Real-world Treatment Responses (rwTR) in Advanced NSCLC Patient Subgroups

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The presenter is an Employee of Genentech, a member of the Roche group.
External Controls – New Opportunities

**Flatiron EHR-derived research grade observational database**

- **Enhanced Clinical RWD**
  Flatiron patient-level data on clinical activity and disease characteristics: tumor histology, stage, demographics, ECOG, smoking status, medication history, lab data, procedures.

- **Mortality**
  Enable comparative analyses of overall survival (OS) by group.

- **Progression**
  Capture outcomes from the patient record such as dates and sites of tumor progression and progression-free survival (PFS).

- **Response to Therapy**
  Patient responses to lines of therapy classified as complete response, partial response, stable disease, or progression.

- **Genomic Data**
  Foundation Medicine sample and genomic data, including alteration class, description, analytic metrics, harmonized variant annotations, associated therapy recommendations.
Real-world Treatment Responses (rwTR) in Advanced NSCLC Patient Subgroups

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rwTR: Approach

1. Response is tied to a **line of therapy**
2. Imaging performed define **scan timepoints**
3. For each scan timepoint:
   
   Flatiron captures and **independently** analyzes **the clinician’s assessment of imaging performed** to assess response
Proposed definition of rwTR: Clinical assessment of change in burden of disease based on radiographic evidence over the course of treatment with a given therapy.
<table>
<thead>
<tr>
<th>Lesions</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>All gone</td>
<td>Complete response</td>
</tr>
<tr>
<td>All decreased</td>
<td>Partial response</td>
</tr>
<tr>
<td>Some decreased</td>
<td>Partial response</td>
</tr>
<tr>
<td>Some remain as stable</td>
<td>Stable disease</td>
</tr>
<tr>
<td>All stable; no change</td>
<td>Stable disease</td>
</tr>
<tr>
<td>Some decreased</td>
<td>Stable disease</td>
</tr>
<tr>
<td>Some increased</td>
<td>Stable disease</td>
</tr>
<tr>
<td>Unequivocal overall increase</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>or new lesions</td>
<td></td>
</tr>
</tbody>
</table>
Flatiron-FMI Clinico-Genomic Database

**Patient Population**

- CG Database ~29,000 patients

**Data Model**

- Enhanced Clinical RWD
- Comprehensive Genomic Data
- Clinical Outcomes
- Advanced Genomic Analysis

**Potential to Refresh the CGDB**

- New Flatiron provider sites, incl. academic centers
- Ongoing FoundationOneR testing → growing FoundationCORE™ database
- New data on existing patients (e.g., progression events, updated variant annotations, new computational metrics...)
- Growth in Flatiron clinical data model to reflect standard of care
- Expansion of FoundationOneR genomic profile and analyses
Figure 2. *BRAF*mut FIH and CGDB study populations.

Total number of patients with *BRAF*mut NSCLC in FIH (N=38)

- Patients with evaluable rwTR* (n=30; 78.9%)
  - BRAF inhibitor-containing regimens in 1L–2L† (n=12)
  - Non-BRAF inhibitor-containing regimens in 1L–2L† (n=37)

Total number of patients in CGDB (N=2,139)

- Patients with evaluable rwTR* (n=595; 27.8%)
  - EGFR-targeted therapy in 1L–2L†: afatinib and erlotinib (n=194)‡
  - PD-1 inhibitor in 1L–3L†: nivolumab (n=249)‡

*Patients with available radiographic and clinical assessment of change in burden of disease with a given therapy.
†Each patient may have multiple rwTR assessment across lines of therapy.
‡Distinct afatinib and erlotinib patients, n=181; distinct nivolumab 1L–3L patients, n=247. The remaining 167/595 patients were not included due to insufficient sample size and/or relevant clinical study references.
Table 2. ORR by line of therapy in the CDGB cohort.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>rwTR, % (n/N)</th>
<th>Reference clinical study / population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EGFRmut</td>
<td>EGFRwt</td>
</tr>
<tr>
<td>Afatinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1L (n=29)</td>
<td>56% (14/25)</td>
<td>25% (1/4)</td>
</tr>
<tr>
<td></td>
<td>LUX-Lung 3 / EGFRmut¹</td>
<td>56%</td>
</tr>
<tr>
<td>2L (n=23)</td>
<td>30% (6/20)</td>
<td>0% (0/3)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1L (n=106)</td>
<td>69% (60/86)</td>
<td>35% (7/20)</td>
</tr>
<tr>
<td></td>
<td>EURTAC / EGFRmut²</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>ENSURE / EGFRmut³</td>
<td>63%</td>
</tr>
<tr>
<td>2L (n=34)</td>
<td>53% (8/15)</td>
<td>15% (3/19)</td>
</tr>
<tr>
<td></td>
<td>BR-21 / EGFR (any)⁴</td>
<td>9%</td>
</tr>
<tr>
<td>Nivolumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All comers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1L (n=63)</td>
<td>33% (21/63)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CheckMate 026 / 1L⁵</td>
<td>26%</td>
</tr>
<tr>
<td>2L (n=131)</td>
<td>28% (37/131)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CheckMate 017 / 2L+ squamous⁶</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>CheckMate 057 / 2L+ non-squamous⁷</td>
<td>19%</td>
</tr>
<tr>
<td>3L (n=55)</td>
<td>15% (8/55)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CheckMate 017 / 2L+ squamous⁶</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>CheckMate 057 / 2L+ non-squamous⁷</td>
<td>19%</td>
</tr>
</tbody>
</table>
Figure 3. rwTR for targeted therapy in 1L (CGDB).
Figure 4. rwTR for PD-L1 therapy in 1L, 2L (CGDB).

<table>
<thead>
<tr>
<th>Line</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Unknown*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L</td>
<td>4</td>
<td>17</td>
<td>23</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>2L</td>
<td>2</td>
<td>35</td>
<td>38</td>
<td>51</td>
<td>5</td>
</tr>
</tbody>
</table>

*Response was not assessed during the line of therapy or the patient's treatment could not be confirmed by the abstractor.
### Table 3. ORR by line of therapy in the BRAFmut cohort.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR, % (N=30)</th>
<th>Reference clinical study, treatment RECIST ORR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L BRAF inhibitor (n=5)</td>
<td>80% (3 dabrafenib + trametinib [D+T], 1 vemurafenib; 4/5)</td>
<td>BRF113928 (cohort C), 1L D+T 61%</td>
</tr>
<tr>
<td>1L non-BRAF inhibitor (n=25)</td>
<td>72% (18/25)</td>
<td>Pointbreak, 1L BEV/carboplatin/pemetrexed 34.1%</td>
</tr>
<tr>
<td>1L platinum doublets ± bevacizumab (BEV; n=20)</td>
<td>70% (14/20)</td>
<td>Pointbreak &amp; E4599, 1L BEV/carboplatin/paclitaxel 33% &amp; 35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JMBD, 1L cisplatin + pemetrexed 30.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E4599, 1L carboplatin + paclitaxel 15%</td>
</tr>
<tr>
<td>2L BRAF inhibitor (n=7)</td>
<td>57% (3 dabrafenib, 1 D+T, 1 vemurafenib; 4/7)</td>
<td>VE-BASKET, 2L vemurafenib 37%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRF113928, 2L dabrafenib 33%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BRF113928 (cohort B), 2L D+T 63%</td>
</tr>
<tr>
<td>2L non-BRAF inhibitor (chemotherapy n=7, chemoimmunotherapy n=5)</td>
<td>42% (5/12)</td>
<td></td>
</tr>
</tbody>
</table>
LIMITATIONS

- The study was descriptive in nature and statistical comparisons were not made.
- The small sample size for specific treatment groups may not reflect the patient population enrolled in clinical trials.

CONCLUSIONS

- This analysis demonstrates the potential of leveraging data routinely captured in EHRs to provide real-world data on the effectiveness of treatment in patients with NSCLC.
- These results show that rwTR for targeted therapies and immunotherapies appear to correlate well with RECIST ORR in pivotal clinical studies matched by EGFR mutation status, therapy, and line of treatment.
- Future work will expand similar rwTR evaluation to more treatment and tumor types.
Develop, Define, and Validate Real-world Endpoints

Repeat

Define potential endpoints and associated policies & procedures

Methodological framework to evaluate approach

Analyze output of endpoint against validation framework

Use output to refine endpoint (iterate)
Opportunities for RWD to enhance traditional drug development

Address challenges in traditional drug development

- Slow enrollment in clinical trials
- Low feasibility especially for small biomarker-defined subpopulations
- Many treatment combinations
- Rapidly changing standard of care

Opportunities

- Basket trials/ umbrella trials
- Single-arm trials
- Adaptive designs

Solution

External controls based on RWD
Illustration of past challenges

*Naïve application of observational data*

Docetaxel as 2L or 3L treatment in aNSCLC

Patients in real world setting →

Clinical trial patients ←

Median OS:
- Docetaxel (OAK) = 9.8 months
- Docetaxel (Flatiron) = 6.3 months
Overall survival in OAK and Flatiron patients

- Atezolizumab (OAK) = 13.31 months
- Docetaxel (Flatiron) = 10.64 months
- Docetaxel (OAK) = 9.76 months

Median OS:
- Atezolizumab (OAK) = 13.31 months
- Docetaxel (Flatiron) = 10.64 months
- Docetaxel (OAK) = 9.76 months
Challenges when creating external controls

- Data Recency / quickly evolving standard of care
- Quality and completeness of data
- Accuracy of diagnosis, biomarker status, treatment, etc.
- Completeness of endpoints / missing date of death
- Confounding / differences in underlying populations
- Scalability across various tumor and treatment types
- Demonstrate RWD outcomes (OS, rwTR, rwP) to be a meaningful endpoint based on a validation framework
- Accepted by oncologist, researchers, regulatory bodies, payers, and industry around suitable applications
Next Steps

Retrospective & Prospective Real World Studies:

- Capture RECIST, rwTR, rwP, imaging, IRF assessment of ORR & PFS to determine correlation within the same patient
- Explore multiple tumor types
- Study the feasibility of capturing this information with the existing EHR; examine specific areas where additional data is needed from EHR to better characterize rwTR & rwP
THANK YOU.

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www.ctti-clinicaltrials.org