STARTRK2 Clinical Trial: A Basket Study of Entrectinib for the Treatment of Solid Tumors with Specific Gene Rearrangements

Zachary Hornby: Chief Operating Officer, Ignyta, Inc.
Genomically Driven Clinical Trial Paradigms in Oncology

• Roy’s Talk

  Single histology: Squamous lung cancer
  Multiple Markers: PI3KCA, CDK4/6, FGFR, c-MET, etc.
  Multiple Drugs: Taselisib, palbociclib, AZD4547, etc.
  “Umbrella Study” Lung-MAP

One Histology, Multiple Drugs

• This Talk

  Multiple histologies: All solid tumors
  Few Markers: NTRK, ROS1, ALK
  Single Drug: Entrectinib
  “Basket Study” STARTRK-2

One Drug, Multiple Histologies
Ignyta: Company Overview

- **Leading oncology precision medicine company**
  - Ignyta (NASDAQ: RXDX) San Diego-based public biotechnology company focused on precision medicine in oncology

- **Robust pipeline of molecularly targeted therapies**
  - Entrectinib: TRK, ROS1, ALK inhibitor with 79% ORR in fusion-positive patients in Ph 1 studies (n=24); achieved complete and durable responses in patients with CNS disease
  - RXDX-105: RET inhibitor with 56% ORR in patients fusion-positive patients in Ph 1/1b (n=9)
  - RXDX-106: Tyro3, AXL, MerTK (TAM) inhibitor with promising preclinical efficacy as both an immunomodulator and a targeted therapy

- **Integrated approach to Rx/ Dx development**
  - CAP-accredited, CLIA-certified, QSR-compliant diagnostic lab with multi-modality assays (e.g., NGS, NanoString, FISH, IHC)
  - Internal Dx allows Ignyta to illuminate the molecular drivers of cancer and quickly advance the most appropriate molecularly targeted therapies to address them
Entrectinib: Investigational, Potentially First- and Best-in-Class TRK Inhibitor and Best-in-Class ROS1 Inhibitor

**Most potent, orally available pan-TRK inhibitor in clinical development**

<table>
<thead>
<tr>
<th>Target</th>
<th>TRKA (nM)</th>
<th>TRKB (nM)</th>
<th>TRKC (nM)</th>
<th>ROS1 (nM)</th>
<th>ALK (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50*</td>
<td>1.7</td>
<td>0.1</td>
<td>0.1</td>
<td>0.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

- TRK, ALK and ROS1, are cell surface receptors that can become rearranged at the genetic level and fused at the protein level.
- Fusion proteins homodimerize and constitutively activate downstream oncogenic signaling pathways, MAPK, PI3K, PLCγ.
- Entrectinib is the most potent pan-TRK and ROS1 inhibitor in clinical development.
- It demonstrates inhibition of its kinase targets and down-stream effectors.
- Entrectinib inhibition of oncogenic fusion proteins results in rapid tumor response in preclinical models and selected patient populations.
- Designed to cross blood brain barrier (BBB) and to address primary brain tumors and secondary CNS metastases.

* Biochemical kinase assay
Gene Rearrangements Targeted by Entrectinib Are Present Across Many Tumor Histologies

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>NTRK1</th>
<th>NTRK2</th>
<th>NTRK3</th>
<th>ROS1</th>
<th>ALK</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC (aden, large cell NE)</td>
<td>&lt;1%</td>
<td></td>
<td></td>
<td>1-2%</td>
<td>3-7%</td>
</tr>
<tr>
<td>CRC</td>
<td>&lt;1%</td>
<td></td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Salivary gland - NOS</td>
<td></td>
<td></td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcomas (including GI ST)</td>
<td>1-9%</td>
<td></td>
<td>2-11%</td>
<td>2-3%</td>
<td>1-5%</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td></td>
<td>3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma</td>
<td>1-3%</td>
<td></td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma (Spitz)</td>
<td>16%</td>
<td></td>
<td>17%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>4%</td>
<td></td>
<td>9%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Papillary thyroid carcinoma</td>
<td>5-13%</td>
<td></td>
<td>2-14%</td>
<td></td>
<td>7%</td>
</tr>
<tr>
<td>Breast - NOS</td>
<td></td>
<td></td>
<td>2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mammary analog secretory carcinoma [MASC]</td>
<td></td>
<td></td>
<td>90-100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile/ secretory breast</td>
<td></td>
<td></td>
<td>92%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

♦ NTRK Fusions have now been detected in >30 solid and hematological malignancies

Source: TCGA, AACR GENIE, Literature, Foundation Medicine, Ignyta proprietary analysis
Entrectinib is highly potent against all tested NTRK fusions. It exhibits high anti-proliferative potency (0.1-5 nM range) regardless of the identity of the fusion partners or tissue of origin.

<table>
<thead>
<tr>
<th>Cell Lines</th>
<th>Fusion</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ba/F3 (+mIL3)</td>
<td></td>
<td>&gt;1000 (control)</td>
</tr>
<tr>
<td>Ba/F3-TPM3-NTRK1</td>
<td>TPM3-NTRK1</td>
<td>2.5</td>
</tr>
<tr>
<td>Ba/F3-LMNA-NTRK1</td>
<td>LMNA-NTRK1</td>
<td>1.4</td>
</tr>
<tr>
<td>Ba/F3-ETV6-NTRK1</td>
<td>ETV6-NTRK1</td>
<td>2.5</td>
</tr>
<tr>
<td>B3/F3-BCAN-NTRK1</td>
<td>BCAN-NTRK1</td>
<td>0.1</td>
</tr>
<tr>
<td>Ba/F3-SQSTM1-NTRK1</td>
<td>SQSTM1-NTRK1</td>
<td>0.7</td>
</tr>
<tr>
<td>Ba/F3-SCYL3-NTRK1</td>
<td>SCYL3-NTRK1</td>
<td>1.3</td>
</tr>
<tr>
<td>Ba/F3-VCL-NTRK2</td>
<td>VCL-NTRK2</td>
<td>4.3</td>
</tr>
<tr>
<td>Ba/F3-AFAP1-NTRK2</td>
<td>AFAP1-NTRK2</td>
<td>2.7</td>
</tr>
<tr>
<td>Ba/F3-ETV6-NTRK2</td>
<td>ETV6-NTRK2</td>
<td>4.5</td>
</tr>
<tr>
<td>Ba/F3-ETV6-NTRK3</td>
<td>ETV6-NTRK3</td>
<td>4.5</td>
</tr>
<tr>
<td>CUTO-3</td>
<td>MPRIP-NTRK1</td>
<td>1.1</td>
</tr>
<tr>
<td>KM12</td>
<td>TPM3-NTRK1</td>
<td>4.5</td>
</tr>
</tbody>
</table>
Situational Challenge: the Targets Are Real, and the Drug Is Active, but How Do We Find, Enroll and Study the Patients?

Challenge: how to design a registration-enabling clinical program and diagnostic approach that finds, and enrolls, these individually rare (within specific histologies) but collectively numerous patients?

- Many of the relevant tumor types (e.g., head and neck cancers) are not frequently genetically tested
- No individual tumor type has sufficient patient numbers to enroll a complete clinical study
- Some of the biomarkers (NTRK) are not on many diagnostic panels

<table>
<thead>
<tr>
<th>Fusion</th>
<th>Confirmed Responses (n)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTRK1/3</td>
<td>3/3</td>
<td>100%</td>
</tr>
<tr>
<td>ROS1</td>
<td>12/14</td>
<td>86%</td>
</tr>
<tr>
<td>ALK</td>
<td>4/7</td>
<td>57%</td>
</tr>
</tbody>
</table>

79% ORR in Phase 1
**Solution:** a flexible trial design and multi-pronged diagnostic workflow

- Basket study: open to all solid tumor patients, and lymphomas, that harbor the requisite biomarker (NTRK, ROS1, or ALK gene fusions)
- Pooled statistical analysis: all baskets contribute to the primary endpoint
- Multiple mechanisms for diagnostic detection: Ignyta central lab, regional commercial labs, local academic labs
- Liberal eligibility criteria for enrollment
- “Just in time” site activation
- Patient advocacy group-driven study awareness
Studies of Tumor Alterations Responsive to Targeting Receptor Kinases: STARTRK-2

Open-Label, Multicenter, Global Phase 2 Basket Study of Entrectinib for the Treatment of Patients with Locally Advanced or Metastatic Solid Tumors that Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements

Possible Chemotherapy per MD

STARTRK Next Generation: STARTRK-NG

Study of Entrectinib in Children With Recurrent or Refractory Solid Tumors and Primary CNS Tumors, With or Without TRK, ROS1, or ALK Fusions

www.startrktrials.com
All Baskets Contribute to Primary Endpoint and Registrational Dataset

• Each basket represents a combination of a target gene fusion and a histology
  • E.g., NTRK+ salivary gland cancer; ROS1+ NSCLC
• However, opportunity for pooled analysis
• I.e., combined statistical analysis for primary efficacy endpoint (ORR) across multiple baskets:

  NTRK+ NSCLC
  NTRK+ CRC
  NTRK+ Tumors
  NTRK+ Salivary
  NTRK+ Sarcoma

• Could lead to an unprecedented “molecular label” where the indication statement is defined by the presence of the genetic aberration (NTRK fusion) rather than where in the body the malignancy is detected
Ignyta has taken a three-pronged approach (Trident) to enable broad diagnostic testing to identify rare patients for enrollment into basket studies.

1. Established CLIA/CAP lab at Ignyta with no cost, proprietary, highly sensitive fusion testing (*NTRK, ROS1, ALK*)

2. Work with diagnostic consortia & commercial labs throughout US, Europe (e.g., EORTC SPECTA) and Asia (proprietary) to ensure testing of relevant biomarkers and that patients benefit from established infrastructure

3. Enable local sites throughout Europe, Asia, and US to perform high-sensitivity local fusion testing; IHC, NGS, and/or NanoString®

NanoString is a registered trademark of NanoString Technologies, Inc.
Ignyta’s Proprietary Trailblaze Pharos™ Assay Enables Enrollment into STARTRK-2 Clinical Study

Gene Fusions for

* NTRK1, NTRK2, NTRK3, ROS1, ALK

Trailblaze Pharos™ has been granted an Investigational Device Exemption (IDE) and Expedited Access Pathway (EAP) by FDA
Draft Issue Brief on Eligibility

- Allow broad enrollment while restricting primary analysis to defined patient population
  - Protect integrity of trial while enabling data collection in broader populations
  - Data may be helpful to inform safe clinical use in “real-world” patients

STARTRK-2 Approach

- Broad Inclusion/Exclusion criteria
  - Consider tumor type, age, minimal organ function, prior treatment history, CNS involvement, etc.
  - Restrict to only what is absolutely necessary to interpret efficacy and safety
  - No requirements for minimal renal function or hematological function
- Allow patients with CNS disease (primary or metastatic)
- Acknowledge that certain patients may contribute only to a subset of endpoints
  - E.g., non-measurable but evaluable disease: PFS, OS, safety, PK
Global Study Increases Catchment Area
“Just in Time” Network Brings the Study to the Patient

- 14 Countries on four continents
- >150 sites worldwide
- >70 sites in the US
- “Just in time” site activation at 150 additional US sites via site management organization (SMO) when patients are detected at non-current sites
  - Central IRB
  - Central contract
- Travel concierge, including internationally, for any patients not near a STARTRK-2 site
Patient and Provider Awareness Initiatives

- Patient Advocacy Group initiatives
  - Conference presentations
- Newsletters
- Banner ads
- E-Blasts

- Search Engine Optimization & Management

- Clinical trial website for each of patients and providers

NTRK Fusion - Now Recruiting for Trial - startrktrials.com

For NTRK/ALK/ROS1 Positive Cancers. See if You Qualify Today,
Now Enrolling Patients • Precision Cancer Medicine • Investigational Medicine

For Providers
About the Trial
Latest Scientific Data
Refer a Patient

STARTRK-2 Clinical Trial

See if participation in the STARTRK-2 study might be right for you.

TRY OUR PATIENT EVALUATION TOOL
Rapid Execution of Just In Time (JIT) Process with Commercial Diagnostic Partner and Site Management Organization (SMO)

**Day 1**: ROS1+ NSCLC case identified via commercial diagnostic partnership

**Day 1**: Proximal clinical site identified within JIT network

**Day 5**: Site initiation visit with fully executed contract in place and study drug at site

**Day 6**: Patient screened for study enrollment

**Day 4**: Central IRB approval obtained

**Day 7**: Patient enrolled into STARTRK-2 clinical study
Sometimes All of the Preparations Are Insufficient; and Compassionate Use Is Required

20-month old boy with recurrent, metastatic infantile fibrosarcoma harboring $ETV6$-$NTRK3$ gene rearrangement (first detected in Ignyta Dx lab)

**Baseline**
- Patient not eating, progressively less active and more sleepy

**Day 35**
- Patient eating, mobile (crawling), more alert

Images: Heym, Cook Children’s
Lessons Learned

• Rare patient populations that are highly actionable are worth pursuing.

• Design your clinical trial enrollment to match the biology of the patients; in this case, across multiple tumors.

• Engage the regulatory agencies early; they are often more flexible than you might think.

• Be open to building rather than buying (e.g., diagnostics); but as the landscape evolves, adapt with it.

• Compassionate use cases may not drive the primary endpoint; but they sure invigorate the team.
Thank You