FRIENDS ANNUAL MEETING

Panel Two:
Examining the Feasibility of Real World Evidence through Pilot Studies
Panelists

- Gideon Blumenthal, MD; US FDA
- Amy Abernethy, MD, PhD; Flatiron Health
- Lisa LaVange, PhD; FDA
- Jane Perlmutter, PhD; Gemini Group
- Michael Taylor, PharmD, PhD; Genentech
FRIENDS ANNUAL MEETING

GIDEON MICHAEL BLUMENTHAL, MD
OHOP, US FDA
Friends of Cancer Research
Annual meeting
November 16, 2016
What is RWD/RWE?

Real World Data (RWD)
- Electronic Health Record (EHR) clinical data
- Patient registries
- Surveys

Real World Evidence (RWE)

Pragmatic trials
- Administrative claims/billing

Mobile health (smartphones, wearables, social media)

“Data generated for purposes other than evidence-generation from a traditional clinical trial”
Why RWE/RWD?

• U.S. adult cancer clinical trials relatively homogenous, expensive, (s)low accrual, administrative burdens

• Questions regarding generalizability once the drug enters the clinic

• New technologies may enable the collection and curation of diverse pipelines of data to enhance learning lifecycle of a therapy
Potential uses for RWD/RWE in oncology

- Labeling expansion for efficacy (rare tumor types)
- Real world dosage and administration
- Post-marketing safety
- Assessment of REMS
- Use in patients excluded from pivotal trials (e.g. autoimmune disease with immune checkpoint inhibitors)
- Assessment of special populations (hepatic/renal impairment, brain mets, leptomeningeal mets, elderly)
- Patient-reported toxicity/efficacy/function
- Prognosis in rare genomic subtypes
- Biomarker prediction (e.g. ORR and DoR based on “liquid biopsy” results versus tissue)
- Drug utilization
Potential issues

- Missing data
- Data curation (structured vs unstructured)
- Cohort selection
- Informed Consent/ HIPAA
- Quality Assurance
Potential Use-Cases discussed in WG

• Observational post-marketing data in rare cancers
• Observational follow up of post-progression cross-over cohort in a randomized controlled trial
• Pragmatic randomized controlled trial exploring 2 different dosing strategies
The panel

• Presentations:
  – Michael Taylor (Genentech)
  – Amy Abernathy (Flatiron)

• Reaction: Lisa Lavange (FDA), Jane Perlmutter (patient advocate)

• Panel discussion/ Q&A
FRIENDS ANNUAL MEETING

MICHAEL D. TAYLOR, PHARM.D., PH.D
Genentech
RWE to Support Regulatory Decisions

*Use cases and considerations*

Michael D. Taylor, PharmD, PhD
Deputy Global Head of Oncology
Real World Data Science
Genentech, A Member of the Roche Group
RWE for Regulatory Decisions

• What?
  – Safety & Effectiveness
  – PMC & Label expansion

• Why?
  – Opportunity to learn
  – Expedite clinical development for serious and life-threatening disease
  – RCT feasibility and appropriateness
RWE Use Cases

- Prospectively designed observational study
- Randomized Phase 2 plus observational study
- Pragmatic trial
Observational Study
Prospectively designed

Phase 1b: Treatment A → Early outcomes → Long-term outcomes

Early outcomes:
1) Treatment A & 2) SOC

Long-term outcomes
Observational Study
Prospectively designed

• Considerations
  – Study outcomes
  – Selection bias and confounding
  – Patient identification
  – Sample size
Randomized Phase 2 Study

Plus observational study

Treatment A ✔ ✔

Physician’s Choice or SOC ✔

Early outcomes

Long-term outcomes

Treatment A ✔

Physician’s Choice or SOC ✔

Early outcomes

Long-term outcomes
Randomized Phase 2 Study

*Plus observational study*

- Study Design & Methodological Issues
  - Trial setting vs observational setting
  - Sample size
- Potential for accelerated approval on randomized Ph2 and conversion with long term observational data
**Pragmatic Trial**

*Explore new dose*

<table>
<thead>
<tr>
<th>Treatment A</th>
<th>Early outcomes</th>
<th>Long-term outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved dose</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Alternate dose</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>

Study data source: Electronic Health Records
Pragmatic trial

• Study Design & Methodological Issues
  – Randomization
  – Consent
Considerations

• Data Quality

• Operational & Logistical Issues
  – Patient level data submission
    • Auditing of source data
    • HIPPA
  – Data standardization across EMR systems
  – Linkage of EMR and claims
  – Consent
Final Thoughts

• Opportunity to learn through pilots and dialogue
  – Test ability of data to answer key questions
  – Test feasibility – can we identify and overcome operational/logistical challenges?

• Opportunity to help patients while learning
Applications of Oncology Real-World Evidence

Amy Abernethy, MD, PhD

www.flatiron.com
Advances in clinical data capture are creating new opportunities for real-world evidence.

- **Clinical Practice** → **EHR DATA** → **Clinical Trial Dataset**

  - **“RWE”**
  - **“EHR as EDC”**

Retrospective Capture with Longitudinal Follow-Up

Prospective Capture

*Retrospective, but near real time in service of prospective work*
Advances in clinical data capture are creating new opportunities for real-world evidence.

Clinical Practice → EHR DATA → Clinical Trial Dataset

"RWE" → Retrospective Capture with Longitudinal Follow-Up → Prospective Capture → "EHR as EDC"

Retrospective, but near real time in service of prospective work

Observational data on off label use → Real-world follow-up on clinical outcomes → Pragmatic trial

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Observational data to complement trials

Case 1: Use of observational data to examine effectiveness of approved agents used in the off-label setting
BRAF V600 inhibitors are approved in melanoma.
Data from Phase II basket trial in non-melanoma cancers had a signal of response in non-small cell lung cancer (N=20).
Among people with BRAF+ non-small cell lung cancer, is there differential improved response when a BRAF inhibitor is administered?
Because of the difficulty of conducting clinical trials in small population, real-world evidence could potentially supplement the clinical trial data.

RWE Application:
RWE database of >25,000 aNSCLC patients allows for identification and investigation of any patient cases with a BRAF V600 mutation, tested as part of routine clinical care.
Centralized, technology-enabled processing allows for further systematic assessment of outcomes by capturing “real-world” tumor endpoints, based on standardized methodology.
RWE Potential Application: Observational data for off-label use of approved agents

Potential selection diagram for BRAF+ patients in the aNSCLC RWE database, based on current cohort:

- **Confirmed Advanced NSCLC**: N = 27,729
- **History of NGS testing**
- **Structured order for a BRAF inhibitor**
- **Free-text search for BRAF mutation**
  - **BRAF V600E mutated**
    - **Treated with a BRAF inhibitor**
    - **Not treated with a BRAF inhibitor**

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**Original Article**

Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations

David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Davis, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jörgen Wolf, M.D., Ph.D., Noopur S. Raju, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena De la Marmol, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hoffmeinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronesi, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.

**ABSTRACT**

**BACKGROUND**

BRAF V600 mutations occur in various nonmelanoma cancers. We undertook a histology-independent phase 2 “basket” study of vemurafenib in BRAF V600 mutation–positive nonmelanoma cancers.

**METHODS**

We enrolled patients in six prespecified cancer cohorts; patients with all other tumor types were enrolled in a seventh cohort. A total of 122 patients with BRAF V600 mutation–positive cancer were treated, including 27 patients with colorectal cancer who received vemurafenib and cetuximab. The primary end point was the response rate; secondary end points included progression-free and overall survival.

**RESULTS**

In the cohort with non-small-cell lung cancer, the response rate was 42% (95% confidence interval [CI], 20 to 67) and median progression-free survival was 7.3 months (95% CI, 3.5 to 10.4). In the cohort with Erdheim–Chester disease or Langerhans’-cell histiocytosis, the response rate was 43% (95% CI, 18 to 71); the median treatment duration was 5.9 months (range, 0.6 to 18.0), and no patients...
Real-world follow up

Case 2: Tracking utilization, effectiveness and safety in the transition from clinical trials to real-world care after regulatory approval
RWE Case Study: Tracking outcomes in the transition from clinical trials to real-world care

Context

- FDA/Flatiron collaborative project to understand safety and outcomes for immune checkpoint inhibitors in aNSCLC as these treatments are adopted post-approval

RWE Application

- Because patients continue to receive care, EHR platform and data processing supports longitudinal tracking
- Allows for “updating the story” with additional information on longer term outcomes - such as time on therapy, safety events and overall survival

Next Steps

- All cases in Flatiron national dataset through March 31, 2016
- Additional phases planned for further investigation based on preliminary findings
# PD-L1 Inhibitor Treatment Patterns

- Evidence of lung cancer diagnosis (ICD code) and at least two visits at a community practice in the Flatiron network after 1/1/2011  
  \( N = 55,975 \)

- Clinical confirmation of non-small cell lung cancer (NSCLC) based on review of unstructured documents  
  \( N = 44,089 \)

- Clinical confirmation of advanced NSCLC (diagnosed stage IIIB - IV) or diagnosed early stage and developed advanced disease  
  \( N = 27,175 \)

- Diagnosis of advanced NSCLC on or after 1/1/2011  
  \( N = 23,319 \)

- Completeness of record: Less than a 90 day gap between advanced diagnosis date and structured first activity date  
  \( N = 20,430 \)

- Usage of a PD-1 inhibitor: Order or administration of nivolumab or pembrolizumab  
  \( N = 1,578 \)

**Final cohort**  
\( N = 1,578 \)
Comparison of PD-1 treated patients in Flatiron dataset to clinical trials

<table>
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<tr>
<th></th>
<th>Nivo (N = 292)*</th>
<th>Pembrolizumab (N = 495)**</th>
<th>Flatiron (N = 1578)</th>
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<td>Median</td>
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<td>64</td>
<td>69.2</td>
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<td>Range</td>
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<td>28-93</td>
<td>32 - 85+</td>
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<td>Not reported</td>
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<td>151 (52)</td>
<td>261 (53)</td>
<td>885 (56)</td>
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<td>White</td>
<td>267 (91)</td>
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<td>Not reported</td>
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<td>13 (1)</td>
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<td>Squamous</td>
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<td>85 (17)</td>
<td>560 (36)</td>
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<tr>
<td>Nonsquamous</td>
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<td>478 (97)</td>
<td>999 (63)</td>
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<td>Mutated (% of tested)</td>
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<td>74 (16)</td>
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<td><strong>ALK status - no. (%)</strong></td>
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<td>Tested</td>
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<td>Mutated (% of tested)</td>
<td>28</td>
<td>77 (26)</td>
<td>114 (31)</td>
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Pragmatic Trial

Case 3: Conducting a prospective pragmatic trial supported by electronic health record data
RWE Case Study: Use of EHR data to support a pragmatic trial

Context

- Hypothetical example presented in white paper - Revised dosing schedule may be safer and equally efficacious compared to that which is approved in the label
- Salford Lung Study serves as a backdrop
  - COPD; new agent vs usual care; conducted in general practices using EHRs

RWE Application

- Use an EHR-derived dataset to plan the study
  - Define standard of care; test eligibility criteria, seek pragmatism in design
- Use EHR data to populate the study dataset
- Use linked EHR data to populate study endpoints
  - Tumor response, mortality
Protocol design informed by common practice patterns

Time between scans
Days

- Ensured protocol design reflects routine clinical practice

Sites selected based on rate of NGS testing in relevant patient populations

NGS results in target patient population
Patients per site

- Selected sites with the greatest potentially eligible patient volume
Clinical Practice → EHR DATA → Clinical Trial Dataset

“RWE”

Retrospective → Prospective

“EHR to EDC”

Pragmatic trial

Retrospective, but near real time in service of prospective work
Conclusions

- Evolving portfolio of example studies where EHR-generated RWE can be used in service of regulatory and clinical decision-making
- Data quality must be characterized and optimized
- Approaches incorporate the longitudinal nature of clinical care
- Incorporate rigorous analysis plans and technology tools to support efficient understanding of information
- Rigorous assessment of outcomes is critical
Panelists

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- **Amy Abernethy, MD, PhD;** Flatiron Health
- **Lisa LaVange, PhD;** FDA
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Supported by:

American Association for Cancer Research
American Society of Clinical Oncology
Susan G. Komen