The use of larotrectinib in the management of locally advanced pediatric NTRK-fusion sarcoma

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Disclosures

- Prior consultation for Loxo Oncology: DuBois and Laetsch
- Employees of Loxo Oncology: Reynolds, Cruickshank, and Cox
- Larotrectinib is an investigational agent
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 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
TRK fusions seen in diverse range of pediatric tumors

- Gliomas
- Thyroid cancer
- Secretory breast carcinoma
- Infantile fibrosarcoma (IFS)
- Spitz nevi
- Congenital mesoblastic nephroma
- Various sarcomas
TRK fusions seen in diverse range of pediatric tumors

- Gliomas
- Thyroid cancer
- Secretory breast carcinoma
- **Infantile fibrosarcoma (IFS)**
- Spitz nevi
- Congenital mesoblastic nephroma
- Various sarcomas
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$_{50}$ in cellular assays)
- Highly selective
- High response rate in adult and pediatric patients with TRK fusions
- Recommended phase 2 dose in adults is 100 mg BID continuously and 100mg/m2 BID in pediatrics (100mg BID maximum)
- Liquid formulation for pediatric patients
Design of pediatric phase I trial (SCOUT)

Eligibility
- 1 month – 21 years of age
- Relapsed/refractory solid tumor (including CNS) or locally advanced IFS
- Patients with locally advanced disease who had not undergone definitive surgery were eligible
- 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 fusions continue to enroll to current dose level during DLT evaluation

Inpatient dose escalation allowed
- Target $AUC_{0-24} \geq 50\%$ of adults at RP2D

TRK fusion status determined by local CLIA (or similarly accredited) laboratories
# Patient and disease characteristics for SCOUT

<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>
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<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>
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<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>
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<tr>
<td>1</td>
<td>6 (25)</td>
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<tr>
<td>≥2</td>
<td>11 (46)</td>
</tr>
</tbody>
</table>

Data cutoff: 17 April 2017

Laetsch et al. Proc ASCO 2017
Efficacy in children with TRK fusions (ASCO 2017)

*Locally advanced patients who underwent surgery

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)

Data cutoff: 17 April 2017

Laetsch et al. Proc ASCO 2017
Current report

• Detailed description of children with sarcoma who underwent surgical resection after treatment with larotrectinib in phase 1
  – Pathologic responses following larotrectinib
  – Surgical outcomes, including margins and wound complications
  – Patients were restaged following surgery according to UICC restaging:
    • R0 = complete tumor resection with free margins
    • R1 = macroscopic resection with invaded margins
    • R2 = macroscopic residual tumor
  – Clinical course after recovery from surgery

UICC (1987) TNM Classification of Malignant Tumours
<table>
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<th>Characteristic</th>
<th>Total (N=5)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age group, n (%)</strong></td>
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</tr>
<tr>
<td>&lt;1 year</td>
<td>1 (20)</td>
</tr>
<tr>
<td>1– &lt;2 years</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2– &lt;12 years</td>
<td>3 (60)</td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>1 (20)</td>
</tr>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>2 (0.4–12)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>2 (40)</td>
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<tr>
<td><strong>Extent of disease at study enrollment, n (%)</strong></td>
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<tr>
<td>Locally advanced</td>
<td>5 (100)</td>
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<tr>
<td>Metastatic</td>
<td>0 (0)</td>
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<td><strong>No. of prior systemic therapies, n (%)</strong></td>
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<td>0</td>
<td>1 (20)</td>
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<td>1</td>
<td>1 (20)</td>
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<tr>
<td>≥2</td>
<td>3 (60)</td>
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</table>

Data cutoff: 17 July 2017
Case 1: 2 yo with progressive *ETV6-NTRK3* IFS

Baseline

Start of Cycle 3

2 yo girl with infantile fibrosarcoma

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

4 cycles larotrectinib → PR → referred for surgery

Pathologic complete response with clear margins (R0 resection); >98% necrosis

No functional deficit post-surgery

Off larotrectinib x 8 months and no evidence of disease

Data cutoff: 17 July 2017

Courtesy of L. Mascarenhas, CHLA
Case 2: 5 mo with progressive *ETV6-NTRK3* IFS

5 mo boy with infantile fibrosarcoma

2 cycles of vincristine/actinomycin-D → progression → vincristine/actinomycin-D/cyclophosphamide → inadequate response

6 cycles larotrectinib → PR → referred for surgery

Pathologic complete response with clear margins (R0 resection)

No functional deficit post-surgery

Off larotrectinib x 6 months and no evidence of disease

Data cutoff: 17 July 2017

Courtesy of N. Federman, UCLA
Case 3: 12 yo with *TPM3-NTRK1* sarcoma

12 yo boy with poorly classified spindle cell sarcoma

No standard therapy option

9 cycles larotrectinib → PR → referred for surgery

Uncomplicated R0 resection → No viable tumor

Surgery occurred at data cut-off date; follow-up off larotrectinib ongoing

Data cutoff: 17 July 2017
Case 4: 2 yo with *PDE4DIP-NTRK1* IFS (1 of 2)

2 yo boy with infintile fibrosarcoma

One cycle vincristine / actinomycin-D / cyclophosphamide / ifosfamide / doxorubicin → surgery → progression

6 cycles larotrectinib → PR → referred for surgery

Uncomplicated R1 resection → Viable tumor seen at margin
While waiting to restart larotrectinib, patient progressed
Re-started, 7 cycles larotrectinib → Second PR → referred for surgery

Second uncomplicated R1 resection → Viable tumor seen at margin

Adjuvant radiotherapy followed by larotrectinib, ongoing

11 months on study

Recurrence after surgery with positive margins

Second PR

Case 4: 2 yo with \textit{PDE4DIP-NTRK1} IFS (2 of 2)
Case 5: 2 yo with SQSTM1-NTRK1 IFS (1 of 2)

2yo girl with infantile fibrosarcoma

3 cycles of vincristine/actinomycin-D/cyclophosphamide → surgery → recurrence → 4 cycles VAC → surgery → recurrence → 2 cycles ifosfamide/etoposide

5 cycles larotrectinib → Partial Response

Data cutoff: 17 July 2017

Courtesy of B. Turpin, Cincinnati
Case 5: 2 yo with *SQSTM1-NTRK1* IFS (2 of 2)

Uncomplicated R1 resection →
Viable tumor without necrosis

Continues on adjuvant larotrectinib

13 months on study
Larotrectinib may facilitate resection of previously unresectable pediatric sarcomas

Promising early experience demonstrates:

1. Pediatric patients with TRK-fusion advanced sarcomas are able to proceed to surgical resection following pre-surgical larotrectinib, in settings where amputation and/or grossly morbid surgery was the only other alternative

2. Extensive necrosis on histopathology

3. No postoperative complications or wound healing issues to date

4. Potential for clean margins without recurrence

5. Potential use of adjuvant larotrectinib
**Next steps**

- Phase 2 portion of SCOUT trial ongoing
  - surgical resection allowed for patients with sarcoma
  - use of larotrectinib in adjuvant setting allowed

- Considering pediatric frontline trial
Acknowledgements

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• Research staff

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