A Multianalyte Algorithmic Analysis (MAAA) to Predicting Response to Checkpoint Inhibitors

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Overview of OmniSeq

OmniSeq is a for-profit Roswell Park Cancer Institute (RPCI) subsidiary based in Buffalo, New York offering NY State CLEP approved assays.

Vision
The Right Drug or the Right Trial... For Every Patient.

Mission
Delivering superior results by improving access to better cancer treatment options through comprehensive molecular profiling.
Two Separate, But Related Questions?

How do we choose the best immunotherapy?

How do we predict immunotherapy response?

Can we develop assays that perform better than PD-L1 IHC?

Foundational tools to guide treatment decisions for I/O
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Foundational tools to guide treatment decisions for I/O
How do we choose the best immunotherapy?

Requires a clinically useful framework.

How do we choose the best immunotherapy?

Requires a clinically useful framework.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Test</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1</td>
<td>IHC</td>
<td>High</td>
</tr>
<tr>
<td>Mutational Burden</td>
<td>DNA-Seq</td>
<td>High</td>
</tr>
<tr>
<td>Microsatellite Instability</td>
<td>PCR</td>
<td>High</td>
</tr>
<tr>
<td>PD-L1/PD-L2 Copy Number</td>
<td>FISH</td>
<td>Positive</td>
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<tr>
<td>Immune Activation</td>
<td>RNA-Seq</td>
<td>High</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>KEYTRUDA pembrolizumab</th>
<th>YERVOY ipilimumab</th>
<th>OPDIVO nivolumab</th>
<th>TECENTRIQ atezolizumab</th>
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<tbody>
<tr>
<td>Melanoma</td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
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</tr>
<tr>
<td>NSCLC</td>
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<td>☀</td>
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<tr>
<td>Bladder</td>
<td></td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
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<tr>
<td>Head &amp; Neck</td>
<td></td>
<td>☀</td>
<td>☀</td>
<td>☀</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
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<tbody>
<tr>
<td>PD-L1</td>
<td>IHC</td>
<td>Not high</td>
</tr>
<tr>
<td>Mutational Burden</td>
<td>DNA-Seq</td>
<td>Not high</td>
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<tr>
<td>Microsatellite Instability</td>
<td>PCR</td>
<td>MSS</td>
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<tr>
<td>PD-L1/PD-L2 Copy Number</td>
<td>FISH</td>
<td>Negative</td>
</tr>
<tr>
<td>Immune Activation</td>
<td>RNA-Seq</td>
<td>Not high</td>
</tr>
</tbody>
</table>
Theoretical Model  →  Data Driven Clinical Model  →  OmniSeq I/O Reference Database

6 Basic Immune Phenotypes

Database Value for Future Clinical Trials Development

Chen & Mellman, Nature 3017
IRC/IA Reference Database Immune Phenotypes

Cluster 1 subnode

Myeloid suppression high while checkpoint blockade moderate or low

IRC/IA Database Value for Future Clinical Trials Development
Cluster 1 subnode

RD-1971: 56 yo female with Stage IV melanoma treated with ipilimumab and progressive disease.
- moderate to low checkpoint blockade
- very high expression of CD68, CD163, CSF1R, CCR2, and CCL2

Myeloid suppression blockade combined with checkpoint inhibitor
Submitted to NY State CLEP

Five Test Elements

• **RNA-seq:** >350 immune related genes (FFPE)
• **DNA-seq:** Full exon >400 genes
• **IHC:** PD-L1 (22C3) FDA-approved, CD3 & CD8
• **PCR:** MSI
• **FISH:** PD-L1/2 copy number

Clinical Utility Pending

• Retrospective Study (On-going)
• RPCI prospective trial (2017)
• Multi-institutional prospective study (TBD)

*Analytical & clinical validity submission in January, 2017*
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*Foundational tools to guide treatment decisions for I/O*
Immune Advance: Predicting Response to CPIs

Number & pattern of immune cells (TILs)
Mutational Burden (MuB)
T-cell receptor signaling (TCRS)

Breast Recurrence Score™
From 0-100

Immune Score
From 0-100
RPCI Retrospective Patient and Specimen Selection

**Included:** All patients treated with nivolumab, pembrolizumab, ipilimumab, atezolizumab as monotherapy or ipilimumab+nivolumab combination therapy at Roswell Park Cancer Institute between 2010-2016

**Excluded:** All patients with surgery or biopsy not performed at RPCI are excluded

**Excluded:** All patients that do not have a FFPE block in the RPCI archives suitable for testing

**Excluded:** Patients not evaluable (NE) by RECIST (n=21) or who had progressive disease and less than 90 days survival post-first dose (n=20)

**Excluded:** Patients with specimen collection dates post-first dose (n=38) and patients with specimens that failed RNA-seq (n=12)

80% Attrition Rate
Machine Learning Model

54 gene expression + MuB (55 Dimensions) feature space
Machine Learning Model: Clinical Benefit

Responders and Non-Responders in the Pilot Retrospective Study at RPCI by Clinical Benefit
Number of Samples, n = 87

<table>
<thead>
<tr>
<th>Clinical Benefit</th>
<th>NPV</th>
<th>PPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>(47/49) 95.9%</td>
<td>(2/49) 100%</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>(6/10) 60%</td>
<td>(4/10) 100%</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>(22/23) 100%</td>
</tr>
</tbody>
</table>

NPV = \(\frac{47}{49}\) \(\frac{2}{49}\) = 95.9%

PPV = \(\frac{6}{10}\) \(\frac{4}{10}\) = 95.7%

No clinical benefit

Clinical benefit
4-Gene Model

RNA-seq >350 immune related genes (FFPE)

- Minimum set of genes with the highest prediction supported by biological explanation

PPV = 73%
NPV = 94%
# Immune Function Model

## Immune Cell Infiltration
- CD8, CD3, CD2, CD4, FOXP3, CD68, CD163, MS4A1 (CD20), CSF1R, SLAMF4

## T-cell Activation
- CD27, CD28, CD40, CD40LG, CD80, CD86, TNFRSF9 (CD137), TNFRSF18 (GITR), ICOS, ICOSLG, LAG3, HAVCR2 (TIM3), PDCD1 (PD-1), CD274 (PD-L1), PDCD1LG2 (PD-L2), CTLA4, OX40, OX40LG, GZMB, IFNG, TNFRSF14, TBX21, VISTA

## Immune Response Regulation
- ADORA2A, GATA3, CD38, ENTPD1 (CD39), IDO1, KLRD1, STAT1, BTLA

## Cytokine Signaling
- IL10, IL1B, TNF, TGFβ1, CCR2, MX1, CXCR6, CXCL10, DDX58, CCL2

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**PPV = 59%**  
**NPV = 83%**  
Indeterminate 33% population
OmniSeq Approach to Predicting Response to CPIs

- Machine Learning Model
- 4-gene Model
- Immune Function Model

Bayesian Model Averaging → Final Prediction

Both Biological and Machine Learning Approach
Bayesian Model Averaging Prediction

RESPONDERS AND NON-RESPONDERS
Percentage of Samples, n = 87

NPV = (54/60) 90.0%

PPV = (24/27) 88.9%

Non Responders
n=60 (68.9%)
No clinical benefit

Responders
n=27 (31.0%)
Clinical benefit
Two Separate, But Related Questions?

How do we choose the best immunotherapy?

How do we predict immunotherapy response?

Same RNA-seq and DNA-seq
Same wet lab SOP
Same baseline bioinformatics

*Foundational tools to guide treatment decisions for I/O*
Horizons of Immune Product Development

Today
Available Q2 CY2017
Understand the immune response better than PD-L1 IHC and mutational burden

Tomorrow
Available 2018
Encouraging early results to predict response to checkpoint inhibitors

Future
Available TBD
Liquid biopsy for immune repertoire, real-time monitoring