Entrectinib, an oral pan-Trk, ROS1, and ALK inhibitor in TKI-naïve patients with advanced solid tumors harboring gene rearrangements

Disclosures

- **Honoraria**: Ignyta, Exelixis, Genentech/Roche
- **Consulting/Advisory Role**: Exelixis, Genentech/Roche, AstraZeneca
- **Speaker’s Bureau**: Ignyta
- **Research Funding**: Foundation Medicine
- **Travel/Accomodations**: Ignyta, Exelixis, Genentech/Roche, AstraZeneca
Recurrent Gene Rearrangements

- **Oncogenic drivers across a variety of cancers**
  - Upstream partner can provide dimerization domains → ligand-independent signaling
  - Activation of downstream pathways

- **Detectable in the clinic**
  - FISH
  - RNAseq
  - DNA-based NGS

- **Select fusions are clinically-actionable**
  - Responses to targeted therapy can be dramatic and durable

Recurrent Gene Rearrangements

- **NTRK1/2/3, ROS1, and ALK** fusions are identified across multiple cancers
  - lower prevalence in more common cancers
Recurrent Gene Rearrangements

- **NTRK1/2/3, ROS1, and ALK** fusions are identified across multiple cancers
  - high prevalence events in rare adult and pediatric cancers

![Graph showing prevalence of NTRK3 in various cancers](image)

**MASC (Mammary Analogue Secretory Carcinoma)**

Drilon et al, Ann Oncol, 2016 Feb 15. PMID: 26884591
Entrectinib (RXDX-101)

- Highly-potent, orally-available, ATP-competitive tyrosine kinase inhibitor
  - Low to sub-nanomolar efficacy against 5 kinases
  - Results in decreased downstream effector activity
    - PLC\(\gamma\), MAPK and PI3K/AKT pathways

- Active *in vitro* and *in vivo*
  - *NTRK1/2/3*-rearranged cancers
  - *ROS1*-rearranged cancers
  - *ALK*-rearranged cancers

<table>
<thead>
<tr>
<th>Kinase</th>
<th>IC(50) (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TrkA</td>
<td>1.7</td>
</tr>
<tr>
<td>TrkB</td>
<td>0.1</td>
</tr>
<tr>
<td>TrkC</td>
<td>0.1</td>
</tr>
<tr>
<td>ROS1</td>
<td>0.2</td>
</tr>
<tr>
<td>ALK</td>
<td>1.6</td>
</tr>
</tbody>
</table>
Entrectinib (RXDX-101)

- Active against potential Trk inhibitor resistance mutations at clinically achievable exposures
  - *NTRK1* F589L (gatekeeper)
  - *NTRK1* V573M
  - *NTRK1* G667S

<table>
<thead>
<tr>
<th>Mutation in TrkA</th>
<th>LOXO-101 IC₅₀ (nM)</th>
<th>Entrectinib IC₅₀ (nM)</th>
<th>Entrectinib Human Exposure Equivalent (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F589L</td>
<td>959.4</td>
<td>9.7</td>
<td>58.2</td>
</tr>
<tr>
<td>V573M</td>
<td>534.5</td>
<td>24.2</td>
<td>145.2</td>
</tr>
<tr>
<td>G667S</td>
<td>185.3</td>
<td>14.6</td>
<td>87.6</td>
</tr>
<tr>
<td>Wildtype</td>
<td>15.0</td>
<td>2.3</td>
<td>13.8</td>
</tr>
</tbody>
</table>

AACR Abstract 2136, Data generated by Ignyta
Phase I Development

STARTRK-1 and ALKA-372-001
Entrectinib: Phase I Studies

**ALKA-372-001 (n=54)**
- Dosing: intermittent & continuous
- NTRK/ROS1/ALK alterations
- Italy
  - FIH study: Nerviano Medical Sciences in October 2012 → Ignyta assumed responsibility in November 2013

**STARTRK-1 (n=65)**
- Dosing: continuous
- NTRK/ROS1/ALK alterations
- US, EU, Asia
  - Ignyta initiated in July 2014

- RP2D: 600 mg PO once daily, continuous
- Total clinical experience: n=119 patients
  - Updated safety and efficacy data
  - Data cut-off: March 7, 2016
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>ALKA-372-001 (n=54)</th>
<th>STARTRK-1 (n=65)</th>
<th>TOTAL (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, median (range)</strong></td>
<td>53 (46-63)</td>
<td>57 (46-66)</td>
<td>55 (46-66)</td>
</tr>
<tr>
<td><strong>Sex, male/female (%)</strong></td>
<td>44/56</td>
<td>48/52</td>
<td>46/54</td>
</tr>
<tr>
<td><strong>ECOG performance status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>30 (56)</td>
<td>22 (34)</td>
<td>52 (44)</td>
</tr>
<tr>
<td>1</td>
<td>21 (39)</td>
<td>41 (63)</td>
<td>62 (52)</td>
</tr>
<tr>
<td>2</td>
<td>2 (4)</td>
<td>2 (3)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Prior Cancer Therapies, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>6 (9)</td>
<td>6 (5)</td>
</tr>
<tr>
<td>1-2</td>
<td>0</td>
<td>15 (23)</td>
<td>15 (13)</td>
</tr>
<tr>
<td>3-4</td>
<td>3 (6)</td>
<td>25 (39)</td>
<td>28 (24)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>51 (94)</td>
<td>19 (29)</td>
<td>70 (59)</td>
</tr>
<tr>
<td><strong>Tumor type, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC</td>
<td>35 (65)</td>
<td>36 (56)</td>
<td>71 (60)</td>
</tr>
<tr>
<td>Gastrointestinal Tract</td>
<td>9 (17)</td>
<td>9 (14)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>CNS</td>
<td>4 (7)</td>
<td>1 (2)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>1 (2)</td>
<td>4 (6)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>Other (e.g., sarcomas, breast, melanoma, RCC, ovarian)</td>
<td>5 (9)</td>
<td>15 (23)</td>
<td>20 (17)</td>
</tr>
</tbody>
</table>
Safety

All patients in dose escalation and expansion phases
- advanced solid tumor
- \( \text{NTRK}1/2/3 \), \( \text{ROS}1 \), or \( \text{ALK} \) alteration
Treatment-Related Adverse Events

Adverse Events (AEs) in >10% of Patients at Any Dose Level (n=119)

<table>
<thead>
<tr>
<th>Adverse Event Term, n (%)</th>
<th>Grades 1-2</th>
<th>Grade 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue/Asthenia</td>
<td>47 (40)</td>
<td>5 (4)</td>
<td>52 (44)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>49 (41)</td>
<td></td>
<td>49 (41)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>33 (28)</td>
<td></td>
<td>33 (28)</td>
</tr>
<tr>
<td>Nausea</td>
<td>29 (24)</td>
<td></td>
<td>29 (24)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>26 (22)</td>
<td></td>
<td>26 (22)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22 (19)</td>
<td>1 (1)</td>
<td>23 (19)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19 (16)</td>
<td></td>
<td>19 (16)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17 (14)</td>
<td>1 (1)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (15)</td>
<td></td>
<td>18 (15)</td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (12)</td>
<td></td>
<td>14 (12)</td>
</tr>
</tbody>
</table>

- AEs were classified via CTCAE v4.0; all reversible with dose modifications
- No evidence of cumulative hepatic or renal toxicity, or QTc prolongation
- Only 2 DLTs occurred (STARTRK-1): grade 3 cognitive disturbance, grade 3 idiopathic eosinophilic myocarditis
## Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event Term, n (%)</th>
<th>Grades 1-2</th>
<th>Grade 3</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>21 (47)</td>
<td></td>
<td>21 (47)</td>
</tr>
<tr>
<td>Fatigue/Asthenia</td>
<td>17 (38)</td>
<td>1 (2)</td>
<td>18 (40)</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (22)</td>
<td></td>
<td>10 (22)</td>
</tr>
<tr>
<td>Weight Increased</td>
<td>8 (18)</td>
<td>1 (2)</td>
<td>9 (20)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7 (16)</td>
<td>1 (2)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8 (18)</td>
<td></td>
<td>8 (18)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7 (16)</td>
<td></td>
<td>7 (16)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>7 (16)</td>
<td></td>
<td>7 (16)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 (13)</td>
<td></td>
<td>6 (13)</td>
</tr>
<tr>
<td>Peripheral Sensory Neuropathy</td>
<td>4 (9)</td>
<td>2 (4)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (4)</td>
<td>3 (7)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>4 (9)</td>
<td>1 (2)</td>
<td>5 (11)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (11)</td>
<td></td>
<td>5 (11)</td>
</tr>
</tbody>
</table>

Adverse Events (AEs) in >10% of Patients at the RP2D (n=45)
Efficacy

Phase 2- Eligible Population
“Phase 2-Eligible Population” (n=25)
- NTRK1/2/3-, ROS1-, or ALK-rearranged solid tumor
- TKI treatment-naïve
- treated at or above RP2D

Molecular Testing: local testing performed
- FISH
- next-generation sequencing

Response Evaluation
- RECIST v1.1, locally assessed and confirmed (n=24)
- volumetric assessment (n=1; primary brain tumor*)

* RECIST criteria not validated in primary brain tumors (FDA-AACR Brain Tumor Endpoints Workshop 2006)
Antitumor Activity

Best Response in TKI Treatment-Naïve $NTRK^-$, $ROS_1^-$, and $ALK$-rearranged Tumors (n=24)

<table>
<thead>
<tr>
<th>Fusion</th>
<th>Confirmed Responses (n)</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$NTRK_1^/$3</td>
<td>3/3</td>
<td>100%</td>
</tr>
<tr>
<td>$ROS_1$</td>
<td>12/14</td>
<td>86%</td>
</tr>
<tr>
<td>$ALK$</td>
<td>4/7</td>
<td>57%</td>
</tr>
</tbody>
</table>
Best Response in TKI Treatment-Naïve NTRK-, ROS1-, and ALK-rearranged Tumors (n=24)

1 additional patient with NTRK+ astrocytoma
- SD by RECIST (not validated for primary brain tumors)
- 45% by exploratory 3-D volumetric assessment

Fusion | Confirmed Responses (n) | ORR (%) |
--------|-------------------------|---------|
NTRK1/3 | 3/3                     | 100%    |

Antitumor Activity
Duration of Clinical Benefit

TKI Treatment-Naïve NTRK-, ROS1-, and ALK-rearranged Tumors (n=25)

- NTRK
- ROS1
- ALK

Duration of Clinical Benefit:

- Time to response (♦)
- Progression by RECIST, continued due to clinical benefit (■)
- Off study (X)

Time on Study (months):
0 3 6 9 12 15 18 21 24 27 30

Tumors:
- NSCLC
- Astrocytoma
- RCC
- Melanoma
- Unknown Primary
- CRC
- NSCLC
- CRC
- NTRK- and ROS1- rearranged Tumors (n=25)
• Response achieved in 100% of tumors
  – Rapid (within 1 month of treatment) and prolonged (~1 year, ongoing) responses were observed
• Response achieved in a variety of histologies and fusion types
  – CRC: LMNA-NTRK1
  – Astrocytoma: BCAN-NTRK1
  – NSCLC: SQSTM1-NTRK1
  – MASC: ETV6-NTRK3
Response to Entrectinib

34/F with metastatic *ETV6-NTRK3*-rearranged MASC

- Resected stage III disease and post-operative RT in 2006
- Recurred in 2011 and treated with 3 lines of cytotoxic chemotherapy and RT
- NGS revealed an *ETV6-NTRK3* rearrangement
- Enrolled onto STARTRK-1 in 2015 → **durable PR**, 10 months of entrectinib treatment

Images: Drilon, MSKCC
CNS Activity
CNS Disease in Cancer

Brain metastases
- 20-40% of all patients with cancer
  - lung (up to 50%)
  - breast
  - melanoma

Primary brain tumors
- astrocytoma (NTRK2 fusions: 3%)
- glioblastoma (NTRK1 fusions: 1-2%)
- pediatric gliomas (NTRK3 fusions: 7%)

Optimal therapy would address both systemic and CNS disease
CNS Activity of Entrectinib

- Entrectinib was designed to cross the blood brain barrier
  - Brain/Blood ratio
    - Mouse: 0.4
    - Rat: 0.6-1.0
    - Dog: 1.2-1.4

- Preclinical CNS activity
  - EML4-ALK-rearranged NCI-H228 cells injected intracranially
  - treated with entrectinib orally vs vehicle for 10 days

<table>
<thead>
<tr>
<th></th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>33.5 days</td>
</tr>
<tr>
<td>Entrectinib</td>
<td>56.5 days</td>
</tr>
<tr>
<td>P-value:</td>
<td>&lt;5x10⁻⁴</td>
</tr>
</tbody>
</table>
Response to Entrectinib

46/M with metastatic SQSTM1-NTRK1-rearranged NSCLC

- Diagnosed in November 2013 with widely metastatic disease
- 4 prior therapies including anti-PD-1 therapy: carboplatin/pemetrexed, pembrolizumab, docetaxel, vinorelbine

- Poor baseline performance status (ECOG 2), on supplemental O₂ and in hospice
- Enrolled in STARTRK-1 March 2015

Extracranial Response to Entrectinib

Baseline

Day 26: - 47% response

Day 317: - 79% response

Images: Farago and Shaw, MGH
Intracranial Response to Entrectinib

Baseline

Day 26: CR

Day 317: CR

Remains on entrectinib and clinically progression-free at >12 months

Images: Farago and Shaw, MGH
• **57/M with low-grade astrocytoma harboring a BCAN-NTRK1 gene rearrangement**
  – Unresectable pontine tumor
  – SD by RECIST (not validated for primary brain tumors)
  – Exploratory 3-Dimensional volumetric tumor assessment performed showed a 45% decrease in tumor burden
  – Improvements in clinical symptoms of ataxia and diplopia

Tumor 3-D volumetric assessments courtesy of P. Brastianos MD (MGH)
Response to Entrectinib

- 20 month-old boy with recurrent, metastatic infantile fibrosarcoma harboring an ETV6-NTRK3 gene rearrangement
  - Presented at birth with left leg mass, requiring through-the-knee amputation
    - Age 4 months, large metastases to left lung identified → 24-weeks of chemotherapy
    - Age 12 months, large right frontal intracranial tumor identified → resected, followed by 5 cycles of salvage chemotherapy
    - Recurrent CNS disease with lesions in the right frontal and temporal lobes, as well as leptomeningeal involvement
  - Received entrectinib starting February 2016
Response to Entrectinib

*ETV6-NTRK3* gene rearranged metastatic fibrosarcoma in 20-month old

**Baseline**
- massive peritumoral edema, midline shift, transtentorial herniation, progressive lethargy

**Day 35**
- decreased tumor and edema, patient with increased alertness, resumed eating and crawling
Entrectinib is a potent TrkA/B/C Inhibitor
- Large safety experience (119 patients)
- Rapid and durable responses

Response in 100% (5/5) of patients achieved in a variety of histologies and fusion types
- CRC: LMNA-NTRK1
- Astrocytoma: BCAN-NTRK1
- Infantile fibrosarcoma: ETV6-NTRK3
- NSCLC: SQSTM1-NTRK1
- MASC: ETV6-NTRK3

Dramatic intracranial activity in 100% of patients with CNS disease (3/3)
- 3/5 of patients treated in Phase 1 setting had primary or metastatic CNS disease
- only Trk inhibitor with demonstrated CNS activity thus far

Response in TKI Treatment-Naïve NTRK-rearranged Tumors (n=5)

![Response in TKI Treatment-Naïve NTRK-rearranged Tumors (n=5) Diagram](image-url)

- mCRC
- Astrocytoma
- Fibrosarcoma
- NSCLC
- MASC

RECIST v1.1
* 3-D volumetric assessment (courtesy of P. Brastianos MD, MGH)
** estimated from radiology assessment
ROS1-Rearranged Cancers

- Response achieved in 86% (12/14) of TKI-naïve tumors
  - Two complete responders
  - Rapid (within 1 month of treatment) and prolonged responses were observed
    - In NSCLC, ORR of 85% (11/13 patients)
    - One additional response in melanoma
  - Longest ongoing response approaching 2 years and 3+ months
Conclusions

• Entrectinib is safe and well-tolerated.
  – 119 patients have been treated: 45 patients at the RP2D of 600 mg daily
  – therapy duration: 19 patients > 6 months (11 patients > 1 year, including 3 patients > 2 years)

• Entrectinib is an active targeted therapy for NTRK-, ROS1-, and ALK-rearranged cancers.
  – confirmed responses observed in 19/24 (79%) patients with extracranial solid tumors; in addition, evidence of tumor shrinkage observed in a patient with NTRK+ astrocytoma
  – brisk (within 4 weeks) and durable (up to 2 years and 3+ months) responses were achieved
  – NTRK-rearranged tumors
    • response achieved in 5 different histologies in both adult and pediatric patients

• Entrectinib is highly CNS-penetrant.
  – durable responses in both primary brain tumors and metastatic disease
  – complete response observed in the CNS
Current Directions

**STARTRK-2**

An 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
Thank You