 per organ</td>
<td>• Up to 10 target lesions/5 per organ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New lesions</td>
<td>Always represent PD</td>
<td>• New lesions do not categorically define PD</td>
<td></td>
</tr>
<tr>
<td>Non-target lesions</td>
<td>Can contribute to defining CR or PD (unequivocal progression)</td>
<td>• Non-Target progression does not define PD</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>• ≥ 20% increase in the SLD (RECIST) compared with baseline/nadir and/or Unequivocal progression of non-target lesions and/or Appearance of new lesions Confirmation of PD not required</td>
<td>• Determined only on the basis of measurable disease • Negated by subsequent non-PD assessment ≥ 4 weeks from the date first documented (lack of confirmation)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ≥ 25% increase in the SPD compared with baseline/nadir • Best response may occur prior to confirmed PD</td>
<td>• ≥ 20% increase in SLD (RECIST) compared with baseline/nadir • Best response may occur after any number of PD assessments</td>
</tr>
</tbody>
</table>
PFS: PD event may be negated by subsequent non-PD assessment ≥ 4 weeks from the date first documented

- However, PD followed by no further assessments is still counted as a PD event
- Confirmed PD dated back to prior PD assessment

---

**imRECIST PFS event?**

<table>
<thead>
<tr>
<th>Event Sequence</th>
<th>PFS Event?</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD &gt;=28 days PD</td>
<td>No</td>
</tr>
<tr>
<td>PD &gt;=28 days CR, PR, SD</td>
<td>No</td>
</tr>
<tr>
<td>PD</td>
<td>Yes</td>
</tr>
</tbody>
</table>

imRECIST definitions extend PFS relative to RECISTv1.1

**POPLAR: Atezolizumab-treated NSCLC Patients by PD-L1 IHC Expression**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median PFS (95% CI) mo per RECIST 1.1</th>
<th>Median PFS (95% CI) mo per imRECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n=144)</td>
<td>2.7 (2.0, 4.1)</td>
<td>4.3 (3.9, 7.0)</td>
</tr>
<tr>
<td>TC3 or IC3^a (n=24)</td>
<td>7.8 (2.7, 12.3)</td>
<td>12.3 (7.8, 17.1)</td>
</tr>
<tr>
<td>TC2/3 or IC2/3 (n=50)</td>
<td>3.4 (1.4, 6.9)</td>
<td>7.8 (4.2, 12.0)</td>
</tr>
<tr>
<td>TC1/2/3 or IC1/2/3 (n=93)</td>
<td>2.8 (2.6, 5.5)</td>
<td>6.8 (4.1, 8.5)</td>
</tr>
<tr>
<td>TC0 and IC0 (n=51)</td>
<td>1.7 (1.4, 4.2)</td>
<td>4.1 (1.6, 4.4)</td>
</tr>
</tbody>
</table>

^aTC3 or IC3 = TC ≥ 50% or IC ≥ 10% PD-L1+ cells; TC2/3 or IC2/3 = TC or IC ≥ 5% PD-L1+ cells; TC1/2/3 or IC1/2/3 = TC or IC ≥ 1% PD-L1+ cells; TC0 and IC0 = TC and IC < 1% PD-L1+ cells, respectively.

Data cutoff: Dec 1, 2015

OS is increased in patients with extended imPFS POPLAR atezolizumab arm (2L/3L NSCLC)

Compare OS according to difference in time between imPFS and rPFS event

<table>
<thead>
<tr>
<th>Condition</th>
<th>ITT N=144</th>
<th>imPFS ≤ 2 months after rPFS N = 93</th>
<th>imPFS &gt; 2 months after rPFS N = 31</th>
<th>No rPFS N = 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS</td>
<td>12.6 mo</td>
<td>7.3 mo</td>
<td>12.4 mo</td>
<td>NR</td>
</tr>
</tbody>
</table>

PFS = PFS event date, includes death
NR = not reached


Data Cut: May 2015
OS is increased in patients with extended imPFS
POPLAR atezolizumab arm (2L/3L NSCLC)

Plot above does not include N=20 patients without a PFS event by RECIST 1.1 or imRECIST that have 100% survival

Excludes Patients w/o Radiographic PFS

OS is increased in patients with extended imPFS IMvigor 210 (2L+ mUC)

PFS = PFS event date, includes death
NR = not reached

• ITT
  N=310
  mOS = 7.9 mo

• imPFS ≤ 2 months after rPFS
  N = 238
  mOS = 6.0

• imPFS > 2 months after rPFS
  N = 35
  mOS = 13.3

• No rPFS
  N = 37
  mOS = NR


Data Cut: March 2016
OS is increased in patients with extended imPFS
IMvigor 210 (2L+ mUC)

Plot above does not include N=37 patients without a PFS event by RECIST 1.1 or imRECIST that have 100% survival

Data Cut: March 2016

Excludes Patients w/o Radiographic PFS

Summary

- Anti-Cancer Immunity may be influenced by tumor, host and environmental factors
  - Responses can be immediate, delayed or can follow inflammation/tumor swelling
  - Non-classical response patterns include 1) Target lesion increase followed by reversion 2) New lesions or Non-target lesion PD in the absence of target lesion PD 3) waxing and waning cancer immune responses
- imRECIST developed to better capture non-classical response patterns and evaluate PFS with CIT
  - Incorporates most irRC principles into a RECIST 1.1 – based framework
  - PFS event may be negated by subsequent non-PD assessment
  - Presence of new lesion does not automatically imply PD
  - imPFS may be a better predictor for OS
- Results to date (NSCLC, mUC with atezolizumab monotherapy):
  - Median PFS increased per imRECIST relative to RECIST 1.1
  - Change in PFS event time (imPFS vs rPFS) associated with longer OS
  - PD associated with new lesions only more common than reversion

Ongoing Analyses and Potential Modifications to imRECIST

• Analysis of OS and imRECIST according to lesion patterns
  • Importance of Non-target lesions and new lesions to clinical outcome
  • Lymph nodes vs other lesion types

• Alternate imRECIST PFS definitions
  • Allowance for PD negation at any subsequent assessment

• Collaboration with Cross-industry, academic and Health Authority efforts to standardize criteria
  • EORTC iRECIST working group
  • Cancer Immunotherapy Consortium of the Cancer Research Institute (CIC)
Acknowledgements

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- Ulrich Beyer
- Colombe Chappey

- Ira Mellman
- Hartmut Koeppen
- Marcin Kowanetz
- Maria Anderson
- Ina Rhee
- Friedrich Graf Finckenstein
- James Reimann
- Cathi Ahearn

- Genentech and Roche Investigators, Cancer Immunotherapy Working Group, Cancer Immunotherapy Committee, CIC/CRI

irRECISt and Survival Modeling

Keaven M. Anderson, Ph.D.
Distinguished Scientist, Late Development Statistics
Merck & Co., Inc., Kenilworth, NJ, USA
Overview

• Merck’s rationale for irRECIST
  – Past and recent data
  – Based presentation by Eric Rubin, Andrea Perrone: ASCO Review of irRECIST, Overview of Merck’s Strategy

• Survival modeling suggestion
  – Based on 2016 ESMO presentation by Blank, Ma, et al.
Rationale for irRECIST

• As market access to immunotherapies increases, OS will be increasingly confounded as a primary endpoint in randomized studies due to crossover
  - PFS will be increasingly important as an endpoint to assess clinical benefit for immunotherapies

• Recent analyses of randomized studies indicate that immunotherapies may yield an improvement in OS with minimal or no improvement in PFS, as assessed by RECIST 1.1

• Using RECIST 1.1 to identify progression times may underestimate PFS effect sizes for immunotherapy

• IrRECIST-like determination of disease progression correlates better with OS than RECIST 1.1-determined progression for immunotherapy in multiple cancer types

• A uniform definition of irRECIST is needed
Association of Overall Survival With Tumor Response (RECIST vs irRC)

MK3475-001 Melanoma

MK3475-001 NSCLC

PD: Progressive disease
DC: Disease control, including CR, PR, and SD
NE: Not evaluable

Analysis cutoff: October 2014.
**KN001 Melanoma Cohort: All Patients**

- **492/655 (75.1%)** have exactly the same PFS using RECIST 1.1 and irRC
  - 20/655 (3.1%) have longer PFS using RECIST 1.1
  - 143/655 (21.8%) have longer PFS using irRC

**PFS Endpoint**

<table>
<thead>
<tr>
<th>PFS Endpoint</th>
<th>Median PFS (months)</th>
<th>Difference (relative to RECIST 1.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on RECIST 1.1</td>
<td>5.30</td>
<td>NA</td>
</tr>
<tr>
<td>Based on irRC</td>
<td>9.24</td>
<td>3.94</td>
</tr>
</tbody>
</table>

**PFS (in days)**

163 PATIENTS with different measures

**PFS Based on RECIST 1.1**

**PFS Based on irRC**

Proportion

0 200 400 600 800 1000

0

20

40

60

80

100

PFS Based on RECIST 1.1

PFS Based on irRC
KN001 Lung Cohort: All Patients

### PFS Endpoint

<table>
<thead>
<tr>
<th>PFS Endpoint</th>
<th>Median PFS (months)</th>
<th>Difference (relative to RECIST 1.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on RECIST 1.1</td>
<td>3.49</td>
<td>NA</td>
</tr>
<tr>
<td>Based on irRC</td>
<td>4.57</td>
<td>1.08</td>
</tr>
</tbody>
</table>

- **423/567 (74.6%)** have exactly the same PFS using RECIST 1.1 and irRC
  - 34/567 (6.0%) have longer PFS using RECIST 1.1
  - 110/567 (19.4%) have longer PFS using irRC
KN001 Lung Cohort: TPS ≥50%

- 92/119 (77.3%) have exactly the same PFS using RECIST 1.1 and irRC
  - 5/119 (4.2%) have longer PFS using RECIST 1.1
  - 22/119 (18.5%) have longer PFS using irRC
**KN006 Melanoma: All patients IRO vs INV**

<table>
<thead>
<tr>
<th>PFS Endpoint</th>
<th>Median PFS (months)</th>
<th>Improvement in Median PFS relative to IPI (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on IRO</td>
<td>2.83</td>
<td>4.93, NA</td>
</tr>
<tr>
<td>Based on irRC (INV)</td>
<td>3.32</td>
<td>8.39, NA</td>
</tr>
<tr>
<td>Difference (irRC – IRO)</td>
<td>0.49</td>
<td>3.46</td>
</tr>
</tbody>
</table>

**Median PFS (months)**

- Based on IRO: 2.83
- Based on INV: 3.32

**Improvement in Median PFS relative to IPI (months)**

- Based on IRO: NA
- Based on INV: 5.07
Part 1 summary

• Conventional imaging criteria by RECIST 1.1 underestimates PFS effective size of immunotherapy

• Data gathering across the industry could support use of irRECIST rather than RECIST to evaluate PFS
Part 2: Long-term survival modeling
Estimating Long-Term Survival: Keynote 006

• Blank, Ma et. al, ESMO, 2016

• Based on Ipilimumb-naïve advanced melanoma patient population
  – March 2015 data cutoff

• Established “cure” (long-term survival) model used to approximate Kaplan-Meier estimate
  – de Castro et al, Computer Methods and Programs in Biomedicine, 2010

• 556 randomized to two pembrolizumab arms; 278 randomized to ipilimumab
Estimated long-term survival 49.2% (Pembrolizumab)

34.8% (Ipilimimab)

Ipilimumab improvement relative to historical 22% long-term survival (Schadendorf et al., J Clin Oncol. 2015) may be due to new therapeutic options for follow-on treatments.
Interim Estimates of Long-Term Survival Stabilize with Increased Follow-up

- Confidence intervals (CI) useful to evaluate accuracy of long-term survival rate and benefit
  - CI shrinks with increased follow-up
  - Model appears useful to project possible future survival rates
Example Hypothetical Model

Allows early overlap with later separation

Survival vs Time

0.4 0.6 0.8 1.0

0 1 2 3 4 5

Time

Treatment  Control  Experimental
Usefulness of model

• Stabilizing point estimates for ‘smooth’ Kaplan-Meier curves

• Confidence intervals (CI) useful to evaluate accuracy of long-term survival rate and benefit
  – CI shrinks with increased follow-up

• Model appears useful to project possible future survival rates
  – Covariates allowed, if needed
  – Late separation easily modeled

• Additional experience with this model may suggest use in immuno-oncology trials
Alternative Survival Endpoints

Tai-Tsang Chen, PhD
Global Biometric Sciences, Bristol-Myers Squibb

AACR-FDA Workshop, Washington, DC
October 13-14, 2016
Disclosure

• Employment: currently employed by Bristol-Myers Squibb as Head of Global Biometric Sciences in Medical and Market Access

• The views expressed in this presentation are personal based on my experience and do not necessarily reflect the views of Bristol-Myers Squibb
Promising Future and Challenges in Cancer Research

*Adapted from Walter Urba, ASCO 2013*
Focus of this Presentation

• The ultimate goal is to identify a short-term endpoint that can be used to predict clinical benefit, i.e., overall survival

• The focus of this presentation is to introduce two alternative survival related endpoints
  – Milestone Survival
  – Restricted Mean Survival
Alternative Survival Endpoints

• Milestone Survival (MS)
  – Defined as the Kaplan-Meier survival probability at a specific time point defined a priori, such as two years
  – Can be measured by the difference or ratio

• Restricted Mean Survival Time (RMST)
  – Area Under the Kaplan-Meier Curve
  – Life expectancy for the restricted (truncated) duration
  – Can be measured by the difference or ratio
Graphical Presentation of Survival Kinetics

A) Proportional hazards

B) Long-term survival

C) Delayed clinical effect

D) Long-term survival and delayed clinical effect

©2015 American Association for Cancer Research
## Comparison of Study Designs Among Survival Endpoints (One Scenario)

<table>
<thead>
<tr>
<th>Measure</th>
<th>PHM</th>
<th>PHCRM</th>
<th>NPHM</th>
<th>NPHCRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Ratio</td>
<td>0.75</td>
<td>0.75</td>
<td>1/0.59</td>
<td>1/0.57</td>
</tr>
<tr>
<td>Delay/Long-Term Survival</td>
<td>NA</td>
<td>NA/0.1</td>
<td>8/NA</td>
<td>8/0.1</td>
</tr>
<tr>
<td>Overall Survival*</td>
<td>90%</td>
<td>91%</td>
<td>91%</td>
<td>89%</td>
</tr>
<tr>
<td>Milestone Survival (2-year)</td>
<td>80%</td>
<td>81%</td>
<td>88%</td>
<td>90%</td>
</tr>
<tr>
<td>Restricted Mean Survival (2-year)</td>
<td>89%</td>
<td>86%</td>
<td>84%</td>
<td>83%</td>
</tr>
</tbody>
</table>

- **Design Assumption**
  - Minimum follow-up duration: 24 months
  - Power based on log-rank test: 90%
  - False positive rate: 5%
  - Control arm: exponential with median of 12 months

*Log-rank test
Why Alternative Survival Endpoints?

• Overall Survival (based on log-rank) remains a good clinical endpoint under the assumptions of proportional hazards and some patterns of non-proportional hazards

• Why do we consider other endpoints?
  – Non-proportionality in hazard ratio among I-O agents
  – The need for describing (time-dependent) treatment effects
  – Unpredictability of the analysis time based on OS
Impact of Misspecification of Long-Term Survival Effect on Trial Duration (N=345)

* Study was designed with a median control of 12 months; a 6-month delay, HR=0.5 and LTS=0. Number of events=\~251.
Reporting the Time-to-Event Outcome: An Illustrative Example based on Simulation

Conventional summary statistics:
- Hazard Ratio (95% CI): 0.88 (0.76, 1.03)
- Median survival (95% CI)
  - Experimental treatment: 9.4 (8.3, 12.5)
  - Control treatment: 11.4 (9.3, 13.2)
- Log-rank statistic p-value: 0.1051

Issues:
- The hazard ratio indicates that the experimental arm has
  - A better performance
  - A constant improvement in the treatment effect relative to the control
- Median survival is better in the control arm
Presentation of Hazard Ratio

Constant Hazard Ratio

Hazard Ratio Over Time
Difference in Milestone Survival Over Time
Restricted Mean Survival Over Time

RMST by Arm

Difference in RMST
The Underlying Kaplan-Meier Curves

Administrative censoring
Summary

• Overall survival remains a very good endpoint under certain assumptions

• Alternative endpoints such as milestone or restricted mean survival
  – Predictable length of study duration (time-driven)
  – Survival endpoints
  – Allow both relative and absolute measure of treatment effects (over time)
  – More powerful under certain patterns of non-proportionality in hazard ratio

• Reporting of milestone survival, restricted mean survival and change in hazard ratio is recommended to complement KM curve
References (in chronological order)


• Royston, P and Palmer, MKB. (2013). Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMRM, 13:152.


Session IIIb Panel Discussion
Use of Alternate Efficacy Endpoints with I-O Products

Moderator: Marc Theoret, MD

Speakers:
Sirisha Mushti, PhD
Xin (Cindy) Gao, PhD
Antoni Ribas, MD, PhD
Jan Bogaerts, PhD
Daniel S. Chen, MD, PhD
Keaven Anderson, PhD
Tai-Tsang Chen, PhD

Panelist: Kun He, PhD
Phase III Design Considerations for Agents with a Potential Predictive Biomarker

Edward L. Korn
Biometric Research Program
National Cancer Institute
I have no financial relationships to disclose.

- and -

I will not discuss off label use and/or investigational use in my presentation.

- and -

The views expressed represent my own and do not necessarily represent the views or policies of the National Cancer Institute.
• Some agents may only benefit a subgroup of a histologically defined population

• Successful evaluation requires co-development of biomarkers to identify sensitive subpopulations

• Various design strategies to integrate treatment and biomarker evaluation are available

• Choice of phase III design depends on the biomarker’s credentials
Focus of this talk

• Binary biomarker separates the population of interest into biomarker-positive (B+) and biomarker-negative (B-) subgroups

• Analytical validity of the biomarker assay has been established

• Biomarker credentials are sufficient to assume that B- patients benefit only if B+ patients benefit
Biomarker with very strong credentials:

Convincing evidence indicates that the benefits of the treatment, if any, are limited to the biomarker-positive subgroup of patients.
Biomarker with very strong credentials: use Enrichment design

Measure biomarker

Biomarker-positive (B+)

Randomize

New Drug Control

Biomarker-negative (B-)

Off Study
Examples:
**BRIM3** (metastatic melanoma)
- vemurafenib vs. standard chemotherapy
- 2107 patients screened to identify 675 patients with BRAF mutation

**KEYNOTE-010** (advanced NSCLC)
- pembrolizumab vs. docetaxel
- 2699 patients screened to identify 1475 patients with PD-L1 expression of at least 1%
Limitations of Enrichment design:

Unless external evidence clearly limits benefit to B+ patients, a positive enrichment study leaves open:

• Whether the treatment benefit extends to biomarker-negative patients

• Whether the costs and inconvenience of routine use of the biomarker to select patients for treatment are justified
Modified enrichment design (example)
CALGB 30801
Chemo+Celecoxib vs Chemo+Placebo in NSCLC

Primary analysis: Cox-2 expression index ≥ 4 subgroup

Measure Cox-2 expression

Cox-2 ≥ 2
Randomize
Celecoxib

Cox-2 < 2
Off Study
Placebo
Biomarker with strong credentials:

Evidence is convincing enough to assume that the treatment is more likely to be effective (and is probably more effective) in the biomarker-positive subgroup than the biomarker-negative subgroup, but the evidence is not sufficiently compelling to rule out a clinically meaningful benefit in the biomarker-negative subgroup.
Biomarker credentials are strong:
use
Biomarker-stratified (randomize-all) designs

Measure biomarker

Biomarker-positive (B+)

Randomize

New Drug

Control

Biomarker-negative (B-)

Randomize

New Drug

Control
Goals of a biomarker-stratified phase III trial

• Assess benefit in each biomarker subgroup

• Recommend drug to patients who benefit

• Do not recommend drug to patients who do not benefit
Different formal analysis strategies for biomarker-stratified trial design

- Subgroup-specific strategies
  - parallel version
  - sequential version

- Biomarker-positive/Overall strategies
  - parallel version
  - sequential version

- MaST
Subgroup-specific parallel strategy

**Test B+**
If significant at level $\alpha_1$

- **YES**: Recommend treatment for B+
- **NO**: Do not recommend treatment for B+

**Test B-**
If significant at level $\alpha-\alpha_1$

- **YES**: Recommend treatment for B-
- **NO**: Do not recommend treatment for B-
Subgroup-specific sequential strategy

Test B+
If significant at level $\alpha$

YES

Test B-
If significant at level $\alpha$

YES
Recommend treatment for all patients

NO
Recommend treatment for B+ only

STOP

NO
Do not recommend the treatment
Example: PRIME study
Chemotherapy ± Panitumumab in metastatic colorectal cancer

- Biomarker: KRAS status

- B+ population  KRAS WT (n=656)
PFS: HR=0.80  (0.66, 0.97)

- B- population  KRAS MT (n=440)
PFS: HR=1.29  (1.04, 1.62)
Biomarker-positive/overall parallel strategy

Test overall population if significant at level $\alpha_1$

- YES: Recommend treatment for all patients
- NO: Do not recommend treatment for all patients

Test B+ if significant at level $\alpha-\alpha_1$

- YES: Recommend treatment for B+
- NO: Do not recommend treatment for B+
Biomarker-positive/overall sequential strategy

Test B+
if significant at level $\alpha$

YES

Test overall population
if significant at level $\alpha$

YES
- Recommend treatment for all patients

NO
- Recommend treatment for B+ only

NO
- STOP

NO
- Do not recommend treatment
Example:

KEYNOTE-010 (pembrolizumab vs docetaxel)

B+ population (PD-L1 \geq 50\%, n=442)
OS: HR=0.53  (0.40, 0.70)

Overall population (PD-L1 \geq 1\%, n=1033)
OS: HR=0.67  (0.56, 0.80)

[analysis plan was more complex than this]
Example: Lapatinib+letrozole vs. Placebo +letrozole in metastatic breast cancer

• HER2-positive (n=219)
  PFS: HR=0.71  p-value=.019

• Overall population (n=1286)
  PFS: HR=0.86  p-value=.026
Problem with biomarker-positive/overall strategies

These strategies may formally recommend treatment for biomarker-negative patients even though the treatment is ineffective in these patients.

**Reason:** Even with no benefit in B- patients a statistically significant effect can be still observed in the overall population if the effect in B+ patients is large.
Example: Lapatinib+letrozole vs. Placebo +letrozole in metastatic breast cancer

• HER2-positive (n=219)
  PFS: HR=0.71  p-value=.019

• Overall population (n=1286)
  PFS: HR=0.86  p-value=.026

• HER2-negative (n=952)
  PFS: HR=0.90  p-value=.188
Example:
KEYNOTE-010

B+ population (PD-L1 ≥ 50%, n=442)
OS: HR=0.53 (0.40, 0.70)

Overall population (PD-L1 ≥ 1%, n=1033)
OS: HR=0.67 (0.56, 0.80)

B- population (1% ≤ PD-L1< 50%, n=591)
OS: HR=0.76 (0.60, 0.96)
Marker Sequential Test
MaST($\alpha, \alpha_1$)

Test B+
If significant at level $\alpha_1$

YES

Test B-
if significant at level $\alpha$

YES
  Recommend treatment for all patients

NO
  Recommend treatment for B+ only

Test overall population
if significant at $\alpha_2=\alpha-\alpha_1$

YES
  Recommend treatment for all patients

NO
  Do not recommend the treatment
MaST design allows one to

• minimize the probability of recommending ineffective treatment for B- patients

• maximizing power for treatments when the treatment effect is similar in the B+ and B- subgroups.
Example using MaST design

ECOG E1910 (NCT02003222)

Blinatumomab in ALL
n=285, MAST

Biomarker: minimal residual disease after induction therapy
Recommendations

Select phase III design based on biomarker’s credentials.

If the biomarker-negative patients are treated in a biomarker-stratified design, then the treatment effect in this subgroup should also be assessed.
References

Trials:

Others:
Immuno-Oncology Combinations – Clinical Trial Design Considerations

Lillian L. Siu, MD
Princess Margaret Cancer Centre
Toronto, Canada
Disclosures (2015-2016)

I have the following financial relationships to disclose:

Consultant for: Boehringer-Ingelheim (uncompensated), Merck (compensated), Pfizer (compensated), Celgene (compensated)

Speaker’s Bureau for: None

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Stockholder in: None

Honoraria from: None

Employee of: None
Requirements for Spontaneous or Therapeutic Immune Response

Chen and Mellman, Immunity 2013 39, 1-10 DOI: (10.1016/j.immuni.2013.07.012)
Immunogenic Tumors

Non-immunogenic Tumors

- Tregs
- Macrophages
- TGFβ
- T cell exhaustion

• Immune Checkpoint Inhibitors
  • Adoptive Cell Therapy

• Vaccines
• CAR T cells
• TCR Transduction
• Oncolytic Viruses
• IO+IO combinations

Courtesy P. Ohashi
PD-1/PD-L1 Combinations in Development

- Anti-CTLA-4 (Ipilimumab, Tremelimumab)
- Other immune checkpoint inhibitors (anti-; LAG3, KIR, TIM3)
- Co-stimulatory molecules (anti-: IDO, OX40, GITR, CD-137/4-1BB)
- Anti-CSF-1R
- Anti-VEGF (Bevacizumab, Aflibercept)
- Cytokines (IFN, IL-21, IL-2)
- Peptide vaccines
- Adoptive cell therapy (ACT)
- Oncolytic viruses (TVEC, etc)
- Targeted therapy (e.g. Dabrafenib +/- Trametinib; Vemurafenib +/- Cobimetinib)
- HDAC inhibitors
- Hypomethylating agents
- PARP inhibitors
- Chemotherapy
- Radiation therapy
At the request of the speaker, this slide has been withheld from the online posting.
<table>
<thead>
<tr>
<th>Rationale</th>
<th>Example</th>
<th>IO Example</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Synergistic effects</strong></td>
<td>▪ Dual HER2 blockade in breast cancer&lt;br&gt;▪ BRAF and MEK inhibition in melanoma</td>
<td>MEK inhibition and immune checkpoint blockade</td>
</tr>
<tr>
<td><strong>Synthetic lethality</strong></td>
<td>▪ PARP inhibition plus RT or DNA damaging agent</td>
<td>TGFβ inducing BRACness resulting in synthetic lethality with PARP inhibition</td>
</tr>
<tr>
<td><strong>Reversal of resistance</strong></td>
<td>▪ Cell cycle inhibition and ER inhibition in breast cancer&lt;br&gt;▪ TIM3 inhibition and PD1/L1 inhibition</td>
<td></td>
</tr>
</tbody>
</table>
# Pembrolizumab: Early Signals of Combo Activity

<table>
<thead>
<tr>
<th>Author</th>
<th>Meeting</th>
<th>Agent #1</th>
<th>Agent #2</th>
<th>Indication</th>
<th>N</th>
<th>ORR</th>
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</thead>
<tbody>
<tr>
<td>San Miguel</td>
<td>ASH 2015</td>
<td>Lenalidomide</td>
<td>Dex</td>
<td>RRMM</td>
<td>17</td>
<td>76%</td>
</tr>
<tr>
<td>Bedros</td>
<td>ASH 2015</td>
<td>Pomalidomide</td>
<td>Dex</td>
<td>RRMM</td>
<td>27</td>
<td>60%</td>
</tr>
<tr>
<td>Papa</td>
<td>ASCO 2016</td>
<td>Pemetrexed</td>
<td>Carboplatin</td>
<td>NSCLC</td>
<td>24</td>
<td>58%</td>
</tr>
<tr>
<td>Long</td>
<td>ASCO 2016</td>
<td>T-vec</td>
<td></td>
<td>Melanoma</td>
<td>21</td>
<td>57.3%</td>
</tr>
<tr>
<td>Long</td>
<td>ASCO 2016</td>
<td>LD-Ipi</td>
<td></td>
<td>Melanoma</td>
<td>153</td>
<td>57%</td>
</tr>
</tbody>
</table>
| Atkins    | SITC 2016 | Axitinib         |          | RCC        | 11 | 54.5%
| McDermott | ESMO 2016 | Pazopanib       |          | RCC        | 20 | 40%  |

*Courtesy P. Bedard*
Phase III Trial of Nivolumab + Ipilimumab vs Nivolumab vs Ipilimumab in Treatment-Naïve Advanced Melanoma (Checkmate 067)

Progression-Free Survival (Intent-to-Treat Population)

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting
Phase III Trial of Nivolumab + Ipilimumab vs Nivolumab vs Ipilimumab in Treatment-Naïve Advanced Melanoma (Checkmate 067): Treatment-Related AEs

Most Common Treatment-related Select AEs

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI (N=313)</th>
<th></th>
<th>NIVO (N=313)</th>
<th></th>
<th>IPI (N=311)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
<td>Grade 3-4</td>
<td>Any Grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Skin AEs, %</td>
<td>60.4</td>
<td>5.8</td>
<td>43.8</td>
<td>2.2</td>
<td>54.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Rash</td>
<td>28.4</td>
<td>2.9</td>
<td>22.7</td>
<td>0.3</td>
<td>21.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>35.1</td>
<td>1.9</td>
<td>20.4</td>
<td>0.3</td>
<td>36.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Gastrointestinal AEs, %</td>
<td>47.6</td>
<td>15.3</td>
<td>21.7</td>
<td>2.9</td>
<td>37.3</td>
<td>11.6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>45.4</td>
<td>9.6</td>
<td>20.8</td>
<td>2.2</td>
<td>33.8</td>
<td>6.1</td>
</tr>
<tr>
<td>Colitis</td>
<td>11.5</td>
<td>8.0</td>
<td>2.2</td>
<td>1.0</td>
<td>11.3</td>
<td>8.0</td>
</tr>
<tr>
<td>Endocrine AEs, %</td>
<td>32.3</td>
<td>5.8</td>
<td>15.7</td>
<td>1.6</td>
<td>11.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>16.0</td>
<td>0.3</td>
<td>9.3</td>
<td>0</td>
<td>4.5</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>10.2</td>
<td>1.0</td>
<td>4.5</td>
<td>0</td>
<td>1.0</td>
<td>0</td>
</tr>
<tr>
<td>Hepatic AEs, %</td>
<td>31.6</td>
<td>19.8</td>
<td>7.3</td>
<td>2.6</td>
<td>7.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>17.9</td>
<td>8.6</td>
<td>3.8</td>
<td>1.0</td>
<td>3.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>15.7</td>
<td>6.1</td>
<td>4.2</td>
<td>1.0</td>
<td>3.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Pulmonary AEs, %</td>
<td>7.3</td>
<td>1.0</td>
<td>1.6</td>
<td>0.3</td>
<td>1.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6.7</td>
<td>1.0</td>
<td>1.3</td>
<td>0.3</td>
<td>1.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Renal AEs, %</td>
<td>6.4</td>
<td>1.9</td>
<td>1.0</td>
<td>0.3</td>
<td>2.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>4.2</td>
<td>0.3</td>
<td>0.6</td>
<td>0.3</td>
<td>1.6</td>
<td>0</td>
</tr>
</tbody>
</table>

• Immune-modulating medicines were used to manage adverse events and led to resolution rates of immune mediated AEs in the vast majority (>85%) of patients

Database lock Nov 2015

Presented By Jedd Wolchok at 2016 ASCO Annual Meeting
### Phase I Dabrafenib + Ipilimumab: Hepatic Toxicities

**Table 1.** Data for Patients with Grade 3 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels While Receiving Combination Therapy with Vemurafenib and Ipilimumab.

<table>
<thead>
<tr>
<th>Study Cohort and Patient No.</th>
<th>No. of Doses of Ipilimumab before ALT–AST Elevation</th>
<th>Time to Onset of ALT–AST Elevation after First Dose of Ipilimumab</th>
<th>Treatment</th>
<th>Time to Resolution of ALT–AST Elevation</th>
<th>Toxicity Relapse with Repeated Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>21 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab permanently discontinued</td>
<td>4 days</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>36 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (2 doses)</td>
<td>6 days</td>
<td>No</td>
</tr>
<tr>
<td>6†</td>
<td>1</td>
<td>21 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab continued (1 dose)</td>
<td>6 days</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>19 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (1 dose)</td>
<td>12 days</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Second cohort</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>15 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 7 days and then restarted with dose reduction; ipilimumab permanently discontinued</td>
<td>10 days</td>
<td>NA</td>
</tr>
<tr>
<td>16‡</td>
<td>1</td>
<td>13 days</td>
<td>Vemurafenib and ipilimumab permanently discontinued</td>
<td>20 days</td>
<td>NA</td>
</tr>
</tbody>
</table>
### Examples of Phase I Trial Designs Used in IO-Based Combinations

<table>
<thead>
<tr>
<th>Combination</th>
<th>N</th>
<th>Tumor type</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab and Nivolumab</td>
<td>86</td>
<td>Melanoma (no prior ICI)</td>
<td>3+3 initially but changed to allow cohort expansion; both agents undergo dose escalation</td>
</tr>
<tr>
<td>PF-05082566 (4-1BB agonist) and Pembrolizumab</td>
<td>23</td>
<td>Solid tumors (prior ICI allowed)</td>
<td>Time-to-event continual reassessment method, after single agent PF-05082566 study, pembrolizumab dose fixed</td>
</tr>
<tr>
<td>MOXR0916 (OX40 agonist) and Atezolizumab</td>
<td>28</td>
<td>Solid tumors (prior ICI allowed)</td>
<td>3+3 after single agent MOXR0916 study, atezolizumab dose fixed</td>
</tr>
</tbody>
</table>

ICI = immune checkpoint inhibitors

Wolchok et al. NEJM 2013; Tolcher et al. ASCO 2016, abs 3002; Infante et al. ASCO 2016, abs 101
In Silico Analysis to Identify Rational IO Drug Combinations

1. Identify immune modulatory targets (costimulatory agents, immune checkpoints)
2. Identify IO drugs for these targets
3. Identify all IO combos (2+) with these drugs

Heatmap (TCGA): immune modulatory targets; disease site; mutational status

Response rates to PD1/L1 inhibitors in different disease sites

PD1/L1 heatmap in different disease sites

Overall Disease site Disease site Disease site Mutational status Mutational status Mutational status Mutational status
INvestigator-initiated Phase II Study of Pembrolizumab Immunological Response Evaluation (INSPIRE)

SCCHN, TNBC, EOC type II, MM, Mixed Solid Tumors (n = 20 each)
Pembrolizumab 200 mg IV Q 3 Weeks

N = 100

Time:
- Baseline
- Response/Primary Progression
- Progression post Response (among Responders)

In vitro predictive assay, CtDNA at multiple time points

Radiomic imaging analysis

Tumor bx: WES, RNASeq

Radiomic imaging analysis

Tumor bx: WES, RNASeq

Radiomic imaging analysis

Tumor bx: WES, RNASeq
At the request of the speaker, this slide has been withheld from the online posting.
## Factors Influencing Choice of Dose Escalation Methods

<table>
<thead>
<tr>
<th>Factors</th>
<th>Dose Escalation Method</th>
<th>Ranking of Importance of Factors in Choice of Dose Escalation Method (rank from most important to least important)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Lack of preclinical data</td>
<td>3+3</td>
<td></td>
</tr>
<tr>
<td>2. Risk of narrow therapeutic index</td>
<td>Rolling 6</td>
<td></td>
</tr>
<tr>
<td>3. Limited patient population</td>
<td>Accelerated titration</td>
<td></td>
</tr>
<tr>
<td>4. Risk of delayed/late toxicity</td>
<td>Modified toxicity probability interval (mTPI)</td>
<td></td>
</tr>
<tr>
<td>5. Lack of biostatistical support</td>
<td>EWOC or other BLRM</td>
<td></td>
</tr>
<tr>
<td>6. Precision of MTD/RP2D is critical</td>
<td>TITE-CRM</td>
<td></td>
</tr>
<tr>
<td>7. High likelihood of no DLT</td>
<td>Other: _________</td>
<td></td>
</tr>
<tr>
<td>8. Need to complete trial as quickly as possible</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
“Zone” Dose Escalation Design

- Results of \( d_2 \) determine the opening or closure of \( d_4 \).
- Results of \( d_3 \) determine the opening or closure of \( d_6 \).
- Dose \( d_5 \) is opened only if the results of both \( d_2 \) and \( d_3 \) indicate that it can be opened.
- In general, the decision to open a combination dose to testing depends upon the results of both its horizontal and vertical neighbors in the lower dose zone.

Reference:
At the request of the speaker, this slide has been withheld from the online posting.
Conclusions

• IO-based combinations currently are largely based on empiricism

• Rational design of combination studies:
  – Need knowledge base of existent studies as “baseline”
  – Non-clinical models are not ideal

• Clinical trial considerations are important:
  – Assessment of additive toxicity (including delayed)
  – Short term read out for efficacy – immunophenotyping, clinical parameters

• Era of triple IO combinations is near
Disclosures:

Grant/Research Support: Merck, Prometheus

Consultant: Amgen, BMS, Green Peptide, Roche, SolaranRx, Novartis
The burden of operable intermediate & high-risk disease numerically dwarfs that of advanced melanoma while the burden of early disease exceeds both.
Multiple Options for Systemic Therapy of Advanced Melanoma

**Targeted:**
- Vemurafenib
- Dabrafenib
- Trametinib
- Cobimetinib
- Dabrafenib/Trametinib
- Vemurafenib/Cobimetinib

***

**Chemotherapy:**
- Dacarbazine
- (Temozolomide)

**Immunotherapy:**
- Interleukin 2
- Ipilimumab
- Pembrolizumab
- Nivolumab
- Talimogene-laherparevce
- Ipilimumab/Nivolumab

**Combinations**

- Ipilimumab/Nivolumab
The Problem for Advanced Melanoma Therapy Development: Time, Numbers, Costs

- Phase III trials of new IO and TT agents have yielded 10 approvals to date, & more pending
- Need is for more efficient evaluation of new agents, combinations, especially after progression on anti-PD1 agents
- Limited capacity to assess the binary, ternary…combinations given:
  - time (7 years on average)
  - patients (hundreds per arm)
  - resources ($$ millions)
Current Phase III Melanoma Research in the National Cooperative Groups

BRAF Mut. V600E/K Melanoma

Is landmark 2 year OS improved with Ipi/Nivo anti-CTLA4/anti-PD1 regimen vs. Dabrafenib/Trametinib BRAFi/MEKi initial therapy

EA6134, M Atkins PI

Wild-type Melanoma

Does GM-CSF improve the OS (and reduce toxicity) of Ipi-Nivo regimen

EA6141 S. Hodi, PI
Phase III Intergroup Trial of Dream Doublets Ipi/Nivo → D/T vs D/T → Ipi/Nivo: EA6134 (n=300, 2 yr. OS)

- **Arm 1:**
  - Ipi 3/Nivo 1 mg/kg q 3wks x 4 +Maint Nivo
  - Randomize

- **Arm 2:**
  - D 150 BID / T 2 mg Qd
  - Randomize

**ECOG PS**
1. 0
2. 1

**LDH**
1. Normal
2. Elevated

**Intergroup protocol EA6134**
- Atkins, Chmielowski, Ribas and Kirkwood
- Open July 2015
**Current Melanoma Research in the Cooperative Groups**

**BRAF Mut. V600E/K Melanoma**

Is landmark 2 year OS improved with Ipi/Nivo anti-CTLA4/anti-PD1 regimen vs. Dabrafenib/Trametinib BRAFi/MEKi

EA6134, M Atkins PI

**Wild-type Melanoma**

Does GM-CSF improve the OS (and reduce toxicity) of Ipi-Nivo regimen

EA6141 S. Hodi, PI
A, Primary efficacy analysis (stratified HR = 0.64; 1-sided 90% repeated CI with upper bound 0.90; P value 1-sided using the stratified log-rank test).
B, Intent-to-treat analysis: No significant difference in progression-free survival between groups (stratified HR = 0.87 [95%CI, 0.64-1.18]; P value 2-sided and calculated using the stratified log-rank test.)
EA6141 Phase II-III (n=240-400, endpoint OS)

Induction Therapy Cycles

**Arm A**
- Nivolumab 1mg/kg IV Day 1
- Ipilimumab 3 mg/kg IV Day 1 Cycles 1-4
- Sargramostim 250 ug SubQ days 1-14 of each cycle
- Every cycle for 4 cycles.

**Arm B**
- Nivolumab 1mg/kg IV Day 1 Cycles 1-4
- Ipilimumab 3 mg/kg IV Day 1 Cycles 1-4
- Every cycle for 4 cycles.

Maintenance Therapy Cycles 5 and higher

- Nivolumab 3mg/kg IV Day 1 of each cycle
- Sargramostim 250 ug SubQ days 1-14 of each cycle
- Nivolumab 3mg/kg IV Day 1 of each cycle
- PD: Discontinue treatment
- **24 weeks** Reassess for evidence of anti-tumor response
- PR, SD, CR: Continue maintenance therapy

Strat Factors:
- BRAF mutant, WT or unknown
- Stage: III/M1a, M1b, M1c

Accrual Goal= 360
1 cycle= 21 days

1. Scans will be done at week 12 but treatment should continue until week 24 regardless of progression unless treatment is contraindicated by Section 5.8.X.
International Melanoma Working Group (IMWG) Challenge: 
Improve Strategy for Development of New Therapies

Melanoma International Collaboration for Adaptive Trials (MICAT)

To transform the development of melanoma therapies at a global level:

Grant McArthur, Mark Middleton, John Kirkwood, Dirk Reitsma, Don Berry, Valerie Guild, Julia Keith
micat@ndi.com
The Problem

Development of combination therapies for cancer is slow, expensive and prone to failure in phase 3.
An adaptive platform trial that enables testing of multiple combinations based upon state-of-the-art biomarkers and option for more rapid regulatory approval
The International Melanoma Working Group Collaboration
Collaborative Phase II → Phase III adaptive design

Academic-industry collaboration to encompass multiple lines of therapy
- Concurrent evaluation of multiple candidate drugs of multiple therapeutic classes to define optimal target population
- Assign patients in each subpopulation to treatment with highest probability of success
- Test treatment interactions with established and emerging biomarkers
- Drop or graduate candidate drugs based on posterior probability of success in Phase III
- Address sequencing and which therapy is best given first (if multiple options exist)
# Benefits of MICAT

- **Speed effective therapies to patients**
- **Adaptive statistical methodology accelerates key development decisions**
- **Higher success rates in late stage development**
- **Sponsors no longer need to invest in individual melanoma trials**
Alternatives

Cooperative groups

Individual industry sponsored phase 2-3 trials

Investigator initiated trials in limited number of centers

Too slow, limited in impact and/or expensive
At the request of the speaker, this slide has been withheld from the online posting.
Design

Can include Personalized vaccine Evaluation of genomic and cellular biomarkers throughout
Launch Planning for 2017

• Robust biomarker platform
  – Genomic WES, WGS, RNAseq, proteomics
  – Immune profiling- tumor cell infiltrates, PD-L1

• Investment to “kick-start” study and facilitate alignment of multiple industry collaborators to initiate the trial

• Precedents: I-SPY, GBM-Agile…
The Problem of Trial Development is Greater for Adjuvant Therapy of Melanoma: Longer Time, Larger Numbers and Costs

- Phase III Trials E1684, E1690, E1694, E1609, WHO16, EORTC 18991 and 18071 have required thousands of patients & nearly a decade of time apiece & $$millions to reach current approvals (HD-IFN, PegIFN & HD-Ipilimumab)

- Limited capacity to evaluate new agents, binary/ternary…combinations in phase III trials for OS, RFS:
  - time (~decade on average)
  - patients (hundreds $\rightarrow$ thousands)
  - societal resources (>$$ millions)
Adjuvant Therapy with IFN, anti-CTLA4, anti-PD1 Blockade: Open Questions

• Dosage optima and duration of treatment required?
  − Randomized discontinuation trials needed

• Optimal combinations?
  − With other immunotherapy, targeted therapy, RT, Vaccines, oncolytic viruses, TLR9 agonists, IDO inhibitors…

• Are therapies more effective earlier in disease progression?
  − US Intergroup S1404: Pembro vs. IFN or Ipi (in progress)
  − EORTC: Pembro vs. placebo with crossover
  − BMS: Nivo vs. Ipi
  − Novartis: Combi-Ad
  − Roche-Genentech: BRIM8

• Biomarker refinement key to optimize future therapy selection
Adjuvant Treatment after Surgery for High Risk Melanoma Is More Effective than for Metastatic Disease

- High-dose Interferon with 16% response rate in advanced disease lowers relapse risk by 33%-40%
- High-dose Ipilimumab with 11% response rate in advanced disease lowers relapse/mortality risk by 25-28%
<table>
<thead>
<tr>
<th>Study/PI</th>
<th>Stage</th>
<th>N</th>
<th>Treatment agent/ dosage/duration</th>
<th>Median follow up (years)</th>
<th>Impact on RFS (%)</th>
<th>Impact on OS (%)</th>
<th>(%) Toxicity</th>
<th>Attrition Rate</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1684</td>
<td>T4, N+</td>
<td>287</td>
<td>IFNα2b 20 MU/m2/D IV for 1 month. Then, 10 MU/m2 SC TIW for 11 months vs. Observation</td>
<td>6.9</td>
<td>0.61; p=.001</td>
<td>0.67; p=.01</td>
<td>26</td>
<td></td>
<td>At 12.6 yr, the impact of competing causes of death on OS to be considered</td>
</tr>
<tr>
<td>E1690</td>
<td>T4, N+</td>
<td>642</td>
<td>IFNα2b 20 MU/m2/D IV for 1 month. Then, 10 MU/m2 SC TIW for 11 months vs. 3 MU/D given SC TIW for 2 years vs. Observation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.3</td>
<td></td>
<td>0.78; p=.05</td>
<td>1.0</td>
<td>13</td>
<td></td>
<td>Cross over of observation pts to HDI at nodal relapse (n=38 pts) expected to affect OS analysis</td>
</tr>
<tr>
<td>E1694</td>
<td>T4, N+</td>
<td>880</td>
<td>IFNα2b 20 MU/m2/D IV for 1 month. Then 10 MU/m2 SC TIW for 11 months vs. GMK vaccine for 96 wks</td>
<td>1.3</td>
<td>0.67; p=.0004</td>
<td>0.72; p=.023</td>
<td>10</td>
<td></td>
<td>Symmetrical impact upon RFS, OS for IFN over GMK led to early closure for vaccine futility at 2 yrs.</td>
</tr>
<tr>
<td>EORTC 18071</td>
<td>N1-2</td>
<td>951</td>
<td>Ipi at 10 µg/kg/3 wks x12 weeks) then 10 µg/kg/3 mos (x3 yrs) vs. Placebo</td>
<td>2.7</td>
<td>0.75; P=.011</td>
<td>0.72; p=.001</td>
<td>44</td>
<td></td>
<td>Impact upon RFS at initial reporting</td>
</tr>
</tbody>
</table>
EORTC 18071/CA184-029 Study Design

**INDUCTION**
- Ipilimumab 10 mg/kg Q3W X4

**High-risk**, stage III, completely resected melanoma

**N=475**

**MAINTENANCE**
- Ipilimumab 10 mg/kg Q12W up to 3 years

**N=476**

**INDUCTION**
- Placebo Q3W X4

**MAINTENANCE**
- Placebo Q12W up to 3 years

**Week 1**

**Week 12**

**Week 24**

- Treatment up to a maximum 3 years, or until disease progression, intolerable toxicity, or withdrawal

Stratification factors:
- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)
- Primary Endpoint: RFS

Eggermont et al., Proc ASCO 2014
At the request of the speaker, two slides have been withheld from the online posting.
EORTC 18071 Final Analysis at 5.3 Years
Overall Survival

Patients Alive (%)

<table>
<thead>
<tr>
<th>Years</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients at risk</td>
<td>162</td>
<td>475</td>
<td>431</td>
<td>369</td>
<td>325</td>
<td>290</td>
<td>199</td>
<td>62</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>214</td>
<td>476</td>
<td>413</td>
<td>348</td>
<td>297</td>
<td>273</td>
<td>178</td>
<td>58</td>
<td>8</td>
</tr>
</tbody>
</table>

Ipilimumab Placebo
Deaths/patients 162/475 214/476
HR (95.1% CI)* 0.72 (0.58, 0.88)
Log-rank P value* 0.001

*Stratified by stage provided at randomization.
Deaths Related to Adjuvant HD Ipilimumab Treatment

- Five patients (1.1%) died of drug-related AEs in the high-dose ipilimumab group:
  - Three patients with colitis (2 with perforations)
  - One patient with myocarditis
  - One patient with Guillain-Barré syndrome
- No deaths due to intervention in placebo group
- Raise question of optimal dosage (3 vs 10 mg/kg) given lesser toxicity of 3mg/kg approved for metastatic melanoma

Eggermont et al., Proc ASCO 2014
US Intergroup Adjuvant Phase III Trial E1609: Ipilimumab vs. HDI
(Accrual of 1678 Pts Completed 2014 with endpoint OS data ~2018)

Pts with resectable IIIB, IIIC M1a, M1b

Surgery

N=1578

Endpoints
- OS co-primary with RFS
- QOL
- Immunological correlates of RFS, OS
  - serial blood serum and lymphocytes
  - baseline tissue blocks

Ipilimumab 10 mg/kg

HDI

Ipilimumab 3 mg/kg
At the request of the speaker, 15 slides have been withheld from the online posting.
Neoadjuvant Therapy has Considerable Advantages

Clinically
• Improves clinical outcome for multiple solid tumors (H&N, breast, bladder, esophageal and rectal)\textsuperscript{1,2,3,4}
  – survival, resectability, local control, organ preservation

• Accelerates progress
  – Neoadjuvant read-out in 2-3 mos cf. ~10 years
  – Improve therapeutic index, cost effectiveness

Experimentally
• Evaluate clinical impact in relation to pathologic, immune, and molecular ∆’s

• Access to tumor tissue and blood (both before and after intervention)
  – Investigation of antitumor mechanisms of action
    • IFN effects upon STAT3, STAT1, and T cell/DC tumor infiltration
    • Ipi effects upon TIL, Treg, MDSC
  – Biomarker studies in blood correlated to tumor

**Enrollment**

Stage IIIB, IIIC melanoma (Tx, N2b, or N3, M0)

- *Excisional biopsy (sample 1)*

**IFN-α2b induction therapy**

(20 MU/m²/d IV 5d/wk, × 4 wks)

**Radical regional lymphadenectomy (sample 2)**

**IFN maintenance therapy**

(10 MU/m²/d tiw, × 48 wks)

---

**Neoadjuvant Evaluation of the Mechanism of HD IFN in Stage IIIB Melanoma**

Schema: UPCI 00-008

Moschos et al., JCO 2006
Before IFN

After IFN
HDI Down-Regulates pSTAT3 Tyr705 And STAT3 Expression in Tumor Cells

Pretreatment

Post treatment

H&E

IHC

Blue = pSTAT3tyr705
Red = STAT3

Wang et al., Clin Cancer Res 2007
Neoadjuvant Ipilimumab in N1b, 2b, N2c, N3 Melanoma

UPCI 08-144

Enrollment

Tx, N2b, N2c or N3, M0

Excisional biopsy (sample 1)

Ipilimumab 10 mg/kg every 21 days x 2

Radical regional lymphadenectomy (sample 2)

Ipilimumab 10 mg/kg every 21 days x 2

Tarhini et al., AACR 2012, ASCO 2012
UPCI 08-144: Disease Response by PET-CT at 6 weeks

Pre-treatment 6 weeks post anti-CTLA4
Randomized Neoadjuvant IFN + Ipilimumab Trial
UPCI 11-063 for N1b,2b, N2c, N3 Melanoma

N1b, N2b, N2c or N3, M0

IFN-Ipilimumab (3 vs. 10 mg/kg) Induction

IFN-Ipilimumab (3 vs. 10 mg/kg) Maintenance

Excisional or partial biopsy (sample 1)

Radical regional lymphadenectomy (sample 2)

Baseline tumor assessment (clinical/radiologic)

Preoperative tumor assessment (clinical/radiologic)

• Ipi 3 or 10 mg/kg IV q 3 wks x 4 bracketing definitive surgery, then q 12 wks x 4
• HDI 20 MU/m²/d IV x 5 d/wk x 4 wks then 10 MU/m²/d SC qod TIW for 48 wks
<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; Median (range))</td>
<td>61 (37-76)</td>
</tr>
<tr>
<td>Cutaneous primary</td>
<td>21 (70)</td>
</tr>
<tr>
<td>unknown primary</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Mucosal</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Male</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Performance Status</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16 (53)</td>
</tr>
<tr>
<td>1</td>
<td>14 (47)</td>
</tr>
<tr>
<td>Recurrent disease after prior surgery</td>
<td>15 (50)</td>
</tr>
<tr>
<td>Presence of in-transit metastases</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Prior adjuvant HDI</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Estimated risk by Stage</td>
<td></td>
</tr>
<tr>
<td>IIIIB</td>
<td>3 (10)</td>
</tr>
<tr>
<td>IIICC</td>
<td>25 (83)</td>
</tr>
<tr>
<td>IV (Not eligible)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

Tarhini et al. 2016 ASCO
### Gr 3-4 immune related AEs by study arm

<table>
<thead>
<tr>
<th></th>
<th>Any Grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3/4 Ipi 3 mg/kg</th>
<th>Grade 3/4 Ipi 10 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Pts.</td>
<td>%</td>
<td>No. Pts.</td>
<td>%</td>
<td>No. Pts.</td>
</tr>
<tr>
<td>Adrenal insuff</td>
<td>10</td>
<td>33</td>
<td>2</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea/ Colitis</td>
<td>15</td>
<td>50</td>
<td>3</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>28</td>
<td>93</td>
<td>5</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Lipase inc</td>
<td>9</td>
<td>30</td>
<td>3</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Rash, maculo-papular</td>
<td>14</td>
<td>47</td>
<td>7</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Autoimmune nephritis</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Tarhini et al. 2016 ASCO
### Response rate (RR) by radiologic (preoperative vs. 6 weeks from baseline) and histologic (6-8 weeks from baseline) assessment

<table>
<thead>
<tr>
<th></th>
<th>All patients (N = 28)</th>
<th>Ipi 3 mg/kg (n = 14)</th>
<th>Ipi 10 mg/kg (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. pts.</td>
<td>%</td>
<td>No. pts.</td>
</tr>
<tr>
<td><strong>Radiologic preoperative RR (WHO; unconfirmed)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 (9 PR, 1 CR)</td>
<td>10</td>
<td>36%</td>
<td>4 (3 PR, 1 CR)</td>
</tr>
<tr>
<td><strong>Pathologic complete RR (no viable tumor on histologic assessment)</strong></td>
<td>9</td>
<td>32%</td>
<td>5</td>
</tr>
</tbody>
</table>

**Among radiologic responders**
- One relapsed and later responded to anti-PD1 antibody therapy

**Among complete pathologic responders**
- None relapsed to date

Tarhini et al. 2016 ASCO
• Relapse: 8 events
• Death: 3 events
Median follow up time for remaining patients: 11 months

PFS and OS (medians not reached for 3 or 10 Ipi+IFN)
Conclusion

• Neoadjuvant combination of Ipi-HDI exhibits promising clinical activity at both 3 & 10 mg/kg
• Less toxicity with Ipi at 3 mg/kg
• Longer follow up needed to define long term benefits and optimal Ipi dosage
• Studies of predictive biomarkers and mechanisms are ongoing
• Next neoadjuvant UPCI study Ipi-Nivo vs Nivo
Current US Intergroup Adjuvant Trial S1404
Tests anti-PD1

Stage IIIB-C (>N1) and IV (M1a, b)
• Pembrolizumab 200mg q 3 weeks x 1 yr vs.
• High-dose IFN (or FDA approved regimen)
  – Primary Endpoint: Overall Survival
  – Secondary Endpoints: RFS, QOL
To Build More Effective Adjuvant Therapy

• Combine IFNα and anti-CTLA4
  – In metastatic melanoma single institution phase II trial (Tarhini et al, 2012)
  – In national cooperative group phase II trial E3611
  – In neoadjuvant treatment of stage IIIB-C melanoma UPCI 11-063 (Tarhini et al., Proc ASCO 2016)

• Combine anti-PD1 & IFNα (Davar, Kirkwood, Zarour, 2016)

• Combine anti-PD1 and anti-CTLA4 (Tarhini, et al., 2016)

• Combine immunotherapy and BRAFi therapy
  – Combine IFNα + BRAFi UPCI 12-107 (Davar, 2016)
  – Combine anti-PD1 and BRAFi (Najjar, Kirkwood, 2016)
Rationale for IFN and Anti-PD1

- PD-1 blockade is most effective in “inflamed” tumors—defined by pre-existing CD8+ T-cell infiltrates
- Gene expression studies in melanoma link CD8+ T-cell infiltrate to inflammatory cytokine profile, type I IFN signaling cascade
- Type I IFN signaling is critical to tumor-antigen specific T-cell priming—and antigen presentation by host APCs
- UPCI 13-105 phase I/II trial tests Peg-IFN with Pembrolizumab to evaluate whether IFNα increases inflammation in the tumor microenvironment and PD-1 efficacy
UPCI 13-105 Phase I/II Trial of Peg-IFN + Pembrolizumab

• Phase I/II study of Pembrolizumab & Peg-IFN alfa-2b
  • Pembrolizumab 2mg/kg q3 weeks.
  • Peg-IFN 1-3ug/kg weekly in 3 dose levels.
• Dose escalation using modified toxicity probability incidence design w/continuous DLT monitoring
• Primary endpoints: safety, dose-limiting toxicities (DLTs)
• Secondary endpoints: ORR (RECIST 1.1), progression free and overall survival
  • 24 pts with advanced melanoma enrolled to date in phase I portion of this study
## UPCI 13-105 Phase I/II Trial of PegIFN+Pembrolizumab

### Response Rates (N=24)

<table>
<thead>
<tr>
<th></th>
<th>Best</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>7 (29%)</td>
<td>7 (29%)</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>8 (33%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>4 (17%)</td>
<td>14 (58%)</td>
</tr>
<tr>
<td>Overall response rate (CR+PR)</td>
<td>9 (38%)</td>
<td>8 (33%)</td>
</tr>
<tr>
<td>Disease control rate (CR+PR+SD)</td>
<td>17 (71%)</td>
<td>10 (42%)</td>
</tr>
</tbody>
</table>
UPCI 13-105 PegIFN + Pembrolizumab
Responses are Durable

Davar, Kirkwood and Zarour Proc ASCO 2016
Preliminary Conclusions of UPCI 13-105
Peg IFN + Pembrolizumab

- Pembrolizumab 2mg/kg q3 weeks + Peg-IFN 3ug/kg wkly is tolerable (RP2D)
  - Best ORR in pretreated patients 38%
  - Responses are durable
  - Accrual increased from 16 → 35 ongoing

- Neoadjuvant trial 14-102 testing HDI + Pembrolizumab in resectable IIIB-C in progress
Adjuvant Therapy Development Requires
Neoadjuvant Evaluation of Combinations

- IFNα and Ipilimumab have significant and durable benefits and are reference standards
  - IFNα complementary to anti-CTLA4 → IFNα+Ipilimumab combinations (UPCI neoadjuvant 11-063)
  - IFNα modulates tumor immune response & induces PDL1 → IFNα + anti-PD1 under exploration (neoadjuvant 14-102)

- Ipilimumab adjuvant benefit and toxicity profile differ from IFN — but optimal dose remains unclear
  - E1609 Intergroup trial of Ipi 3 & Ipi 10 vs IFNα will mature in next yr
  - Combinations of Ipi and IFNα under exploration for advanced/adjuvant

- Anti-PD1 combinations for advanced melanoma and adjuvant therapy need further exploration
  - Intergroup S1404 will define the role of adjuvant anti-PD1 alone
  - IDO inhibitors, TLR9 agonists, third generation CBI agents next
Thanks to our patients, program, and cooperative group members

UPCI Melanoma Program
Melanoma and Skin Cancer SPORE
ECOG-ACRIN Melanoma Committee
International Melanoma Working Group

Hassane Zarour
Ahmad Tarhini
Diwakar Davar
Yana Najjar

Lisa Butterfield
Louis Falo
Laura Ferris
Matt Holtzman

Craig Slingluff
David Lawson
F. Steven Hodi
Leslie Fecher

Helen Gogas
Valerie Guild
Peter Hersey
Grant MacArthur
Mark Middleton
Designing Late-Stage Randomized Clinical Trials with Cancer Immunotherapy: Can We Make It Simple?

Tai-Tsang Chen, PhD
Global Biometric Sciences, Bristol-Myers Squibb

AACR-FDA Workshop, Washington, DC
October 13-14, 2016
Disclosure

• Employment: currently employed by Bristol-Myers Squibb as Head of Global Biometric Sciences in Medical and Market Access

• The views expressed in this presentation are personal based on my experience and do not necessarily reflect the views of Bristol-Myers Squibb
Background


Non-Proportional Hazards Cure Rate Model

* CT: Chemotherapy; IO: Cancer immunotherapy; TT: Targeted therapy
** OS: Overall survival; PFS: Progression-free survival
Lesson Learned 1: Unique Survival Kinetics

Long-Term Survival

- **Study Design**
  - Enrolling an adequate number of patients
  - Identifying long-term survivors
  - Exploring novel endpoints

- **Statistical Analysis**
  - Milestone survival or Restricted mean survival
  - Hazard (ratio) over time

Delayed Clinical Effect

- **Study Design**
  - Accounting for the delayed duration in sample size determination
  - Increasing information fraction at the interim analysis

- **Statistical Analysis**
  - Milestone survival or Restricted mean survival
  - Hazard (ratio) over time
  - Weighted log-rank test
  - Ensure sufficient follow-up duration
Lesson Learned 2: The Tail of the Curve

• The primary focus of the OS trial has shifted from the improvement in OS to raising the tail of the curve

• There should exist an improvement in the tail of the curve that is considered clinically meaningful by treating physicians

• The tail needs to be accounted for somehow in the design or analysis
The Tail of the Curve: Milestone Survival

• Milestone survival
  – Defined as the Kaplan-Meier survival probability at a specific time point, such as two years
  – Previously proposed as an intermediate endpoint at the interim analysis
  – Overall survival remains as the primary endpoint at the final analysis

• A subset of patients with a pre-determined minimum follow-up duration is included in the interim milestone analysis

• Pros:
  – A preview of what the tail may look like
  – Early access of efficacious treatments to patients

• Cons:
  – Totality of data not accounted for with moderate correlation between overall survival and milestone survival
  – Censoring prior to milestone impacts milestone survival estimate

Proposed Design of Future Late-Stage IO Studies

• We want to design a study so that
  – Overall survival remains the primary endpoint – AND –
  – It is less sensitive to the uncertainty of the survival kinetics – AND –
  – The tail of the curve is accounted for.

• Proposal: Designing the study using milestone survival and analyzing the data with co-primary endpoints of OS and MS
  – Treatment effect
  – Follow-up duration
  – False positive error rate
  – Sample size determination
An Illustrative Example: Treatment Effect and Follow-Up Duration

- Treatment effect and study duration are defined
- Agnostic to survival kinetics
An Illustrative Example (cont’d):
False Positive Rate with Correlated Endpoints

- Family-wise type I error of 5%
- For moderate correlation between OS and MS (0.5-0.8)
  - A ratio of 3-to-1 (OS/MS) gives a type I error rate of 0.04~0.045 to OS endpoint
  - Assuming a correlation of 0.7, the alpha allocation is 0.042 and 0.014
- Study is designed using milestone survival with alpha of 0.014
An Illustrative Example (cont’d): Sample Size Determination

- Endpoint used in sample size determination:
  - Milestone survival
- Treatment effect: Improvement in 2-year MS of 20% (31% to 51%)
- Type I error rate: 0.014
- Power: 0.9
- Accrual rate: ~34 per month
- Sample size: 342 randomized patients
- Accrual duration: 10 months
- Follow-duration: 24 months
  - Determined by milestone survival
  - Mitigate the issue of censoring
An Illustrative Example (cont’d): Statistical Analysis of OS and MS

• Timing of analysis:
  – 2 years after last patient came on study
  – ~3 years (34 months) after the time of first patient on study

• Analysis of OS endpoint
  – Power ranges from 95% to 90% from no delay to 8 months delay
  – Type I error rate of 4.2%

• Analysis of MS endpoint
  – Type I error rate of 1.4%
Advantages of the Proposed Design

• Simplification in time to event study design
• OS remains an important endpoint
• No Assumption in the shape of OS curves
• Agnostic to uncertainty of delayed duration and long-term survival
• Predictable timing of analysis
• Assessment of the tail of OS curve
• MS can capture unique late separation with a higher bar
• Minimal loss of false positive rate in OS
• Mitigate the risk of inflated false negative rate
Summary

• A simpler design for future late-stage IO studies using milestone survival with one fourth of false positive rate under moderate correlation

• The probabilities of study success can be assessed under plausible OS assumptions

• Clinically meaningful milestone and improvement

• The design can be extended to situations where follow up duration is less than the milestone (e.g., 18 months follow up for a 2-year MS), in which case the sample size will be inflated to account for censoring prior to milestone

• Proposed design encompasses clinically meaningful information and statistical simplicity
References (in chronological order)


Assay Design; Special Considerations for I-O Companion Dx Tests

David L. Rimm M.D.-Ph.D.
Professor of Pathology
Yale University School of Medicine
Disclosures:

• In the last 12 months I have been engaged in the following relationships:
  • I am a consultant/Advisor to Astra Zeneca, Bethyl Labs, Biocept, BMS, FivePrime, Merck, Novartis, OptraScan, Perkin Elmer and Ultivue
  • I hold equity in Metamark Genetics and Pixel Gear
  • Cepheid, Genoptix, Gilead Sciences, Pierre Fabre, Perkin Elmer and OncoplexDx fund research in my lab.
Critical Components for a Broadly Reproducible Companion Dx Assay for I-O Therapy

• Control pre-analytic conditions (core bx may be best)
• Quantitatively titer a monoclonal antibody for IHC assays
• Choose an analysis method that can be achieved by pathologists or choose a machine
• Standardize the assay with a control series (isogenic cells) for multi-site and longitudinal reproducibility
ER status more negative if surgery is on Friday than on Monday?

Control the Pre-Analytic Conditions:
- Use core bx when possible
- Stain slides immediately after they are cut
- Choose targets that are stable to warm and cold ischemia

<table>
<thead>
<tr>
<th></th>
<th>cases</th>
<th>ER neg rate</th>
<th>PgR neg rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>1252</td>
<td>18.4%</td>
<td>26.0%</td>
</tr>
<tr>
<td>Tuesday</td>
<td>1176</td>
<td>21.1%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Wednesday</td>
<td>784</td>
<td>21.7%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Thursday</td>
<td>904</td>
<td>21.1%</td>
<td>28.7%</td>
</tr>
<tr>
<td>Friday</td>
<td>919</td>
<td>23.5%</td>
<td>30.0%</td>
</tr>
</tbody>
</table>

Frequency of ER/PgR negativity significantly increased with each day of the week, both for ER ($P = 0.03$) and PgR ($P = 0.059$ for trends; n=5077).
Critical Components for a Broadly Reproducible Companion Dx Assay for I-O Therapy

- Control pre-analytic conditions (core bx may be best)
- Quantitatively titer a monoclonal antibody for IHC assays
- Choose an analysis method that can be achieved by pathologists or choose a machine
- Standardize the assay with a control series (isogenic cells) for multi-site and longitudinal reproducibility
“Blueprint” image comparison

Example of PD-L1 Tumor Expression
NCCN/BMS PD-L1 Assay Comparison Study
NCCN/BMS Average Scores for Tumor Cells

Samples

Average Pathologist Readings in Tumor

Negative < 1%
1-5%
>5-10%
>10-25%
>25-49%
>=50%

22c3
28-8
SP142
E1L3N
Mean of antibodies

NCCN/BMS Average Scores for Tumor Cells

Samples

0 10 20 30 40 50 60 70 80 90

25-49%
20-24%
10-14%
5-9%
1-4%
0-0%
50% or more

Mean of antibodies
NCCN/BMS Average Scores for Immune Cells

- 22c3
- 28-8
- SP142
- E1L3N
- Mean of antibodies

Yale School of Medicine

Samples

IASLC Chicago
NCCN/BMS Distribution of Tumor Scores by Assay

Summary
• The SP142 assay selects over 50% fewer patients for both tumor cells and immune cells
• The other 3 assays are the same (more or less)
Titer Optimization for SP142
Critical Components for a Broadly Reproducible Companion Dx Assay for I-O Therapy

• Control pre-analytic conditions (core bx may be best)
• Quantitatively titer a monoclonal antibody for IHC assays
• Choose an analysis method that can be achieved by pathologists or choose a machine
• Standardize the assay with a control series (isogenic cells) for multi-site and longitudinal reproducibility
Pathologist vs Pathologist

DAB semi vs DAB semi

QIF (AQUA) vs QIF (AQUA)

y = 0.9211x
R² = 0.914

y = 0.9086x
R² = 0.9629

y = 0.9809x
R² = 0.9948

Percent Positive Nuclei (Path. 1)

Percent Positive Nuclei (User 1)

Nuclear AQUA Score (User 2)
**ICC for the Pathologists and Scores**

The ICC for each antibody allows us to assess the agreement between readers for tumor cell and immune cell scores.

### ICC for pathologists by each antibody in Tumor Cells

<table>
<thead>
<tr>
<th>Antibody</th>
<th>22c3</th>
<th>28-8</th>
<th>SP142</th>
<th>E1L3N</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All, N=90</td>
<td>0.882</td>
<td>0.832</td>
<td>0.869</td>
<td>0.859</td>
<td>0.86(0.02)</td>
</tr>
</tbody>
</table>

### ICC for pathologists by each antibody in Immune Cells

<table>
<thead>
<tr>
<th>Antibody</th>
<th>22c3</th>
<th>28-8</th>
<th>SP142</th>
<th>E1L3N</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>All, N=90</td>
<td>0.207</td>
<td>0.172</td>
<td>0.185</td>
<td>0.229</td>
<td>0.19(0.03)</td>
</tr>
</tbody>
</table>

### Cutoff at >50% and >1%

<table>
<thead>
<tr>
<th>Cut-off</th>
<th>Fleiss Kappa</th>
<th>Kendall Concordance</th>
<th>Fleiss Kappa</th>
<th>Kendall Concordance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average of all 4 assays</td>
<td>0.749</td>
<td>0.775</td>
<td>0.537</td>
<td>0.612</td>
</tr>
</tbody>
</table>
Measurement Systems: Absorptive vs Emissive
RNA expression signatures

Relationship between immune gene signatures and clinical response to PD-1 blockade with pembrolizumab (MK-3475) in patients with advanced solid tumors

Mark Ayars, 1,2 Jared Luceford, 1 Michael Nebozhyn, 1 Erin Murphy, 3 Andrey Loboda, 1 Andrew Albright, 1 Jonathan Cheng, 1 S Peter Kang, 1 Scott Ebbinghaus, 1 Jennifer Yearley, 1 Veena Shankaran, 3 Tanguy Seiwert, 2 Antoni Ribas, 2 and Tom McClanahan 1

<table>
<thead>
<tr>
<th>Signature</th>
<th>HNSCC</th>
<th>Gastric Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR</td>
<td>PFS</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TCR signaling</td>
<td>0.071</td>
<td>0.002</td>
</tr>
<tr>
<td>Expanded immune</td>
<td>0.015</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>De novo</td>
<td>0.018</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Mutational Load
Mutation load and predicted class I neoantigens in Yale NSCLC treated with immune checkpoint blockers

- Mutational load and class-I neoantigens are significantly associated with response, but not with survival in NSCLC

Sensitivity=68%
Specificity=58%
Critical Components for a Broadly Reproducible Companion Dx Assay for I-O Therapy

• Control pre-analytic conditions (core bx may be best)
• Quantitatively titer a monoclonal antibody for IHC assays
• Choose an analysis method that can be achieved by pathologists or choose a machine
  • Standardize the assay with a control series (isogenic cells) for multi-site and longitudinal reproducibility
Antibody Comparison on Horizon Discovery PD-L1 Developmental TMA
Questions?
Back-up slides
NanoString Releases Details on Tumor Inflammation Signature Assay From Merck CDx Collaboration

Aug 12, 2016 | Andrew P. Han
A Quantitative Comparison of Antibodies to Programmed Cell Death 1 Ligand 1

Patricia Gaule, PhD; James W. Smithy, BS; Maria Toki, MD; Jamaal Rehman, MD; Farah Patell-Socha, PhD; Delphine Cougot, PhD; Philippe Collin, PhD; Paul Morrill, PhD; Veronique Neumeister, MD; David L. Rimm, MD, PhD

**IMPORTANT** Assessment of PD-L1 (programmed cell death 1 ligand 1) expression by immunohistochemical analysis has been used as a predictive diagnostic test to identify
Comparison by Quantification (QIF and DAB)
### PD-L1 Diagnostic Development for NSCLC: Current and Future IVD Landscape

<table>
<thead>
<tr>
<th>Ab clone/epitope</th>
<th>28-8</th>
<th>22C3</th>
<th>SP142</th>
<th>SP263</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVD class III diagnostic partner</td>
<td>Dako</td>
<td>Dako</td>
<td>Ventana</td>
<td>Ventana</td>
</tr>
<tr>
<td>Drug</td>
<td>Nivolumab</td>
<td>Pembrolizumab</td>
<td>Atezolizumab</td>
<td>Durvalumab</td>
</tr>
<tr>
<td>PD-L1 scoring method</td>
<td>% tumor cells</td>
<td>% tumor cells</td>
<td>% tumor cells &amp; % immune cells</td>
<td>% tumor cells</td>
</tr>
<tr>
<td>FDA IVD status for NSCLC</td>
<td>Complementary</td>
<td>Companion</td>
<td>Under Evaluation</td>
<td>Under Evaluation</td>
</tr>
<tr>
<td>PD-L1 thresholds under evaluation</td>
<td>≥1%, ≥5%, or ≥10%</td>
<td>≥1%, ≥50%</td>
<td>IC1/2/3 (≥1%, ≥5% &amp; ≥10%)</td>
<td>TC1/2/3 (≥1%, ≥5% &amp; ≥50%)</td>
</tr>
</tbody>
</table>

### Unified Scoring System for assessment of PD-L1 expression used for this study

#### Part 1: Tumor Cell staining

<table>
<thead>
<tr>
<th>Category</th>
<th>Range</th>
<th>Drugs Justifying Category Cut-point</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Negative or 0%</td>
<td>All drugs</td>
</tr>
<tr>
<td>B</td>
<td>1% to 4%</td>
<td>Nivolumab and Pembrolizumab</td>
</tr>
<tr>
<td>C</td>
<td>5% to 9%</td>
<td>Nivolumab and Atezolizumab</td>
</tr>
<tr>
<td>D</td>
<td>10% to 24%</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>E</td>
<td>25% to 49%</td>
<td>Durvalumab</td>
</tr>
<tr>
<td>F</td>
<td>50% or more</td>
<td>Pembrolizumab and Atezolizumab</td>
</tr>
</tbody>
</table>

#### Part 2: Immune Cell staining

<table>
<thead>
<tr>
<th>Category</th>
<th>Range</th>
<th>Drugs Justifying Category Cut-point</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Negative or 0%</td>
<td>All drugs</td>
</tr>
<tr>
<td>B</td>
<td>1% to 9%</td>
<td>Atezolizumab (IC1 and IC2)</td>
</tr>
<tr>
<td>C</td>
<td>10% or more</td>
<td>Avelumab and Atezolizumab</td>
</tr>
</tbody>
</table>

IASLC Chicago
# Results: Summary Data for Tumor

<table>
<thead>
<tr>
<th>Tumor -percentage</th>
<th>22c3</th>
<th>28-8</th>
<th>SP142</th>
<th>E1L3N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage &lt;1%</td>
<td>32</td>
<td>19</td>
<td>61</td>
<td>25</td>
</tr>
<tr>
<td>Percentage &gt;=1% and &lt;5%</td>
<td>20</td>
<td>27</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>Percentage &gt;=5% and &lt;10%</td>
<td>5</td>
<td>8</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Percentage &gt;=10% and &lt;25%</td>
<td>5</td>
<td>5</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Percentage &gt;=25% and &lt;50%</td>
<td>11</td>
<td>10</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Percentage &gt;=50%</td>
<td>17</td>
<td>21</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Percent cases “positive” at &gt;50%</td>
<td>19%</td>
<td>23%</td>
<td>6%</td>
<td>24%</td>
</tr>
<tr>
<td>Percent cases “positive” at &gt;1%</td>
<td>64%</td>
<td>79%</td>
<td>32%</td>
<td>72%</td>
</tr>
</tbody>
</table>
Workshop Concluding Remarks

Maytreyee Hazarika, MD
Workshop Co-Chair
Adjourn
Thank You for Attending!