A pediatric phase 1 study of larotrectinib, a highly selective inhibitor of the tropomyosin receptor kinase (TRK) family

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Role of TRK in normal biology and cancer

Neurotrophin family of receptors

- **TRKA (NTRK1)**: Pain, thermoregulation
- **TRKB (NTRK2)**: Movement, memory, mood, appetite, body weight
- **TRKC (NTRK3)**: Proprioception

TRK uncommonly expressed in normal tissues or cancer

TRK fusions

- Ligand binding domain (LBD) replaced by 5’ fusion partner
- Drives overexpression and ligand-independent activation

TRK uncommonly expressed in normal tissues or cancer

Fusion drives abnormally high expression and activation of TRK kinase domain
Pediatric cancers and TRK fusions

- Gliomas
- Thyroid cancer
- Secretory breast carcinoma
- Infantile fibrosarcoma
- Spitz nevi
- Congenital mesoblastic nephroma
- Various sarcomas

- Rare neoplasm with high TRK fusion frequency
Larotrectinib (LOXO-101)

- Larotrectinib is the first and only selective pan-TRK inhibitor in clinical development
- Highly potent against TRKA, TRKB, TRKC (5–11 nM IC\textsubscript{50} in cellular assays)
- Highly selective
- Responses seen in adult patients with TRK fusions
- Recommended phase 2 dose in adults is 100 mg BID continuously
- Liquid formulation for pediatric patients
Pediatric phase I trial design (SCOUT)

Eligibility
- 1 month – 21 years of age
- Relapsed/refractory solid tumor (including CNS) or locally advanced IFS
- Evaluable or measurable disease by RECIST v1.1
- Karnofsky/Lansky status ≥50
- Adequate organ function

Objectives
- Safety, including dose-limiting toxicities (DLTs)
- Pharmacokinetics
- Maximum tolerated dose (MTD)
- Antitumor activity

Modified rolling 6 design
- Patients with TRK fusion continue to enroll to current dose level during DLT evaluation

Intrapatient dose escalation allowed
- Target $\text{AUC}_{0-24} \geq 50\%$ of adults at RP2D

TRK fusion status determined by local CLIA (or similarly accredited) laboratories

Data cut-off: April 14, 2017
## Patient and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>5 (21)</td>
</tr>
<tr>
<td>1–2 years</td>
<td>2 (8)</td>
</tr>
<tr>
<td>2–12 years</td>
<td>10 (42)</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>7 (29)</td>
</tr>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>4.5 (0.1–18.0)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>12 (50)</td>
</tr>
<tr>
<td><strong>Extent of disease at study enrollment, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Locally advanced</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>10 (42)</td>
</tr>
<tr>
<td><strong>No. of prior systemic therapies, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (29)</td>
</tr>
<tr>
<td>1</td>
<td>6 (25)</td>
</tr>
<tr>
<td>≥2</td>
<td>11 (46)</td>
</tr>
</tbody>
</table>
## Range of histologies treated

<table>
<thead>
<tr>
<th>Cancer types, n (%)</th>
<th>TRK fusion (n=17)</th>
<th>Non-TRK fusion (n=7)</th>
<th>Total (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile fibrosarcoma (IFS)</td>
<td>8 (47)</td>
<td>0</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Soft tissue sarcoma, various</td>
<td>7 (41)</td>
<td>0</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Primary CNS</td>
<td>0</td>
<td>5 (71)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>2 (12)</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>0</td>
<td>1 (14)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>0</td>
<td>1 (14)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>
Dose escalation

Dose level 1 (starting)
100 mg BID AED* (n=4)

Dose level 2
150 mg BID AED* (n=11)

Dose level 3
100 mg/m² BID max 100 mg (n=9)

Interim PK analysis
Protocol modification to only BSA-based dosing

Recommended Phase 2 Dose
100 mg/m² BID max 100 mg

No DLTs

*Adult equivalent doses by SimCyp modeling

Laetsch, 10510
Pharmacokinetics

Concentration-time

Larotrectinib in plasma (ng/mL)

Time (hours)

Estimated plasma AUC$_{0-24}$ (ng*h/mL)

AUC$_{0-24}$ in patients treated with 80–125 mg/m$^2$ BID

Age (years) and mean BID dose

*One patient included in both <2 and 2–11 year categories (due to aging while on study)
## Treatment-emergent AEs related to study drug*

### 100 mg/m² (n=9)

<table>
<thead>
<tr>
<th></th>
<th>Gr 1</th>
<th>Gr 2</th>
<th>Gr 3</th>
<th>Gr 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>33%</td>
<td>–</td>
<td>11%</td>
<td>–</td>
<td>44%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22%</td>
<td>–</td>
<td>11%</td>
<td>–</td>
<td>33%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>11%</td>
<td>11%</td>
<td>–</td>
<td>–</td>
<td>22%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11%</td>
<td>11%</td>
<td>–</td>
<td>–</td>
<td>22%</td>
</tr>
<tr>
<td>Anemia</td>
<td>22%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>22%</td>
</tr>
<tr>
<td>Constipation</td>
<td>22%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>22%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>–</td>
<td>–</td>
<td>11%</td>
<td>–</td>
<td>11%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11%</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>11%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11%</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>11%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>11%</td>
</tr>
</tbody>
</table>

### Total (n=24)

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<th>Gr 3</th>
<th>Gr 4</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>17%</td>
<td>–</td>
<td>4%</td>
<td>–</td>
<td>21%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8%</td>
<td>4%</td>
<td>4%</td>
<td>–</td>
<td>17%</td>
</tr>
<tr>
<td>Increased AST</td>
<td>33%</td>
<td>4%</td>
<td>–</td>
<td>–</td>
<td>38%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13%</td>
<td>8%</td>
<td>–</td>
<td>–</td>
<td>21%</td>
</tr>
<tr>
<td>Anemia</td>
<td>13%</td>
<td>4%</td>
<td>–</td>
<td>–</td>
<td>17%</td>
</tr>
<tr>
<td>Constipation</td>
<td>13%</td>
<td>4%</td>
<td>–</td>
<td>–</td>
<td>17%</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>21%</td>
<td>4%</td>
<td>4%</td>
<td>–</td>
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<td>–</td>
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<tr>
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<td>–</td>
<td>–</td>
<td>–</td>
<td>13%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8%</td>
<td>4%</td>
<td>–</td>
<td>–</td>
<td>13%</td>
</tr>
</tbody>
</table>

*In ≥10% of patients
High response rate in children with TRK fusions

Note: 3 Non-NTRK fusion patients not shown due to clinical disease progression without post-baseline tumor measurements. 4 TRK fusion patients not shown due to having non-measurable disease (n=2) or no disease assessments yet/continuing treatment (n=2). *Pathologic CR
Efficacy regardless of tumor type

Note: 3 Non-NTRK fusion patients not shown due to clinical disease progression without post-baseline tumor measurements. 4 TRK fusion patients not shown due to having non-measurable disease (n=2) or no disease assessments yet/continuing treatment (n=2). *Pathologic CR
Efficacy regardless of TRK gene

Note: 3 Non-NTRK fusion patients not shown due to clinical disease progression without post-baseline tumor measurements. 4 TRK fusion patients not shown due to having non-measurable disease (n=2) or no disease assessments yet/continuing treatment (n=2). *Pathologic CR
Efficacy regardless of fusion partner

Note: 3 Non-NTRK fusion patients not shown due to clinical disease progression without post-baseline tumor measurements. 4 TRK fusion patients not shown due to having non-measurable disease (n=2) or no disease assessments yet/continuing treatment (n=2). *Pathologic CR
### Clinical activity of larotrectinib

<table>
<thead>
<tr>
<th></th>
<th>TRK fusions (n=17)*</th>
<th>Non-fusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Confirmatory response data available (n=11)</td>
<td>All patients (n=13)</td>
</tr>
<tr>
<td><strong>Objective response rate</strong> (95% CI)</td>
<td>91% (59–100%)</td>
<td>92%** (64–100%)</td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
<td>64%</td>
<td>62%**</td>
</tr>
<tr>
<td><strong>Complete response</strong></td>
<td>27%</td>
<td>31%**</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*4 patients not evaluable due to having non-measurable disease (n=2) or no disease assessments yet/continuing treatment (n=2)

**Includes unconfirmed responses with confirmatory scans pending (1 PR, 1 CR). Both remain in response and ongoing on study.
Responses occur early and are durable

- Treatment after surgery
- Treatment ongoing
- Pathologic CR
- Post-surgery observation
- Time to first response

*Only patient with TRK fusion to develop PD
Confirmed TRKC G623R solvent front resistance mutation
Patient re-responded to LOXO-195*

*Patients had non-measurable disease at baseline

Laetsch, 10510
Drilon A, Cancer Discovery, Online First (03-JUNE-2017)
Rapid response in infant with ETV6-NTRK3 infantile fibrosarcoma (IFS)

Baseline

Before Cycle 3

After four doses

31 do infant with IFS of the scalp
Rapid recurrence following surgical resection
Marked clinical improvement after four doses of larotrectinib
CR after 2 cycles of larotrectinib
Remains on therapy after 2 cycles
Rapid and durable response in patient with metastatic STRN-NTRK2 fusion sarcoma

Baseline

Before Cycle 2

11 yo girl with retroperitoneal undifferentiated sarcoma harboring STRN-NTRK2 fusion
Refractory to vincristine/ doxorubicin/cyclophosphamide, ifosfamide/etoposide, sorafenib, and vincristine/irinotecan
PR after 1 cycle of larotrectinib with rapid clinical improvement
Remains in response after 13 cycles
ETV6-NTRK3 infantile fibrosarcoma patient

2 yo girl with infantile fibrosarcoma

2 cycles of vincristine/actinomycin-D/cyclophosphamide → progression
→ leg amputation was only alternative option

4 cycles larotrectinib → referred for surgery

Pathologic complete response with clear margins

No functional deficit post-surgery
Larotrectinib is active and well-tolerated in children with TRK fusion cancers

• Larotrectinib demonstrated a favorable tolerability profile and histology-independent activity in pediatric patients harboring TRK fusions

• Recommended phase 2 dose in children: 100 mg/m² BID continuously, cap 100 mg/dose
  – No DLTs at any dose level
  – Similar exposure to adults at RP2D
  – Highly active

• Phase 2 portion of trial is enrolling globally (Abstract TPS10577)
  – Infantile fibrosarcoma
  – Other CNS and extracranial TRK fusion solid cancers
Acknowledgements

The authors would like to thank

• Patients and their families
• Research staff

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