PANEL 1: CASE STUDIES: DATA COLLECTION AND APPLICATION OF RWE

Amy Abernethy, Flatiron Health (Moderator)
Jane Perlmutter, Gemini Group
Allen Melemed, Eli Lilly and Company
Maria Koehler, Pfizer Oncology
Sean Khozin, US FDA
Amy Abernethy, Flatiron Health
Meeting Goals

• Identify disease and drug candidates in oncology as potential case studies

• Develop strategies for optimal regulatory use of real-world evidence in oncology

• Outline potential pilots in oncology that could be used for clinical evidence generation to support regulatory decisions
Defining the Discussion

• **Real World Data (RWD)** - Data collected from sources outside of conventional randomized controlled trials
  • Electronic health records (EHRs), randomized trial supplements, pragmatic clinical trials, patient registries, administrative claims, surveys, and mobile health-generated data (e.g., smartphones, wearables, social media)

• **Real World Evidence (RWE)** - Evidence derived from RWD
  • Clinical research evidence summarizing the use, benefits and risks of medicines when prescribed in scenarios that fall outside the bounds of the classic clinical trial settings
  • Reflective of the heterogeneous patients seen in real world practice settings
Defining the Discussion

EXPLORE...

• **Value of incorporating RWE into drug development**
  • Supplementing post-market data collection
  • Decreasing costs and development timelines
  • Potential to reflect novel outcomes
  • Minimizing the number of patients exposed to a less efficacious therapy

• **Requirements and considerations for RWE in drug development**
  • Feasibility of data collection
  • Data quality concerns (e.g., missing information, non-systematic data collection)
  • Endpoints
  • Patient confidentiality and data security
Case Example: RWE for Label Expansion

**Situation:** Positive preliminary results were reported last August in the New England Journal of Medicine for vemurafenib’s efficacy in some non-melanoma cancers

**Objective:** Explore the utility of Flatiron real-world data to support understanding of role of vemurafenib in NSCLC patients with BRAF V600E mutations

- **Diagnosis of lung cancer (ICD-9 / ICD-10) and at least 2 visits since 2011**
- **Confirmation of advanced diagnosis after 1/1/2011**
- **Documentation of BRAF V600E mutation**
- **Treated with BRAF inhibitor**
  - Monitor for: • Response • Mortality
- **Not treated with BRAF inhibitor**
  - Monitor for: • Mortality

*STUDY & VALIDATION IN PROGRESS*
# Case Example: RWE for Label Expansion

Leveraging real-world data for potential label expansion requires alignment on variables and endpoints that go beyond what is typically found in real-world data.

<table>
<thead>
<tr>
<th>Key Questions</th>
<th>Context and Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real-World Tumor Response (rwTR)</td>
<td>Assessment of change in burden of disease over the course of treatment with BRAF inhibitor, including:</td>
</tr>
<tr>
<td></td>
<td>- Assessment of initial response, maximum response, and time to occurrence, provide insights into the depth, timing, and duration of response</td>
</tr>
<tr>
<td>Real-World Progression (rwP)</td>
<td>All distinct episodes in which the treating clinician concludes that there has been growth in the disease of interest</td>
</tr>
<tr>
<td></td>
<td>- Distinct episodes are disease-specific time intervals in which the patient is assessed for progression</td>
</tr>
<tr>
<td></td>
<td>- Source information considered includes radiology, laboratory evidence, pathology, clinical assessment</td>
</tr>
</tbody>
</table>

*STUDY & VALIDATION IN PROGRESS*
Case Example: RWE for Label Expansion

The ability to **measure, track, and improve quality** is essential to leveraging real-world data to generate meaningful real-world evidence. As RWE expands into new use cases, understanding the standards for quality and validating these methods will be critical.

**Example: Inter-rater agreement for NSCLC disease characteristics**

<table>
<thead>
<tr>
<th>Question</th>
<th>N</th>
<th>Question Type</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the patient have non-small cell lung cancer?</td>
<td>150</td>
<td>boolean</td>
<td>0.99</td>
</tr>
<tr>
<td>Does the patient have advanced lung cancer?</td>
<td>150</td>
<td>boolean</td>
<td>0.96</td>
</tr>
<tr>
<td>What is the date of initial diagnosis with NSCLC?</td>
<td>150</td>
<td>date</td>
<td>0.78</td>
</tr>
<tr>
<td>What is the date of diagnosis with advanced or metastatic NSCLC?</td>
<td>150</td>
<td>date</td>
<td>0.73</td>
</tr>
<tr>
<td>What was the patient's stage at initial diagnosis?</td>
<td>150</td>
<td>drop down</td>
<td>0.85</td>
</tr>
<tr>
<td>What is the patient's NSCLC histology?</td>
<td>150</td>
<td>drop down</td>
<td>0.95</td>
</tr>
<tr>
<td>What is the patient's smoking status?</td>
<td>150</td>
<td>drop down</td>
<td>0.93</td>
</tr>
</tbody>
</table>

**Note:**

*Date matching agreement currently based on exact date (agreement goes up by ~0.02 when allowing for agreement within a 2-week window and by ~0.04 when allowing for agreement within 1-month)*
RWE Proposals – Vision for the Future

Utilizing RWE with the intent of answering specific clinical questions and, when appropriate, informing product labels, in the following areas:

1. Expanding the safety profiles of a therapeutic

2. Identifying populations with enhanced benefit/risk for an already approved therapy to inform clinical practice

3. Piloting studies to determine the potential correlation between feasible real world measures (such as time to treatment switching) and more traditional clinical trial endpoints (such as time to progression)

4. Building evidence for a supplemental package to expand the indication profile for a therapeutic

5. Supporting efficacy results observed in clinical trial setting, particularly in areas of unmet medical need, when a new drug shows substantial clinical benefit. Real world studies that are able to support the preliminary magnitude of effectiveness in a larger cohort may be sufficient to serve as post-market confirmation of clinical benefit
Meeting Goals (Reprise)

• Identify disease and drug candidates in oncology as potential case studies

• Develop strategies for optimal regulatory use of real-world evidence in oncology

• Outline potential pilots in oncology that could be used for clinical evidence generation to support regulatory decisions
Jane Perlmutter, Gemini Group
janep@gemini-grp.com
Why Is this Topic Important to Patients?

- Patients don’t have the luxury of patience
- Patients in clinical trials are not representative of patients who are treated in all clinics
- Clinical trials have limitations (e.g., drug approval versus treatment optimization)
- Most patients would like to contribute to advancing medical knowledge even if they can’t/don’t participate in clinical trials
What are Patient Concerns?

- Loss of privacy/security
- Consenting
- Hoarding of data
A Lucky Patient’s Story

- **June**: Diagnosed with metastatic esophageal cancer
- **July**: Treated with two cycles of Oxiplatum and 5FU with no improvement; scheduled insertion of a feeding tube
- **August**: Approved to receive Ketruda through Merck’s EAP; began treatment
- **September**: After two cycles of Ketruda began eating normally; had no side effects
- **March**: Had a repeat endoscopy
Many Patients are Not so Lucky

- One year survival of metastatic esophageal cancer is <25%; five year survival <5%
- There are other cancers for which these therapies are likely to be beneficial, but
- Many patients don’t have access to off-label drugs
- Not all patients will respond; but many likely will
- If we continue to do thing as we always have, It will waste many years and patient lives
Proposal

• Rapidly approve new indications for already approved breakthrough therapies (i.e. PD-1 inhibitors)
• Site of origin and biomarker agnostic
• Supplement clinical trial data with high quality RWE

- Multi-organ completed trials
- Ongoing trials
- N of one trials
- TAPUR, etc.
- Off-label use, especially EAPs
Help Patients NOW!

• Determine from FDA
  – What RWE will be acceptable for approval of new indications of breakthrough therapies (PD-1 inhibitors)
  – How much data will be required for a few of the most compelling cases

• Determine from sponsors what data are already available

• Report on progress at FOCR annual meeting in November
Cyramza (Ramucirumab) Case Study

Allen Melemed, Eli Lilly and Company
Ramucirumab’s approval was based on clinical trials conducted before immune...
Emergence of the PD-1 therapy class (nivolumab and pembrolizumab) has dramatically impacted treatment patterns in aNSCLC
Objectives:
To describe patient characteristics, safety, real-world progression, response, and mortality in patients with advanced NSCLC receiving treatment with ramucirumab plus docetaxel (R/D) either prior to or following treatment with a PD-1 inhibitor (PD-1).

Specifically, this analysis will be designed to:
- Describe the demographics and clinical characteristics of patients in this cohort, including:
  - Stratification by patient subcohort of interest (e.g., histology, biomarker status, LOT)
- Describe the treatment sequencing of R/D, PD-1 and other therapies in this population
  - Lines of therapy
  - Treatments received before and after R/D among patients who received both R/D and PD-1

Source data
Continually aggregating real-world EHR dataset of 1.3M+ patients
Data will be extracted from structured data as well as unstructured (free-text) records to increase quality and completeness of key variables

Data cutoff date
March 31, 2016

FLATIRON
By accessing and processing the complete electronic health record, the Flatiron real world database significantly improves completeness and accuracy of key data variables.
Study design: Ramucirumab / PD-1 treatment sequencing

Patients diagnosed with advanced NSCLC since 2011 (N = 23,139)
51% of these patients are active as of December 2014 (Cyramza plus docetaxel approval)

- Usage of a PD-1 inhibitor: Order or administration of nivolumab or pembrolizumab
  N = 1,845

Completeness of record: Less than a 30 day gap between advanced diagnosis date and structured first activity date
N = 1,578

Cyramza and a PD-1 inhibitor order/administration in distinct lines of therapy
N = 62

- Cyramza → PD-1
  N = 40
- PD-1 → Cyramza
  N = 23

Note: One patient, who received a PD-1 inhibitor followed by Cyramza followed by a different PD-1 inhibitor, was considered in both cohorts.

Data cutoff: March 31, 2016
## Baseline patient characteristics

**Ramucirumab / PD-1 cohort**

<table>
<thead>
<tr>
<th></th>
<th>All N=63</th>
<th>Cyramza → PD-1 N=40</th>
<th>PD-1 → Cyramza N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>26 (41.3%)</td>
<td>17 (42.5%)</td>
<td>9 (39.1%)</td>
</tr>
<tr>
<td>Male</td>
<td>37 (58.7%)</td>
<td>23 (57.5%)</td>
<td>14 (60.9%)</td>
</tr>
<tr>
<td><strong>Group stage at diagnosis:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I-II</td>
<td>6 (9.52%)</td>
<td>4 (10.0%)</td>
<td>2 (8.70%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>13 (20.6%)</td>
<td>10 (25.0%)</td>
<td>3 (13.0%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>43 (68.3%)</td>
<td>26 (65.0%)</td>
<td>17 (73.9%)</td>
</tr>
<tr>
<td>Group stage is not reported</td>
<td>1 (1.59%)</td>
<td>0 (0.00%)</td>
<td>1 (4.35%)</td>
</tr>
<tr>
<td><strong>Histology:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-squamous cell carcinoma</td>
<td>48 (76.2%)</td>
<td>33 (82.5%)</td>
<td>15 (65.2%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>15 (23.8%)</td>
<td>7 (17.5%)</td>
<td>8 (34.8%)</td>
</tr>
<tr>
<td><strong>Smoking status:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of smoking</td>
<td>52 (82.5%)</td>
<td>34 (85.0%)</td>
<td>18 (78.3%)</td>
</tr>
<tr>
<td>No history of smoking</td>
<td>11 (17.5%)</td>
<td>6 (15.0%)</td>
<td>5 (21.7%)</td>
</tr>
<tr>
<td><strong>Age at advanced diagnosis (years), Median [IQR]</strong></td>
<td>62.0 [59.0;68.0]</td>
<td>62.0 [60.0;68.0]</td>
<td>61.0 [55.0;67.5]</td>
</tr>
<tr>
<td><strong>Follow-up time from advanced diagnosis (months), Median [IQR]</strong></td>
<td>20.0 [13.1;27.2]</td>
<td>21.5 [15.1;30.2]</td>
<td>16.4 [11.3;25.6]</td>
</tr>
<tr>
<td><strong>Follow-up time from initiation of PD-1 (months), Median [IQR]</strong></td>
<td>3.52 [1.91;6.13]</td>
<td>2.53 [1.41;3.74]</td>
<td>6.84 [5.18;8.48]</td>
</tr>
<tr>
<td><strong>Follow-up time from initiation of Cyramza (months), Median [IQR]</strong></td>
<td>6.97 [2.66;9.88]</td>
<td>8.58 [6.85;10.8]</td>
<td>1.84 [1.08;3.71]</td>
</tr>
<tr>
<td><strong>% deceased</strong></td>
<td>15 (23.8%)</td>
<td>12 (30.0%)</td>
<td>3 (13.0%)</td>
</tr>
</tbody>
</table>

Note: One patient, who received a PD-1 inhibitor followed by Cyramza followed by a different PD-1 inhibitor, was considered in both cohorts.
Baseline patient characteristics
*Ramucirumab / PD-1 cohort*

<table>
<thead>
<tr>
<th></th>
<th>All (N=63)</th>
<th>Cyramza → PD-1 (N=40)</th>
<th>PD-1 → Cyramza (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% PD-L1 Tested:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 Status:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 positive</td>
<td>3 (33.3%)</td>
<td>2 (28.6%)</td>
<td>1 (50.0%)</td>
</tr>
<tr>
<td>PD-L1 negative not detected</td>
<td>4 (44.4%)</td>
<td>3 (42.9%)</td>
<td>1 (50.0%)</td>
</tr>
<tr>
<td>Unknown/results pending</td>
<td>2 (22.2%)</td>
<td>2 (28.6%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>% EGFR Tested:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFR Status:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation positive</td>
<td>5 (10.0%)</td>
<td>3 (8.82%)</td>
<td>2 (12.5%)</td>
</tr>
<tr>
<td>Mutation negative (wild-type)</td>
<td>45 (90.0%)</td>
<td>31 (91.2%)</td>
<td>14 (87.5%)</td>
</tr>
<tr>
<td>% ALK Tested:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK Status:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALK positive</td>
<td>1 (2.17%)</td>
<td>1 (3.23%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>ALK negative not detected</td>
<td>44 (95.7%)</td>
<td>30 (96.8%)</td>
<td>14 (93.3%)</td>
</tr>
<tr>
<td>Unknown/results pending</td>
<td>1 (2.17%)</td>
<td>0 (0.00%)</td>
<td>1 (6.67%)</td>
</tr>
</tbody>
</table>

Note: One patient, who received a PD-1 inhibitor followed by Cyramza followed by a different PD-1 inhibitor, was considered in both cohorts.
## Baseline patient characteristics

**Overall NSCLC cohort and ramucirumab / PD-1 cohort**

<table>
<thead>
<tr>
<th></th>
<th>Overall* N=23,139</th>
<th>PD1/Cyramza Cohort N=63</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11019 (47.6%)</td>
<td>26 (41.3%)</td>
</tr>
<tr>
<td>Male</td>
<td>12120 (52.4%)</td>
<td>37 (58.7%)</td>
</tr>
<tr>
<td><strong>Group stage at diagnosis:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage 0-II</td>
<td>3009 (13.0%)</td>
<td>6 (9.52%)</td>
</tr>
<tr>
<td>Stage III</td>
<td>4578 (19.8%)</td>
<td>13 (20.6%)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>14421 (62.3%)</td>
<td>43 (68.3%)</td>
</tr>
<tr>
<td>Group stage is not reported</td>
<td>1131 (4.89%)</td>
<td>1 (1.59%)</td>
</tr>
<tr>
<td><strong>Histology:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-squamous cell carcinoma</td>
<td>15831 (68.4%)</td>
<td>48 (76.2%)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>5823 (25.2%)</td>
<td>15 (23.8%)</td>
</tr>
<tr>
<td><strong>Smoking status:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of smoking</td>
<td>19626 (84.8%)</td>
<td>52 (82.5%)</td>
</tr>
<tr>
<td>No history of smoking</td>
<td>2800 (12.1%)</td>
<td>11 (17.5%)</td>
</tr>
<tr>
<td>Unknown/not documented</td>
<td>713 (3.08%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td><strong>Age at advanced diagnosis (years), Median [IQR]</strong></td>
<td>69.0 [61.0;76.0]</td>
<td>62.0 [59.0;68.0]</td>
</tr>
<tr>
<td><strong>Follow-up time from advanced diagnosis (months), Median [IQR]</strong></td>
<td>6.71 [2.50;15.0]</td>
<td>20.0 [13.1;27.2]</td>
</tr>
<tr>
<td><strong>% deceased</strong></td>
<td>12617 (54.5%)</td>
<td>15 (23.8%)</td>
</tr>
</tbody>
</table>

*Overall includes patients in Flatiron’s network diagnosed advanced NSCLC, and includes patients in the PD1/Cyramza cohort

Note: One patient, who received a PD-1 inhibitor followed by Cyramza followed by a different PD-1 inhibitor, was considered in both cohorts.
## Baseline patient characteristics

### Overall NSCLC cohort and ramucirumab / PD-1 cohort

<table>
<thead>
<tr>
<th></th>
<th>Overall* N=23,139</th>
<th>PD1/Cyramza Cohort N=63</th>
</tr>
</thead>
<tbody>
<tr>
<td>% PD-L1 Tested:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 Status:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>negative</td>
<td></td>
<td></td>
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<tr>
<td>not determined</td>
<td></td>
<td></td>
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<tr>
<td>% EGFR Tested:</td>
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<tr>
<td>positive</td>
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<td></td>
</tr>
<tr>
<td>not determined</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Overall includes patients in Flatiron’s network diagnosed with advanced NSCLC, and includes patients in the PD1/Cyramza cohort*
Key takeaways:
- Treatment patterns are iatrogenic in real-world clinical practice.
- Initially patients receive the second therapy interest, i.e., the first line later, while the remainder receive the second therapy interest two lines after the first.
Uptake of different sequences over time

Initiation date of the first treatment in the sequence

Cumulative count of patients*

*Cumulative denotes total number of patients that have initiated the first treatment in the sequence as of X month
Questions for Discussion

● What kind of information would be helpful for prescribers to address both efficacy and safety of different sequencing?
  ○ What endpoints should be considered? Evaluating...
  ○ Toxicity should be assessed.

● What is a sufficient sample size for each arm?
  ○ Are the numbers needed different for a safety question versus an efficacy question?
  ○ What other options are available to answer these questions in the absence of adequate patient counts?
    ■ A pragmatic trial may “force” the randomization if we are unable to get enough Cyramza → PD.1 patients

● Are data of sufficient quality to be considered credible for stakeholders?
● What types of action could be taken based upon this information?
  ○ Publication, calculator, Clinical guideline, website, trial
Expected uptake of sequences over time

Cumulative count of patients*

Initiation date of the first treatment in the sequence

*Cumulative denotes total number of patients that have initiated the first treatment in the sequence as of X month
Key Questions for Discussion

- Is the dominant question efficacy or toxicity?
- Is a sufficient sample size for each arm?
- Are data of sufficient quality to be considered credible for stakeholders?
- What types of action could be taken based upon this information?

Next Steps

- Incorporate feedback from today’s discussion into the study design
- Determine timeline for full study (dependent on adequate sample size required)
- Develop statistical analysis plan
A Blueprint for Breakthrough: Exploring Utility of Real World Evidence

Maria Koehler MD PhD
Vice President Strategy, Innovation and Collaboration
Pfizer Oncology NY, NY
Panel 1: Identify Case Studies and Explore Characteristics of Data Quality to Improve Collection

Crizotinib for ALK-positive NSCLC: Yesterday’s Development and Today’s Proposal

1. Brief overview of crizotinib early development that led to accelerated approval through Designation era
2. FD discussions and post approval commitments
3. Post approval real world data
4. Alternative development challenge
Discovery of EML4-ALK Fusion Gene in 2007


Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer

Manabu Soda1,2, Young Lim Choi1, Munehiro Enomoto1,2, Shuji Takada1, Yoshihiro Yamashita1, Shunpei Ishikawa5, Shin-ichiro Fujiwara1, Hideki Watanabe1, Kentaro Kurashina1, Hisashi Hatanaka1, Masashi Bando2, Shoji Ohno2, Yuichi Ishikawa1, Hiroyuki Aburatani1,2, Toshiro Niki1, Yasunori Sohara1, Yukihiro Sugiyama1 & Hiroyuki Mano1,2

K Ras / EGFR / B-raf / HER2 / PIK3CA / ALK / MET / Other

ALK (~5%)
### Crizotinib: Selective Inhibitor of ALK, MET and ROS1

#### Upstate 102 Kinase Panel

#### Cellular Selectivity on 10 of 13 Relevant Hits

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC50 (nM) Mean*</th>
<th>Selectivity Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Met</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>A K</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>ROS</td>
<td></td>
<td>–</td>
</tr>
<tr>
<td>RON</td>
<td></td>
<td>–</td>
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<td>B I</td>
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<td>IRK</td>
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<td>S y</td>
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<td>V FR</td>
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<td>–</td>
</tr>
<tr>
<td>PD FRβ</td>
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<td>–</td>
</tr>
</tbody>
</table>

*Measured using IS capture method

**High Probability of ALK, MET and ROS1 Inhibition at Clinically Relevant Doses**
Study A8081001: Tumor Responses to Crizotinib for NSCLC Evaluable Patients with ALK Fusions

Tumor Size Change

One patient had clinical progression and discontinued without radiographic confirmation

Kak et al. ASCO 2009
ALK-Positive Non-Small Cell Lung Cancer Tumor Responses to Crizotinib by Patient

**Complete Response**  
1  

**Partial Response**  
67  
69  

**Duration of Response Median**  
41.9 weeks (6.1, 42.1)  
48.1 weeks (4.1, 76.6)

- RR for chemotherapeutic agents approved for the treatment of metastatic NSCLC is ~30–35% in first-line chemotherapy

Camidge DR, oral presentation at ASCO 2011; abstract 2501
Riley GJ, oral presentation at WCLC 2011; abstract 1616
Crizotinib US NDA Approval

Crizotinib FDA approval

• Accelerated approval (AA) based on data from two studies
  – **A8081001**: Phase I with extension phase NSCLC
  – **A8081005**: Single Arm Phase II

• **NDA approved August 26th, 2011 – in 4.9 mo**
  – Treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test

• Abbott’s Dx PMA simultaneously approved
  – The **Bysis ALK Break Apart FISH Probe** is a qualitative test to detect rearrangements involving the ALK gene via FISH in FFP NSCLC tissue specimens to aid in identifying those patients eligible for treatment with **ALK ORI** (crizotinib)
Post-Marketing Requirements & Commitments

- With rapid development and approval, come Post-Marketing Requirements (PMRs) & Commitments (PMCs)

- 314.510 Subpart B Post-Marketing Requirements
  - Study A8081007 2nd Line Phase 3 randomised vs chemo
  - Study A8081014 1st Line Phase 3 randomised vs chemo

- Other safety & non-safety related PMRs & PMCs
  - Assess visual effects
  - Dose adjustment strategy for hepatic and renal (severe) impairment
  - Dose adjustment strategy for CYP3A inhibitors/inducers
  - Dosing strategy with gastric pH elevating agents
  - Response in ALB-negative NSCLC (20 additional patients in 1001)
    - Including assessment of other biomarkers
  - Final Tc prolongation potential evaluation
  - Exposure-Response analyses of Phase 3 trials
PROFILE 1007: Phase 3 Second-line Study of Crizotinib vs. Pemetrexed or Docetaxel in ALK-Positive NSCLC

Key Entry Criteria
- ALK-positive by central FISH testing\(^a\)
- Stage IIIb/IV NSCLC
- Prior 1 prior chemotherapy (platinum-based)
- ECOG PS 0–2
- Measurable disease
- Treated brain metastases allowed

Endpoints
- Primary
  - PFS (RECIST 1.1, independent radiology review)
- Secondary
  - ORR, DCR, DR
  - OS
  - Safety
  - Patient reported outcomes (EORTC QLQ-C30, LC13)

Randomize

N=318

CROSSOVER TO CRIZOTINIB ON PROFILE 1005

Crizotinib 250 mg BID PO, 21-day cycle (n=159)

Pemetrexed 500 mg/m\(^2\) or Docetaxel 75 mg/m\(^2\) IV, day 1, 21-day cycle (n=159)

\(\text{\(a\)}\)ALK status determined using standard ALK break-apart FISH assay \(\text{\(b\)}\)Stratification factors: ECOG PS (0/1 vs 2), brain metastases (present/absent), and prior EGFR TKI (yes/no)

Shaw et al., ESMO 2012
Eligibility Criteria:

• **ALK**-positive locally advanced/metastatic non-squamous NSCLC
• No prior treatment for advanced disease

**PROFILE 1014: Phase 3 First-line Study of Crizotinib vs. Platinum/Pemetrexed in **ALK**-Positive NSCLC**

- **Randomize**
  - **Crizotinib 250 mg PO BID**
    - continuous dosing schedule
    - N=167
  - **Cisplatin/pemetrexed or carboplatin/pemetrexed IV**
    - Day 1, 21-day cycle
    - N=167

- **Based on RECIST v 1.1 and confirmed by independent radiology review**

ClinicalTrials.gov ID: NCT0111100

• **Primary endpoint**: PFS
• **Secondary endpoints**: OS, ORR, R, safety, oL, lung cancer-specific symptoms
Crizotinib: Rapid Timeline From Compound Identification to Approval and Challenges with Post-approval Development

Identification of the transforming EML4–ALK fusion gene in non-small-cell lung cancer

- Crizotinib: Rapid Timeline From Compound Identification to Approval and Challenges with Post-approval Development

- ...treatment of patients with locally advanced/metastatic NSCLC that is ALK+ as detected by an FDA-approved test

- ...treatment of adults with previously treated ALK+ advanced NSCLC

- Now Crizotinib is on the Market

- Pfizer Oncology
## Crizotinib Efficacy Across Phase 1, 2 and 3 Studies in ALK-Positive NSCLC was very similar

### Approval and Post-approval Commitments

<table>
<thead>
<tr>
<th></th>
<th>PROFILE 1001(^1) (N=143)</th>
<th>PROFILE 1005(^2) (N=259)</th>
<th>PROFILE 1007(^3) (N=172)</th>
<th>PROFILE 1014(^4) (N=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Line of therapy</td>
<td>Any line</td>
<td>2(^{nd}) line and beyond</td>
<td>2(^{nd}) line</td>
<td>1(^{st}) line</td>
</tr>
<tr>
<td>ORR</td>
<td>61%</td>
<td>60%</td>
<td>65%</td>
<td>74%</td>
</tr>
<tr>
<td>DOR, median (mo)</td>
<td>11.3</td>
<td>10.5</td>
<td>7.4</td>
<td>11.3</td>
</tr>
<tr>
<td>PFS, median (mo)</td>
<td>9.7</td>
<td>8.1</td>
<td>7.7</td>
<td>10.9</td>
</tr>
</tbody>
</table>

\(^1\)Camidge et al., Lancet Onc 13(10): 1011-9, 2012  
\(^2\)Kim et al., ASCO 2012  
\(^3\)Shaw et al., NEJM 368(25): 2385-94, 2013  
\(^4\)Solomon et al., NEJM 371(23): 2167-77, 2014

ASCO 2016 abs 9066  
OS HR 0.85 – cross over
What did subsequent studies in real world teach us?
Confirmation of Crizotinib’s Effect Thru Retrospective Analysis

Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis

Alice T Shaw, Benow Y Yeap, Benjamin J Solomon, Gregory J Riely, Justin Gainor, Jeffrey A Engelman, Geoffrey I Shapiro, Daniel B Costa, Sai-Hong I Ou, Mohit Butaney, Rani Salgia, Robert G Maki, Mariella Varela-Garcia, Robert C Doebele, Yung-Joe Bang, Kimary Kulig, Paulina Salzer, Yiyun Tang, Keith D Wilner, Eunice L Kuok, Jeffrey W Clark, A John Jaffe, D Ross Camidge

*Lancet Oncol 2011; 12: 1004-12

This analysis, performed while the Ph 3 confirmatory trials were ongoing, confirms crizotinib’s effect vs historical chemotherapy treated control pts
US/Canada Crizotinib Retrospective Chart Review

Methods

• Retrospective cohort study in 212 patient (de-identified)

• Physicians (N=107 in US, N=40 in Canada) treating patients with NSCLC were recruited

• For patients meeting the study inclusion criteria, data were retrospectively abstracted by the participating physicians using a secure, web-based data collection form
Results: Response Rate During Crizotinib Treatment

- The estimated crizotinib ORR was 66% for the overall cohort (69% for first-line initiators vs. 60% for second-later-line initiators)
Based on Kaplan-Meier estimation, 1- and 2-year survival rates from crizotinib initiation were 82% (95% CI, 77%-87%) and 49% (95% CI, 39%-60%), respectively.

Median PFS from crizotinib initiation was 9.5 months (95% confidence interval 8.7-10.1 months), in the overall cohort.

Median OS from crizotinib initiation was 23.4 months (95% CI, 19.5 months to not reached), or 2 years (95% CI, 1.6 years to not reached), for the overall cohort.

Note: 95% confidence interval shown in parentheses.
Retrospective Chart Review Indicates Concordance Between the Real World Clinical Effectiveness and Clinical Trial Efficacy Results

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<td>60%</td>
<td>65%</td>
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<td>DOR, median (mo)</td>
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<td>7.7</td>
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1Camidge et al., Lancet Onc 13(10): 1011-9, 2012
2Kim et al., ASCO 2012
3Shaw et al., NEJM 368(25): 2385-94, 2013
4Solomon et al., NEJM 371(23): 2167-77, 2014
Abstract 1355
Crizotinib outcome and post-progression management in ALK+ NSCLC: IFCT-1302 CLINALK

Michaël Duruisseaux,¹ Benjamin Besse,² Jacques Cadranel,³ Maurice Pérol,⁴ Elisabeth Quoix,⁵ Julien Mazières,⁶ Renaud Descourt,⁷ Eric Dansin,⁸ Clarisse Audiger-Valette,⁹ Lionel Moreau,¹⁰ José Hureaux,¹¹ Remi Veillon,¹² Josiane Otto,¹³ Anne Madroszyk,¹⁴ Alexis B. Cortot,¹⁵ Francois Guichard,¹⁶ Pascaline Boudou-Rouquette,¹⁷ Alexandra Langlais,¹⁸ Pascale Missy,¹⁸ Franck Morin,¹⁸ Gérard Zalcman,¹⁹ Denis Moro-Sibilot²⁰

On behalf of the French Cooperative Thoracic Intergroup

¹CHU de Grenoble, Grenoble, France; ²Institut Gustave Roussey, Villejuif, France; ³Hôpital Tenon/AP-HP, Paris, France; ⁴Centre Léon Bérard, Lyon, France; ⁵CHU de Strasbourg, Strasbourg, France; ⁶CHU de Toulouse, Toulouse, France; ⁷CHU Morvan, Brest, France; ⁸Centre Oscar Lambret, Lille, France; ⁹CHITS de Toulon Sainte-Musse, Toulon, France; ¹⁰CH de Colmar, Colmar, France; ¹¹CHU d’Angers, Angers, France; ¹²CHU de Bordeaux, Bordeaux, France; ¹³CRLCC de Nice, Nice, France; ¹⁴CRLCC de Marseille, Marseille, France; ¹⁵CHU de Lille, Lille, France; ¹⁶Polyclinique de Bordeaux, Bordeaux, France; ¹⁷Hôpital Cochin/AP-HP, Paris, France; ¹⁸French Cooperative Thoracic Intergroup (IFCT), Paris, France; ¹⁹Hôpital Bichat/AP-HP, Paris, France; ²⁰CHU de Grenoble, Grenoble, France
Study Design

- Non-interventional, retrospective, multicenter study
- **Primary endpoint:** Overall Survival measured from the start of crizotinib
- **Secondary endpoints:** PFS, ORR at 3 months (RECIST 1.1), efficacy of subsequent systemic therapies
- **Statistical analysis:** stratified Cox regression model for risk of death, logistic regression model for probability of objective response in evaluable patients
- **Inclusion period:** from November 18, 2011 to December 31, 2013

**Inclusion criteria:**
- Advanced stage III or stage IV NSCLC
- ALK FISH +
- > 18 years
- Crizotinib treatment in the setting of:
  - Expanded access program (EAP)
  - Approved drug
- No enrollment in crizotinib clinical trial
- At least 1 week of crizotinib

**Databases screened:**
- Crizotinib French expanded access program
- From IFCT network (117 centers)

**Patients enrolled:** n=318
- 210/311 patients from the crizotinib expanded access program:
  - 34 patients unmet inclusion criteria
  - 67 patients excluded (missing data)
- 118 patients treated with crizotinib as approved drug
## Baseline Characteristics at Time of Crizotinib Treatment Start

<table>
<thead>
<tr>
<th>Baseline characteristics, n (%)</th>
<th>Median (range)</th>
<th>n=318</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.4 (19.2-88.4)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Female / Male</td>
<td>157 (49.4) / 161 (50.6)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Non-Asian / Asian / MD</td>
<td>282 (98.6) / 4 (1.4) / 32</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Never / Former or Current / MD</td>
<td>172 (55.1) / 140 (44.9) / 6</td>
</tr>
<tr>
<td>Current smoker at time of crizotinib initiation</td>
<td>Yes / No / MD</td>
<td>30 (9.6) / 282 (90.4) / 6</td>
</tr>
<tr>
<td>Histology</td>
<td>Adenocarcinoma / Large cell / Other / MD</td>
<td>289 (91.8) / 19 (6.0) / 7 (2.2) / 3</td>
</tr>
<tr>
<td>ECOG Performance Status (PS)</td>
<td>0-1 / 2-4 / MD</td>
<td>222 (78.5) / 61 (21.5) / 35</td>
</tr>
<tr>
<td>Stage</td>
<td>IV / III / MD</td>
<td>265 (85.0) / 47 (15.0) / 6</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>Yes / No / MD</td>
<td>101 (34.9) / 188 (65.1) / 29</td>
</tr>
<tr>
<td>Line of therapy before crizotinib</td>
<td>0 / 1 / 2 / &gt;2</td>
<td>17 (5.3) / 171 (63.8) / 58 (18.2) / 72 (22.7)</td>
</tr>
<tr>
<td>Drugs received before crizotinib</td>
<td>Platinum based / Pemetrexed based / MD</td>
<td>254 (89.1) / 217 (76.1) / 16</td>
</tr>
</tbody>
</table>
Primary and Secondary Endpoints

**Primary Endpoint:** Overall Survival

**Secondary Endpoint:** Progression-free Survival

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>Events, n (%)</th>
<th>168 (52.9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (mo)</td>
<td>18.7</td>
</tr>
<tr>
<td></td>
<td>95%CI</td>
<td>15.2-22.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Progression-free Survival</th>
<th>Events, n (%)</th>
<th>262 (82.4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (mo)</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>95%CI</td>
<td>5.7-8.6</td>
</tr>
</tbody>
</table>

*Overall survival is measured from the start of treatment with crizotinib, analysis cut-off April 5, 2016; CI: confidence interval.*
Crizotinib: Rapid Approval, Excellent Initial Activity and Challenges with Post-approval Development Requires Alternative Solutions to Phase 3 randomized trials?

- ALK-positive advanced NSCLC is a serious and life-threatening disease with a high unmet medical need
  - Orphan Drug Designation
  - Fast Track Designation
  - No existing therapy indicated specifically for ALK-positive NSCLC

- ALKOR provided a meaningful therapeutic benefit
  - Generally safe and well tolerated
  - Associated with high, durable ORR
  - These data were reasonably likely to predict clinical benefit of crizotinib in patients with ALK-positive advanced NSCLC

- Phase 3 randomized trials were already underway
  - 2nd-line Phase 3 Study A8081007 – initiated January 2010
  - 1st-line Phase 3 Study A8081014 – initiated January 2011

Would that be BTD today?
## Clinical Development of Crizotinib in ALK-Positive Advanced NSCLC

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Setting</th>
<th>Trial Design</th>
<th>Primary Endpoints</th>
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</thead>
<tbody>
<tr>
<td>A8081001</td>
<td>All Lines Solid Tumors ALK-Positive NSCLC</td>
<td>Single-Arm, Open-Label</td>
<td>Safety, PK, ORR</td>
</tr>
<tr>
<td>Phase 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A8081005</td>
<td>≥2nd-Line</td>
<td>Single-Arm, Open-Label</td>
<td>ORR, Safety</td>
</tr>
<tr>
<td>Phase 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A8081007</td>
<td>2nd-Line</td>
<td>Crizotinib vs. Pemetrexed or Docetaxel, Open-Label</td>
<td>PFS ✓</td>
</tr>
<tr>
<td>Phase 3</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>A8081014</td>
<td>1st-Line</td>
<td>Crizotinib vs. Pem/Carbo or Pem/Cis, Open-Label</td>
<td>PFS ✓</td>
</tr>
<tr>
<td>Phase 3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Could we have used RWE studies as confirmatory studies in lieu of traditional randomized Phase 3 studies in as the initial evidence is strong?

What type of real world evidence would FDA accept in distinct situations: Pragmatic Randomized Trials? Contemporaneous “historical” controls? Registries?

 Basis for approval – data from 255 ALK-positive NSCLC patients  ✓ Completed
The information in this presentation are my own and do not necessarily reflect the views and policies of FDA
Disclosures

• None
Substantial evidence from adequate and well controlled investigations

Risk

Benefit

Efficacy

Safety

Premarket

Postmarket

Uncertainty

Reduced data quality

α, endpoints

Descriptive

Marketing approval

data quantity

\( f(\text{time}) \)
Uncertainty management

• Using novel pipelines of high quality data in regulatory decision making can reduce uncertainty
  – RWE
  – Patient reported
  – Biometrics (wearables, implantable, etc)
Real world evidence in the expanding universe of big data
The grand unified theory = learning health system

Volume Velocity
Build/purchase, deploy

Variety

Veracity
Pilots and use cases

Organizational, sociopolitical
Information Exchange and Data Transformation (INFORMED)

- Formal submission
- Regulatory
- Research
- Direct

Real world, biometrics, omics, social media

Real world data working group

Data exchange/visualization/analytics*

Data exported for further analysis if needed

*STechnology and software development
“This is what using an EMR feels like”