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

Turpin B,1 Albert CM,2 Mascarenhas L,3 Federman N,4 Nagasubramanian R,5 Zeigler D,6 Reynolds M,7 Smith S,7 Cruickshank S,7 Cox MC,7 Pappo AS,8 Hawkins DS,2 DuBois SG,9 Laetsch TW10

1Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2Seattle Children’s Hospital, University of Washington, Fred Hutchinson Cancer Research Center, Seattle, WA; 3Children’s Hospital Los Angeles, Keck School of Medicine, University of Southern California, Los Angeles, CA; 4University of California, Los Angeles, Los Angeles, CA; 5Nemours Children’s Hospital, Orlando, FL; 6Kids Cancer Centre, Children’s Cancer Institute, University of New South Wales, Sydney, Australia; 7Loxo Oncology, Inc, South San Francisco, CA; 8St Jude Children’s Research Hospital, Memphis, TN; 9Dana-Farber/Boston Children’s Cancer and Blood Disorders Center, Boston, MA; 10University of Texas Southwestern Medical Center/Children’s Health, Dallas, TX
Disclosure information

AACR Pediatric Cancer Research: From Basic Science to the Clinic
Brian Turpin

I have no financial relationships to disclose

I will be discussing the use of the investigational drug, larotrectinib
TRK fusions are rare but recurrent oncogenic drivers in a variety of adult and pediatric cancers

- Beyond the embryo, tropomyosin receptor kinase (TRK) proteins TRKA, TRKB, and TRKC are primarily limited to the nervous system
  - Regulate pain, proprioception, appetite, and memory
  - TRK is uncommonly expressed in normal tissues

- Recurrent chromosomal fusion events have been identified across diverse pediatric and adult cancers

![Diagram showing NTRK1/2/3 kinases and their interactions with ERK and AKT]

- Gliomas
- Thyroid cancer
- Secretory breast carcinoma
- Infantile fibrosarcoma
- Congenital mesoblastic nephroma
- Various sarcomas
Larotrectinib is the first and only selective pan-TRK inhibitor in clinical development

- Larotrectinib is a highly potent and selective small-molecule inhibitor of TRKA, TRKB, and TRKC (5–11 nM IC$_{50}$ in cellular assays)
- Prolonged responses in adult patients with TRK fusions (Recommended phase 2 dose in adults is 100 mg BID)
- Favorable tolerability profile
- Liquid formulation for pediatric patients
- This is an updated analysis from a multicenter, rolling 6 phase 1 study of larotrectinib in patients with refractory solid or CNS tumors aged ≥1 month – 21 years (NCT02637687)
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

Data cut-off: July 17, 2017

n=17 TRK fusion patients
n=7 non-fusion patients

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

Intrapatient dose escalation allowed

- Target AUC_{0–24} ≥50% of adults at RP2D

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

*This report is limited to patients enrolled in the Phase 1 dose escalation portion of the trial. Additional patients have been enrolled in the Phase 1 expansion and Phase 2 portions of the trial and those data will be reported at a later date.
<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 (0.1–18.3)</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>11 (46)</td>
</tr>
<tr>
<td>Metastatic</td>
<td>8 (33)</td>
</tr>
<tr>
<td>CNS</td>
<td>5 (21)</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>1–2</td>
<td>9 (38)</td>
</tr>
<tr>
<td>≥3</td>
<td>8 (33)</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>CNS</td>
<td>0</td>
<td>5 (71)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Papillary thyroid</td>
<td>2 (12)</td>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>0</td>
<td>1 (14)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>0</td>
<td>1 (14)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>
No maximum tolerated dose was defined

Dose level 1 (starting)
100 mg BID AED* (n=4)
No DLTs

Dose level 2
150 mg BID AED* (n=11)
No DLTs

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

Interim PK analysis
Protocol modification to only BSA-based dosing

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

*Adult equivalent doses by SimCyp modeling
Adult and pediatric pharmacokinetics show concordance

**Concentration-time**

![Graph showing concentration-time relationship for different groups.]

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

![Graph showing AUC\(_{0-24}\) values for different age groups.]

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>C(_{\text{max}}) (ng/mL)</th>
<th>T(_{\text{max}}) (h)</th>
<th>AUC(_{0-24}) (ng(\cdot)h/mL)</th>
<th>T(_{\text{v}}) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peds liquid</td>
<td>6</td>
<td>1010 ± 740</td>
<td>0.75 (0.5–1)</td>
<td>5570 ± 5400</td>
<td>1.9 ± 0.3</td>
</tr>
<tr>
<td>Peds capsule</td>
<td>3</td>
<td>882 ± 295</td>
<td>2 (1–2)</td>
<td>6689 ± 3860</td>
<td>1.5 ± 0.2</td>
</tr>
<tr>
<td>Adult capsule</td>
<td>29</td>
<td>998 ± 419</td>
<td>1</td>
<td>8340 ± 3520</td>
<td>2.0 ± 0.7</td>
</tr>
</tbody>
</table>

\(\text{C}_{\text{max}}, \text{AUC}_{0-24}, \text{and } T_{\text{max}}\) are mean ± standard deviation. \(T_{\text{v}}\) is median (range).

*One patient included in both <2 and 2–11 year categories (due to aging while on study)*
Adverse events related to larotrectinib* were generally low grade

<table>
<thead>
<tr>
<th>Event</th>
<th>100 mg/m² (n=9)</th>
<th>Total (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr 1</td>
<td>Gr 2</td>
</tr>
<tr>
<td>Increased AST</td>
<td>33%</td>
<td>11%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>22%</td>
<td>–</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>22%</td>
<td>–</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>22%</td>
<td>–</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Anemia</td>
<td>22%</td>
<td>–</td>
</tr>
<tr>
<td>Constipation</td>
<td>22%</td>
<td>–</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>11%</td>
<td>–</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>11%</td>
<td>–</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11%</td>
<td>–</td>
</tr>
<tr>
<td>Blood alk phosph increased</td>
<td>–</td>
<td>11%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>–</td>
<td>11%</td>
</tr>
</tbody>
</table>

*In >10% of patients in 100 mg/m² group
Larotrectinib is highly effective in children with TRK fusions (INV)

Maximum change in tumor size (%)

3 non-TRK fusion patients not shown due to clinical disease progression without post-baseline tumor measurements
2 TRK fusion patients not shown due to having non-measurable disease at baseline
*Locally advanced patients who underwent surgery; INV = assessed by investigators
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Larotrectinib is highly effective in children with TRK fusions

<table>
<thead>
<tr>
<th></th>
<th>TRK fusions – IRC (n=17)*</th>
<th>TRK fusions – INV (n=17)*</th>
<th>Non-fusions – INV (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate</td>
<td>93% (68–100%)</td>
<td>93% (68–100%)</td>
<td>0</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>80%</td>
<td>67%**</td>
<td>0</td>
</tr>
<tr>
<td>Complete response</td>
<td>13%</td>
<td>27%</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease</td>
<td>7%</td>
<td>7%</td>
<td>0</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0</td>
<td>0</td>
<td>100%</td>
</tr>
</tbody>
</table>

*2 patients not evaluable due to having non-measurable disease at baseline

**Includes 2 patients with unconfirmed partial responses as of July 17, 2017, which were subsequently confirmed

IRC = assessed by blinded independent review committee; INV = assessed by investigators
Larotrectinib responses occur early and are durable

Overall treatment duration (months)
Early and sustained response in a 6-year old boy with inoperable relapse of high-grade spindle cell sarcoma with a TPM3-NTRK1 fusion

Diagnosed at birth with a localized high-grade spindle cell sarcoma of the foot (ETV6 FISH negative)

Underwent amputation after minimal response to ifosfamide/doxorubicin

Multifocal pulmonary relapse at age 5

TPM3-NTRK1 fusion identified

Near complete response after 1 cycle of larotrectinib, ongoing > 1 year
Amputation-sparing response in a 2-year old patient with relapsed IFS with a SQSTM1-NTRK1 fusion (1 of 2)

Data cutoff: July 17, 2017

2-yr girl developed large ETV6 FISH-negative infantile fibrosarcoma shortly after birth.

Recurrences after VAC chemotherapy/R1 resection, ablation and repeat surgery.

Attempt to spare amputation after rapid subscapular relapse with ifosfamide/etoposide → No Response.

NGS revealed an SQSTM1-NTRK1 fusion.

5 cycles larotrectinib → Partial Response.
Amputation-sparing response in a 2-year old patient with relapsed IFS with a SQSTM1-NTRK1 fusion (2 of 2)

Uncomplicated R1 resection → Viable tumor without necrosis
Continues on adjuvant larotrectinib

13 months on study

After 12 cycles

Data cutoff: July 17, 2017
Dramatic early radiographic and clinical response in a 3-year old girl with a glioblastoma multiforme with an ETV6-NTRK3 fusion

Diagnosed at 5 months of age

Failed treatment with multiple surgical resections, intensive chemotherapy, focal radiation therapy

ETV6-NTRK3 fusion identified

Completed 2 cycles of larotrectinib and ongoing

Significant improvement in milestones within 2 weeks of commencing treatment

First TRK fusion GBM patient treated to response with a TRK inhibitor

Baseline

After 2 cycles
Larotrectinib is highly active and well-tolerated in children with TRK fusion cancers

- Larotrectinib continues to demonstrate 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 maximum tolerated dose reached
  - Similar exposure to adults at RP2D
  - Highly active

- Phase 2 portion of trial is enrolling globally
  - Infantile fibrosarcoma
  - Other CNS and extracranial TRK fusion solid cancers
The authors would like to thank

- Patients and their families
- Research staff

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