Dual translational biomarker strategies to stratify patients for personalized cancer immunotherapy

Jianda Yuan MD, PhD
Translational Oncology
Early Oncology Development
Merck Research Lab
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Outline

- Broad clinical responses by PD-1 blockade pembrolizumab treatment and challenges in personalized cancer immunotherapy.

- Translational biomarker strategies and the emerging potential biomarkers for pembrolizumab:
  - PD-L1 IHC
  - IFN-γ gene signature or Tumor Inflammation Signature (TIS)
  - Microsatellite instability (MSI)
  - Tumor Mutational Burden (TMB)

- Dual biomarker strategies with different biology for personalized combination cancer immunotherapy. (Maximize clinical efficacy)
Keytruda Monotherapy Has Shown Activity in >20 Tumors

KEYTRUDA: Improvements in Overall Survival

1. Section 14.2, Figure 3, KEYTRUDA prescribing information; 2. Section 14.2, Figure 4, KEYTRUDA prescribing information; 3. Section 14.1, Figure 1, KEYTRUDA prescribing information; 4. Section 14.5, Figure 5, KEYTRUDA prescribing information

1L NSCLC

2L NSCLC

1L Melanoma

2L Bladder

Overall Survival %

Time in Months
Keytruda FDA Approval Timeline

2014
- 09/2014: 2L+ Unresectable or Metastatic Melanoma
- 10/2015: 2L Advanced NSCLC
- 12/2015: 1L Unresectable or Metastatic Melanoma

2015
- 08/2016: 1L Metastatic NSCLC (TPS>50%, 2L TPS>1%)

2016
- 10/2016: 1L Metastatic NSCLC (TPS>50%, 2L TPS>1%)
- 03/2017: 2L Locally Advanced or Metastatic Urothelial Carcinoma
- 05/2017: 1L NSCLC in Combination with carboplatin and pemetrexed
- 09/2017: 2L Gastric (TPS>1%)

2017
- 08/2016: Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma
- 03/2017: Relapsed or Refractory Classical Hodgkin Lymphoma (Adult and Pediatric)

2018
- 10/2015: 2L Advanced NSCLC

12 Breakthrough Designations
<table>
<thead>
<tr>
<th>Presenter</th>
<th>Data Presented</th>
<th>Combination agent(s)</th>
<th>Indication</th>
<th>N</th>
<th>ORR</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Ribas</td>
<td>SMR 2016</td>
<td>SD-101</td>
<td>Melanoma</td>
<td>5</td>
<td>80%</td>
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<tr>
<td>Kaufman</td>
<td>SITC 2016</td>
<td>Cavatak</td>
<td>Melanoma</td>
<td>10</td>
<td>70%</td>
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<tr>
<td>Taylor</td>
<td>ESMO 2016</td>
<td>Lenvatinib</td>
<td>All comers</td>
<td>13</td>
<td>69%</td>
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<tr>
<td>Atkins</td>
<td>ESMO 2016</td>
<td>Axitinib</td>
<td>RCC</td>
<td>52</td>
<td>67%</td>
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<tr>
<td>Ribas</td>
<td>ASCO 2016</td>
<td>Dabraf-tramet</td>
<td>melanoma</td>
<td>15</td>
<td>60%</td>
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<tr>
<td>Bedros</td>
<td>ASH 2015</td>
<td>Pomalidomide-dex</td>
<td>RRMM</td>
<td>27</td>
<td>60%</td>
<td></td>
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<tr>
<td>Gangadhara</td>
<td>ESMO 2016</td>
<td>Epacadostat</td>
<td>melanoma</td>
<td>19</td>
<td>58%</td>
<td>Treatment naive melanoma</td>
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<tr>
<td>Long</td>
<td>ASCO 2016</td>
<td>T vec</td>
<td>melanoma</td>
<td>21</td>
<td>57%</td>
<td></td>
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<tr>
<td>Long (KN-029 EC)</td>
<td>ASCO 2016</td>
<td>ipilimumab</td>
<td>melanoma</td>
<td>107</td>
<td>57%</td>
<td></td>
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<tr>
<td>Langer</td>
<td>2016 Lanc Oncol</td>
<td>Pemetrexed-carbo</td>
<td>NSCLC</td>
<td>60</td>
<td>55%</td>
<td>Chemo alone 29%; pfs 8 mos vs 4.9 mos</td>
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<tr>
<td>Gadgeel</td>
<td>ASCO 2016</td>
<td>Paclitaxel-carbo</td>
<td>NSCLC</td>
<td>25</td>
<td>52%</td>
<td></td>
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<tr>
<td>Mateos</td>
<td>ASCO 2016</td>
<td>Lenalidomide-dex</td>
<td>RRMM</td>
<td>40</td>
<td>50%</td>
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<tr>
<td>Gadgeel</td>
<td>ASCO 2016</td>
<td>Paclitaxel-carbo-bev</td>
<td>NSCLC</td>
<td>25</td>
<td>48%</td>
<td></td>
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<tr>
<td>Davar (Pitt OCSP)</td>
<td>ASCO 2016</td>
<td>PEG-IFN</td>
<td>melanoma</td>
<td>24</td>
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<td>Algazi</td>
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<td>Melanoma</td>
<td>15</td>
<td>40%</td>
<td>High risk biomarker group</td>
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<td>McDermott</td>
<td>ESMO 2015</td>
<td>Pazopanib</td>
<td>RCC</td>
<td>20</td>
<td>40%</td>
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<td>Tolanez</td>
<td>SABCS 2016</td>
<td>Eribulin</td>
<td>TNBC</td>
<td>39</td>
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<td>Atkins (KN-029)</td>
<td>ASCO 2016</td>
<td>ipilimumab</td>
<td>RCC</td>
<td>10</td>
<td>30%</td>
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<tr>
<td>Herbst</td>
<td>ESMO 2016</td>
<td>Ramucirumab</td>
<td>NSCLC</td>
<td>27</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Besse</td>
<td>World Lung 2016</td>
<td>Necitumumab</td>
<td>NSCLC</td>
<td>34</td>
<td>29%</td>
<td></td>
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<tr>
<td>Stenehjem</td>
<td>ESMO 2016</td>
<td>FOLFOX</td>
<td>GI</td>
<td>7</td>
<td>29%</td>
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**Multiple Strategies May Work to Overcome Primary Resistance to PD1 Blockade**
Challenges in the Era of Combination Cancer Immunotherapy

Many anti PD-1/L1-based combos exhibit initial clinical signals (ORR) in small Ph1b/2a clinical studies and beyond:
• What is additive vs. synergistic?
• False discovery rate (enormous combinatorial diversity)
• How do we prioritize and differentiate the promising combos?

How do we identify the patients likely to benefit from specific combos?
• Avoidance of unnecessary toxicity
• Maximize efficacy/show unambiguous clinical benefit
• Cost/value
An Melanoma Example: Radiographic Response to Two Pembrolizumab Combos

<table>
<thead>
<tr>
<th>Stage</th>
<th>Response</th>
<th>Count</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>IIIIB (n = 1)</td>
<td>1/1 (100%)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>IIIIC (n = 7)</td>
<td>5/7 (71%)</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>IV Ma (n = 2)</td>
<td>1/2 (50%)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>IV M1b (n = 3)</td>
<td>3/3 (100%)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>IV M1c (n = 8)</td>
<td>4/8 (50%)</td>
<td>8</td>
<td></td>
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Presented by G. Long SMR 2015

Pembrolizumab + TVEC in Melanoma

*Subjects was PD per new brain lesions but off tx prior to imaging of TL
**PD per new lesions
***PD per new 7 mm brain lesions but target disease has decreased
 ****off tx
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- Dual biomarker strategies with different biology for personalized combination cancer immunotherapy. (Maximize clinical efficacy)
Dynamic Translational Immuno-oncology Biomarker Research Strategies

To elucidate target engagement, pharmaco-kinetics and pharmaco-dynamics changes
To understand the potential mechanisms of action
To find new correlates associated with clinical benefits and/or immune related adverse events
To identify new targets and patients potentially responding to therapy
To provide combination therapies upon understanding of mechanisms of action and resistance

Right dose  MOA  Right patient  New target  Right combo
Merck is a Leader in Identifying Predictive Biomarkers for Cancer Immunotherapy

Ligand Expression on Tumor
- PD-L1 Expression
- First PDL-1 Companion Diagnostic Approved

Immunogenic Microenvironment
- Immune-Related Gene Expression Profile (GEP) or Tumor Inflammation Signature (TIS)
- First collaboration to explore RNA tumor microenvironment signature

Increased Antigenicity due to High DNA Mutation Burden
- DNA Mismatch Repair Deficiency, DNA Polymerase mutation
- First to identify MSI-High as a predictive biomarker (with Hopkins investigators)
- First FDA tumor agonistic approval 2017

Goal is to identify patients most likely to benefit from treatment
Our clinical trials and predictive biomarker approaches are based on strong biomarker hypotheses, with use of prospectively defined cutoffs, based on ROC analyses in independent training sets
NSCLC: Superior Overall Survival vs. Chemotherapy in PD-L1-Defined Subgroups

KEYNOTE 010: Advanced NSCLC
PD-L1 ≥1% TPS

12 mo

Overall Survival, %

HR 0.71 (95% CI 0.58-0.88)
HR 0.61 (95% CI 0.49-0.75)


KEYNOTE 024: Previously Untreated NSCLC
PD-L1 ≥50% TPS

Events, Median, HR (95% CI)

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<thead>
<tr>
<th></th>
<th>n</th>
<th>mo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>44</td>
<td>NR</td>
<td>0.60</td>
</tr>
<tr>
<td>Chemo</td>
<td>64</td>
<td>NR</td>
<td>(0.41-0.89)</td>
</tr>
</tbody>
</table>

M Reck et al. NEJM 2016
Derivation of T-Cell Inflamed Gene Expression Profile (GEP)

Signatures Defined and Validated in Melanoma

Signatures Validated and Refined in SCCHN and Gastric CA

Final GEP Generated Using Penalized Regression Model in 9 Solid Tumors

(N=19 training, N=62 validation)

SCCHN (N=43)

Gastric CA (N=33)

N=220 (gastric, TNBC, SCCHN, urothelial, anal, biliary, colorectal, esophageal and ovarian cancers)
Pembrolizumab in MSS Colorectal and MSI Colorectal and Non-Colorectal Tumors

Presented by Dung Le, ASCO 2015

Presented by L. Diaz, ASCO 2016

FDA Approval MSI-H/dMMR on May 23rd, 2017
Tumor Mutational Burden Predicts Response to Pembrolizumab Across Tumor Types

Subgroup of patients from KEYNOTE N012 and KEYNOTE 028 (n=119, representing 20 tumor types)

P = 0.0036

Non-responder [PD/SD] N=94

Responder [CR/PR] N=16

Rizvi NA et al. Science 2015;348:124-128
Dual biomarker strategies with different biology for personalized combination cancer immunotherapy. (Maximize clinical efficacy)

Translational biomarker strategies and the emerging potential biomarkers for pembrolizumab:

- PD-L1 IHC
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Broad clinical responses by PD-1 blockade pembrolizumab treatment and challenges in personalized cancer immunotherapy
Keytruda Biomarkers: Different Biology Assessed by TMB vs. PD-L1/GEP

- TMB measures tumor antigenicity
- PD-L1/GEP measure activated T-cells in TME

Illustrations:
- Neoantigens
- Different immune cell interactions
- MHC1, TCR, CD28, B7, IFN-γ, PD-L1, PD-L2
PD-L1/GEP and TMB: Independent Measures with Comparable Predictive Value (Low Correlation)

- Pre-specified hypothesis testing using KN028/12 as validation set.
- When jointly modeled, ML showed significant association with response ($p=0.0078$) after adjusting for GEP (also significant, $p=0.0251$).

**Low correlation between TMB and T-cell inflamed gene signature (NanoString)**

**High and comparable predictive value of gene signature and ML**

- $r = 0.281$ (Pr = 0.006)
- $r$ in responders = 0.321 (Pr = 0.242)
- $r$ in non-responders = 0.192 (Pr = 0.091)
Key Takeaways for Dual Biomarker Strategies for Combination Cancer Immunotherapy

- PD-(L)1 blockade cancer immunotherapies especially pembrolizumab have broad clinical activity, and represent the backbone of cancer immunotherapy.
- Biomarkers measuring either T cell activation in TME (PD-L1, GEP) or tumor antigenicity (MSI and TMB) independently predict patients response to PD-(L)1 blockade immunotherapies with low correlation.
- Dual biomarker strategies as part of precision immuno-oncology to triage patients to the appropriate combination cancer therapies.
THANK YOU!