The Tissue-Agnostic Development of Larotrectinib / Vitrakvi

Josh Bilenker, MD
CEO, Loxo Oncology
A wholly owned subsidiary of Eli Lilly and Company
Tissue-Agnostic DD: Philosophical Underpinnings

- The molecular classification of cancer is valid
- Context-independent drug activity
- Biology >> statistical purity
- Intellectual flexibility in the service of patient access
A Development Plan Born Out of Necessity: Rarity and Diversity of NTRK Fusions

**Adult**
- Brain cancers (0.4–3.1%)¹
- Salivary (MASC; 90–100%)¹
- Secretory breast cancer (92%)²
- Pancreatic cancer³
- Cholangiocarcinoma (3.6%)¹
- Thyroid cancer (1.5–14.5%)¹
- Lung cancer (0.2–3.3%)¹
- GIST (3.2%)⁴
- Colon cancer (1.5%)¹
- Melanoma (0.3%)¹,⁵
- Sarcomas (1%)⁵

**Pediatric**
- Spitzoid neoplasms (16.4%)⁶
- Gliomas (7.1%)¹
- Thyroid (9.4–25.9%)⁷,⁸
- Infantile fibrosarcoma (91–100%)⁹
- Congenital nephroma (83%)¹
- Secretory breast cancer (92%)²
- Sarcomas (1%)⁵

Many NTRK Gene Fusions Discovered During the Development of Vitrakvi

- Colorectal cancer found to harbor OncD
- Papillary thyroid cancer (NTRK1)
- Acute lymphoblastic leukemia (ETV6-NTRK3)

Timeline:
- 1982: Study reveals that OncD contains sequence from TPM3 and previously unknown kinase which receives name trk
- 1986
- 1989
- 1998: Congenital fibrosarcoma (ETV6-NTRK3)
- 1999: Congenital mesoblastic nephroma (ETV6-NTRK3)
- 2002: Acute lymphoblastic leukemia (ETV6-NTRK3)
- 2013: NSCLC (NTRK1)
- 2014
- 2016: Pediatric spitzoid tumors (NTRK1)
- Younger papillary thyroid cancer (NTRK1,3)
- Myopericytic/hemangiopericytic pattern soft tissue sarcoma (NTRK1)
- Congenital mesoblastic nephroma (ETV6-NTRK3)
Descriptive ORR Statistics: Lumping vs Splitting

Sensitivity Analysis: Lower Bound of 2-sided 95% CI

<table>
<thead>
<tr>
<th>Observed ORR</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>0.5%</td>
<td>2%</td>
<td>6%</td>
<td>9%</td>
<td>12%</td>
</tr>
<tr>
<td>35%</td>
<td>5%</td>
<td>12%</td>
<td>15%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>50%</td>
<td>15%</td>
<td>19%</td>
<td>27%</td>
<td>34%</td>
<td>39%</td>
</tr>
<tr>
<td>65%</td>
<td>28%</td>
<td>35%</td>
<td>41%</td>
<td>48%</td>
<td>54%</td>
</tr>
<tr>
<td>80%</td>
<td>28%</td>
<td>44%</td>
<td>56%</td>
<td>64%</td>
<td>70%</td>
</tr>
</tbody>
</table>
Pooled Analysis of Three Larotrectinib Clinical Trials

TRK fusion status determined by local CLIA

Primary endpoint: ORR

Dosing
- Adults: 100 mg BID
- Children with BSA <1 m²: 100 mg/m² BID

Adult Phase 1 (NCT02122913)
- Age ≥18 years
- Advanced solid tumors

n=8

Supplementary
n=2

Integrated
N=122 patients with TRK fusion cancers

SCOUT pediatric Phase 1/2 (NCT02637687)
- Age ≤21 years
- Advanced solid tumors

n=12

n=25

NAVIGATE adult/adolescent Phase 2 ‘basket trial’ (NCT02576431)
- Age ≥12 years
- Advanced solid tumors
- NTRK gene fusion

n=35

n=40

n=2

N=122 patients with TRK fusion cancers
# Vitrakvi Package Insert

## Table 5  Efficacy Results by Tumor Type

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Patients (N=55)</th>
<th>ORR</th>
<th>95% CI</th>
<th>DOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft tissue sarcoma</td>
<td>11</td>
<td>91%</td>
<td>(59%, 100%)</td>
<td>3.6, 33.2+</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>12</td>
<td>83%</td>
<td>(52%, 98%)</td>
<td>7.7, 27.9+</td>
</tr>
<tr>
<td>Infantile fibrosarcoma</td>
<td>7</td>
<td>100%</td>
<td>(59%, 100%)</td>
<td>1.4+, 10.2+</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5</td>
<td>100%</td>
<td>(48%, 100%)</td>
<td>3.7, 27.0+</td>
</tr>
<tr>
<td>Lung</td>
<td>4</td>
<td>75%</td>
<td>(19%, 99%)</td>
<td>8.2, 20.3+</td>
</tr>
<tr>
<td>Melanoma</td>
<td>4</td>
<td>50%</td>
<td>NA</td>
<td>1.9, 17.5+*</td>
</tr>
<tr>
<td>Colon</td>
<td>4</td>
<td>25%</td>
<td>NA</td>
<td>5.6*</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumor</td>
<td>3</td>
<td>100%</td>
<td>(29%, 100%)</td>
<td>9.5, 17.3</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2</td>
<td>SD, NE</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Appendix</td>
<td>1</td>
<td>SD</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Breast</td>
<td>1</td>
<td>PD</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1</td>
<td>SD</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Vitrakvi Package Insert (AEs)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>VITRAKVI</th>
<th>VITRAKVI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 176</td>
<td>N = 176</td>
</tr>
<tr>
<td></td>
<td>All Grades* (%)</td>
<td>Grade 3-4** (%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>29</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Nervous System</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>28</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased weight</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Vascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>

* National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v 4.03.
** One Grade 4 adverse reaction of pyrexia.
Vitrakvi PMRs and PMCs

- Increased patient experience for more precise ORR and response duration, especially for certain tumor types (IRC)

- Longer follow-up for response duration for primary analysis set (IRC)

- Long-term effects on growth and development in pediatric patients

- Dosage modification study

- Validation of a companion diagnostic for patient identification

- CYP3A4 inhibitor study
Tissue-Agnostic DD: International Differences

Use of biomarkers in the context of orphan medicines designation in the European Union

Stelios Tsigkos¹*, Jordi Lliinares¹, Segundo Mariz¹, Stiina Aarum¹, Laura Fregonese¹, Bozenna Dembowska-Baginska², Rembert Elbers⁴, Pauline Evers², Tatiana Foltanova³, Andre Lhoir², Ana Corrêa-Nunes², Daniel O’Connor², Albertha Voordouw⁵, Kerstin Westermark² and Bruno Sepodes²,⁶

http://www.ojrd.com/content/9/1/13
European Concerns Around Orphan Subsetting

Limitations based on the "plausible link to the condition"

Limitations based on the "exclusion of effects"
Key Obstacle: Testing
Sponsors Cannot Run an NGS Business On The Side

- Tissue exhaustion
- Logistical complexity
- Regulatory complexity
- Cost
- Prevalence uncertainty
Instead, We Rely On Other Business Models

Costs subsidized by:

- Philanthropy
- Perceived “big data” value
- Pharma collaborations
- Investor aspirations
- Academic commitment
- Self-pay
Hope On the Horizon

*But When Will Others Follow CMS?*

---

### CMS finalizes coverage of Next Generation Sequencing tests, ensuring enhanced access for cancer patients

**Date**

2018-03-16

**Title**

CMS finalizes coverage of Next Generation Sequencing tests, ensuring enhanced access for cancer patients

**Contact**

press@cms.hhs.gov

---

**CMS finalizes coverage of Next Generation Sequencing tests, ensuring enhanced access for cancer patients**

A new opportunity for cancer patients as advanced diagnostic laboratory tests now have expanded Medicare coverage
Democracy Through Affordable, Local Testing

Regulatory issues
• What price perfection? *The test that is never run has zero sensitivity*
• Hard to source tissue for clinical validation
• “Google Ads” problem around clinical claims

Clinical issues
• Onc / pathologist coordination
• Onc / pathologist education
• Financial incentives