An Overview of How Real World Evidence, Data Sharing, and Precompetitive Collaboration May Influence the Development of PD-1/PDL-1 Combination Therapies

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Flatiron Health
Overview

- Case examples
- Some practical issues
- Data sharing mechanics
- Precompetitive collaboration?
- Policy implications
Real-world data enables a different kind of discovery
Cohort Demographics
As of June 2018

Patients in cohort: 48,856 (Community: 44,770 | Academic: 4,086)

Histology
- Squamous cell carcinoma: 69.10%
- Non-squamous cell carcinoma: 25.20%
- Not otherwise specified: 5.70%

Smoking Status
- History of smoking: 86.20%
- No history of smoking: 12.10%
- Unknown / not documented: 1.70%
PDL1 Biomarker Testing and FDA Approvals of Immune Checkpoint inhibitors in NSCLC

**PDL1 Status Among Tested Patients**
- Positive: 16.5%
- Negative: 35.7%
- Unknown: 47.8%

**PDL1 Testing Rate Among Actively Treated Patients**

- **Opdivo for recurrent squamous cell [Mar 2015]**
- **Keytruda for recurrent NSCLC [Oct 2015]**
- **Keytruda for recurrent PDL1+ NSCLC [Oct 2015]**
- **Keytruda for first line PDL1+ NSCLC [Oct 2016]**
- **Keytruda plus chemo for first line NSCLC, regardless of PDL1 [May 2017]**
- **Keytruda for any MSI-High tumor [May 2017]**

**Keytruda for recurrent PDL1+ NSCLC [Oct 2016]**

**Keytruda for any MSI-High tumor [May 2017]**
Patient Share by Therapy Class — PD1/PDL1

All Lines

Q3 2014: 0%
Q2 2018: 47%
Patient Share by Therapy Class — PD1/PDL1

2nd or 3rd Line+

Q3 2014

Q2 2018
Patient Share by Therapy Class — PD1/PDL1

1st Line


Non-platinum-based chemotherapy combinations | Anti-VEGF-based therapies | Clinical study drug-based therapies | Platinum-based chemotherapy combinations | PD-1/PD-L1-based therapies | EGFR-antibody based therapies | Other therapies | ALK inhibitors | Single agent chemotherapies | EGFR TKIs

0%  (Q3 2014) | 0%  | 0%  | 0%  | 5%  | 4%  | 7%  | 11% | 13% | 14% | 16% | 22% | 29% | 37% | 41% | 44% | 48%  (Q2 2018)
Cancer Drug Keytruda Keeps Some Patients Alive For 3 Years

by MAGGIE FOX

The drugs must be infused and they are pricey. Keytruda costs about $12,500 a month, or $150,000 a year.
Characteristics of Real-World Metastatic Non-Small Cell Lung Cancer Patients Treated with Nivolumab and Pembrolizumab During the Year Following Approval

1344 patients treated with PD1 inhibitors in the first year after approval

1 year follow up
Table 1. Characteristics of a cohort of 1,344 metastatic NSCLC patients who received nivolumab or pembrolizumab in the metastatic setting in U.S. community practices

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at PD-1 initiation, years, median (IQR)</td>
<td>69.0</td>
<td>(61.0–75.0)</td>
</tr>
<tr>
<td>Age categories at PD-1 initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;49 years</td>
<td>45</td>
<td>(3.4)</td>
</tr>
<tr>
<td>50–64 years</td>
<td>435</td>
<td>(32.4)</td>
</tr>
<tr>
<td>65–74 years</td>
<td>500</td>
<td>(37.2)</td>
</tr>
<tr>
<td>75+ years</td>
<td>364</td>
<td>(27.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>597</td>
<td>(44.4)</td>
</tr>
<tr>
<td>Men</td>
<td>747</td>
<td>(55.6)</td>
</tr>
</tbody>
</table>

Median age in clinical trials = 62; <8% were 75 or over
No difference in overall survival by age group or line of therapy

Findings: Stratification by line of therapy in which patients received their first PD-1 inhibitor did not reveal significant differences in OS estimates. 

- **Age**
  - Number at risk:
    - <49: 45, 435, 499, 365
    - 50-64: 29, 251, 302, 216
    - 65-74: 19, 166, 208, 139
    - 75+: 9, 102, 128, 68

- **Line**
  - Number at risk:
    - 1: 227, 669, 272, 176
    - 3: 92, 257, 103, 80
    - 4+: 49, 146, 62, 50

\[ p = 0.39 \] (Age)
\[ p = 0.56 \] (Line)
**Findings:** Patients who were PD-1 positive had a significantly longer median survival time (by ~5 months) and higher 1-year survival probability than those who were PD-1 negative.

**Overall Survival by PDL1 expression**

- **Strata:** PD-L1 positive, PD-L1 negative/not detected
- **Number at risk:**
  - PD-L1 positive: 55, 31, 23, 12, 4, 1
  - PD-L1 negative/not detected: 37, 17, 8, 3, 0, 0

**Survival Summary:**

<table>
<thead>
<tr>
<th>Strata</th>
<th># of Patients</th>
<th># of Events</th>
<th>Median Survival</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 positive</td>
<td>55</td>
<td>32</td>
<td>11.25</td>
<td>5.9</td>
<td>15.44</td>
</tr>
<tr>
<td>PD-L1 negative/not detected</td>
<td>37</td>
<td>31</td>
<td>5.05</td>
<td>4.1</td>
<td>9.21</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strata</th>
<th>5-Year Survival Probability</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-L1 positive</td>
<td>0.47</td>
<td>0.34</td>
<td>0.63</td>
</tr>
<tr>
<td>PD-L1 negative/not detected</td>
<td>0.19</td>
<td>0.09</td>
<td>0.39</td>
</tr>
</tbody>
</table>
What does this story really tell us?
Exploding R&D Pipelines

Combination therapies

Segmenting patients & personalization

Rising cost & complexity of care

Value-based care
Better pricing models
Competition

Speed, Biology, Evidence, Cost, Complexity, Impact
“SEC. 505F. UTILIZING REAL WORLD EVIDENCE.

(a) In General.—The Secretary shall establish a program to evaluate the potential use of real world evidence—

(1) to help to support the approval of a new indication for a drug approved under section 505(c); and

(2) to help to support or satisfy post-approval study requirements.”
Current drug development paradigm

- Regulatory Approval
- General uptake in the market

Time

Total Patients Exposed

I  II  III  IV / Observational
21st Century Cures - Shift towards earlier approvals

- Use of RWE to Monitor Earlier

- Regulatory Approval

- Total Patients Exposed

- Time

I II

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What are real-world data?
What are RWD and where do they come from?

Real world *data* are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can come from a number of sources, for example:

- Electronic health records (EHRs)
- Claims and billing activities
- Product and disease registries
- Patient-generated data including in home-use settings
- Data gathered from other sources that can inform on health status, such as mobile devices

What is RWE?

Real world *evidence* is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

This Website was designed to capture up-to-date information about the status of FDA activities around the development and use of RWD and RWE.
Contemporary features

Aggregated at scale
Cleaned and curated
Common data model
Linkable
Readily analyzable
Quality assessment
Meta-characteristics of RWD and RWE

Regulatory grade RWE, a potential checklist

- **Clinical Depth**
  Data granularity to enable appropriate interpretation and contextualization of patient information.

- **Completeness**
  Inclusion of both structured and unstructured information supports a thorough understanding of patient clinical experience.

- **Longitudinal Follow-up**
  Ability to review treatment history and track patient journey going forward over time.

- **Quality Monitoring**
  Systematic processes implemented to ensure data accuracy and quality.

- **Timeliness / Recency**
  Timely monitoring of treatment patterns and trends in the market to derive relevant insights.

- **Scalability**
  Efficient processing of information with data model that evolves with standard of care.

- **Generalizability**
  Representativeness of the data cohorts to the broader patient population.

- **Complete Provenance**
  Robust traceability throughout the chain of evidence.
Aggregate across silos

2M
Active Patients

2,500
Clinicians

265
Cancer Clinics

800
Unique Sites of Care
For every PD-1/PD-L1 test a patient receives, Flatiron biomarker Data Model captures:

- Test status
- Test result
- Date biopsy collected
- Date biopsy received by laboratory
- Date result received by provider
- Lab name
- Sample type
- Tissue collection site
- Type of test (e.g., FISH)
- Assay / kit (e.g., Dako 22C3)
- Percent staining & staining intensity

Section of PD-L1 Report

Tissue Collection Site: Lung, Right Upper Lobe Tissue

Lab Name: Flatiron
Data curation is a part of the endeavor

Expert Abstractors
A network of abstractors comprised of oncology nurses, certified tumor registrars, and oncology clinical research professionals.

Flatiron Technology
Software helps trained human abstractors efficiently organize and review unstructured documents to capture key data elements in predetermined forms.
Document clinical data quality and completeness

### Completeness of technology-enabled abstraction
*Example: Advanced NSCLC*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Structured data only</th>
<th>Flatiron data completeness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic diagnosis</td>
<td>26%</td>
<td>100%</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0% (^1)</td>
<td>94%</td>
</tr>
<tr>
<td>Histology</td>
<td>37%</td>
<td>99% (^2)</td>
</tr>
<tr>
<td>Stage</td>
<td>61%</td>
<td>95%</td>
</tr>
<tr>
<td>ALK results (of those tested)</td>
<td>9%</td>
<td>100% (^3)</td>
</tr>
<tr>
<td>EGFR results (of those tested)</td>
<td>11%</td>
<td>99% (^3)</td>
</tr>
</tbody>
</table>

1. 58% are free text in dedicated field in EHR (requiring hand abstraction)
2. Including 8% of patients with results pending or unsuccessful test
3. Including 6% of patients with results pending or unsuccessful test

### Accuracy of technology-enabled abstraction
*Example: Sites of metastases*

<table>
<thead>
<tr>
<th>Site of met</th>
<th>Inter-abstractor agreement</th>
<th>Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>97%</td>
<td>0.93</td>
</tr>
<tr>
<td>Brain</td>
<td>96%</td>
<td>0.91</td>
</tr>
<tr>
<td>Liver</td>
<td>92%</td>
<td>0.83</td>
</tr>
<tr>
<td>Lung</td>
<td>94%</td>
<td>0.87</td>
</tr>
</tbody>
</table>
Emerging use cases
Case study 1

ROCHE

Development of an External Control Arm as a Comparator for a Single Arm Trial

Alectinib
Assessing outcomes and safety of patients excluded from a clinical trial

Kadcyla, Post-Marketing Commitment
NCI + FLATIRON

Patients excluded from a clinical trial
Evaluating patients with renal and hepatic dysfunction
Answering questions quickly
With IO in lung cancer, should we treat past progression?
Multiple organizations are working on this
Friends of Cancer Research Pilot Project

### Correlation of real-world endpoints to overall survival among immune checkpoint inhibitor-treated aNSCLC patients

- **6 datasets**
- **6 months project timeline with 2 months of analysis time**
- Prespecified and agreed upon cohort selection and analysis plan
- **Variables currently available**
- **N=269 to 6924**
Correlation of real-world endpoints to overall survival among immune checkpoint inhibitor-treated aNSCLC patients

- **Lots of activities and vendors out there**—6 came together willingly to share their data + run analyses in < 2 months
- **Similarity** in demographic and clinical characteristics **despite differences in data source**
- Again, challenge is that **we don’t have data standards** for many things (e.g., PDL1 testing) so we have to invent it
- **Harmonization** can be achieved through translation tables between datasets, instead of predefining the same common data model up front
What if you combined (all of) the datasets?
Friends of Cancer Research Pilot Project

Correlation of real-world endpoints to overall survival among immune checkpoint inhibitor-treated aNSCLC patients
DATA SHARING HAS INCREDIBLE POTENTIAL TO STRENGTHEN ACADEMIC research, the practice of medicine, and the integrity of the clinical trial system. Some benefits are obvious: when researchers have access to complete data, they can answer new questions, explore different lines of analysis, and more efficiently conduct large-scale analyses across trials. Other advantages, such as providing a guardrail against conflicts of interest in a clinical trial system in which external sponsorship of research is common and necessary, are less visible yet just as critical.
Data Sharing Consortiums

**Historical definition:** “the practice of making data used for scholarly research available to other investigators” (Wikipedia & NIH)

Aggregation of datasets (different variables, to generate critical mass)

Increasing focus on real-world data collected as a routine byproduct of care
A few comments about data sharing

- It isn’t free…
- Precompetitive collaboration? Precompetitive for which parties and when?
- Need common standards (e.g., PDL1, endpoints)
- ...

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Policy Context for Data Sharing

- Enabling policy (21st Century Cures, PDUFA VI)
- Privacy, security and governance
  - Need approaches to maintain privacy while ensuring adequate contextual information
- Incentives for data sharing
- Mortality data!
- Regulatory policy that drives standards
  - Consistent approach to documenting data quality
  - Consistent endpoint definitions
  - Incorporating machine learning and AI
Take Home Summary

- Real world data offer the opportunity to observe the interrelationship between diagnosis, treatment, and outcomes at scale
- To achieve this we must solve the challenges of data aggregation, curation, and confident assessment of data quality - this can be achieved
- Interesting challenges such as mortality data
- Data sharing isn’t free