Larotrectinib efficacy and safety in TRK fusion cancer: an expanded clinical dataset showing consistency in an age and tumor agnostic approach

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Disclosures

Advisory roles: Bayer, Pfizer
Grants: none
Stocks: none
Others: none
Larotrectinib is a selective, CNS-active TRK inhibitor

*NTRK* gene fusions are rare but recurrent oncogenic drivers

- Larotrectinib is a highly potent small-molecule inhibitor of TRKA, TRKB, and TRKC (5–11 nM IC$_{50}$ in cellular assays)
- Demonstrated activity in CNS disease$^1$
- Liquid formulation allows dosing of children as young as at birth and delivers equivalent pharmacokinetics to capsules

Adult phase I
- Age ≥18 years
- Advanced solid tumors

SCOUT: pediatric phase I/II
- Age ≤21 years
- Advanced solid tumors

NAVIGATE: adult/adolescent phase II 'basket' trial
- Age ≥12 years
- Advanced solid tumors
- TRK fusion cancer

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

Primary endpoint
- Best objective response rate (RECIST 1.1)

Secondary endpoints
- Duration of response
- Progression-free survival
- Safety

Dosing
- Single-agent larotrectinib, administered predominantly at 100 mg BID continuously
- Treatment beyond progression permitted if patient continuing to benefit

Patients with TRK fusion cancer: Primary dataset

- n=8
- n=12
- n=35
- n=55

Data cutoff: 30 July 2018

BID, twice-daily; CLIA, clinical laboratory improvement amendments; RECIST, Response Evaluation Criteria In Solid Tumors
Patients with TRK fusion cancer: Supplementary dataset

**Adult phase I**
- Age ≥18 years
- Advanced solid tumors

**SCOUT: pediatric phase I/II**
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  - Duration of response
  - Progression-free survival
  - Safety
- Dosing
  - Single-agent larotrectinib, administered predominantly at 100 mg BID continuously
  - Treatment beyond progression permitted if patient continuing to benefit

**Patients with TRK fusion cancer:**
- **Primary**
  - n=8
  - n=12
  - n=35
  - n=55
- **Supplementary**
  - n=2
  - n=25
  - n=40
  - n=67

**Total patients with TRK fusion cancer:** 122

Data cutoff: 30 July 2018

BID, twice-daily; CLIA, clinical laboratory improvement amendments; RECIST, Response Evaluation Criteria In Solid Tumors
## Patient demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Primary (n=55)</th>
<th>Supplementary (n=67)</th>
<th>Integrated (n=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>29 (53)</td>
<td>31 (46)</td>
<td>60 (49)</td>
</tr>
<tr>
<td>Female</td>
<td>26 (47)</td>
<td>36 (54)</td>
<td>62 (51)</td>
</tr>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>45.0 (0.3–76.0)</td>
<td>35.0 (0.1–80.0)</td>
<td>41.0 (0.1–80.0)</td>
</tr>
<tr>
<td><strong>Age group, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>6 (11)</td>
<td>12 (18)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>2–&lt;6 years</td>
<td>5 (9)</td>
<td>2 (3)</td>
<td>7 (6)</td>
</tr>
<tr>
<td>6–&lt;15 years</td>
<td>1 (2)</td>
<td>13 (19)</td>
<td>14 (11)</td>
</tr>
<tr>
<td>15–39 years</td>
<td>12 (22)</td>
<td>9 (13)</td>
<td>21 (17)</td>
</tr>
<tr>
<td>≥40 years</td>
<td>31 (56)</td>
<td>31 (46)</td>
<td>62 (51)</td>
</tr>
<tr>
<td><strong>ECOG PS, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (44)</td>
<td>33 (49)</td>
<td>57 (47)</td>
</tr>
<tr>
<td>1</td>
<td>27 (49)</td>
<td>26 (39)</td>
<td>53 (43)</td>
</tr>
<tr>
<td>2</td>
<td>4 (7)</td>
<td>8 (12)</td>
<td>12 (10)</td>
</tr>
<tr>
<td><strong>No. of prior systemic regimens, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>27 (49)</td>
<td>39 (58)</td>
<td>66 (54)</td>
</tr>
<tr>
<td>2</td>
<td>9 (16)</td>
<td>16 (24)</td>
<td>25 (20)</td>
</tr>
<tr>
<td>≥3</td>
<td>19 (35)</td>
<td>12 (18)</td>
<td>31 (25)</td>
</tr>
</tbody>
</table>

ECOG PS, Eastern Cooperative Oncology Group performance status
Diversity of cancers treated

**Primary dataset (n=55)**

- Appendix: 13%
- Bone sarcoma: 7%
- Breast: 7%
- Cholangiocarcinoma: 5%
- Colon: 5%
- Gastrointestinal stromal tumor: 7%
- Infantile fibrosarcoma: 7%
- Lung: 4%
- Melanoma: 2%
- Thyroid: 2%
- Unknown primary: 2%
- Congenital mesoblastic nephroma: 2%

**Supplementary dataset (n=67)**

- Appendix: 16%
- Bone sarcoma: 19%
- Breast: 3%
- Cholangiocarcinoma: 3%
- Colon: 3%
- Gastrointestinal stromal tumor: 6%
- Infantile fibrosarcoma: 4%
- Lung: 4%
- Melanoma: 2%
- Thyroid: 2%
- Unknown primary: 2%
- Congenital mesoblastic nephroma: 2%
- Infantile myofibromatosis: 2%
- Inflammatory myofibroblastic kidney tumor: 2%
- Inflammatory myofibroblastic tumor: 2%
- Lipofibromatosis: 2%
- Myopericytoma: 2%
- Sarcoma NOS: 2%
- Small round cell sarcoma: 1%
- Spindle cell sarcoma: 1%
- Stromal sarcoma: 1%
- Not determined: 1%

NOS, not otherwise specified
Primary dataset: Larotrectinib has proven efficacy in TRK fusion cancer

**17 Jul 2017**

- **n=55**

**30 July 2018**

- **n=55**

<table>
<thead>
<tr>
<th>ORR (95% CI)†</th>
<th>Inf</th>
<th>Gastrointestinal stromal tumor</th>
<th>Melanoma</th>
<th>Soft tissue sarcoma</th>
<th>Infantile fibrosarcoma</th>
<th>Thyroid</th>
<th>Salivary gland</th>
<th>Breast</th>
<th>Appendix</th>
<th>Pancreas</th>
<th>Lung</th>
<th>Colon</th>
<th>Cholangiocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>80% (67–90%)</td>
<td>93.2</td>
<td></td>
<td></td>
<td></td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.2</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Best response†

<table>
<thead>
<tr>
<th></th>
<th>17 Jul 2017 (n=55)</th>
<th>30 July 2018 (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>64%</td>
<td>62%</td>
</tr>
<tr>
<td>CR</td>
<td>16%</td>
<td>18%</td>
</tr>
</tbody>
</table>

*Patient had TRKCl solvent front resistance mutation (G623R) at baseline due to prior therapy; Surgical CR; †RECIST 1.1

Note: One patient not shown here. The patient discontinued treatment prior to any post-baseline tumor measurements.

CR, complete response; ORR, objective response rate; PR, partial response

Investigator response assessments, as of 30 July 2018
Supplementary dataset: Larotrectinib efficacy consistent with primary dataset

<table>
<thead>
<tr>
<th></th>
<th>Primary (n=55)</th>
<th>Supplementary* (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)†</td>
<td>80% (67–90%)</td>
<td>81% (69–91%)</td>
</tr>
<tr>
<td>Best response†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>62%</td>
<td>65%</td>
</tr>
<tr>
<td>CR</td>
<td>18%</td>
<td>17%</td>
</tr>
</tbody>
</table>

*Evaluable patients; includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment; †Surgical CR; †RECIST 1.1

Note: One patient not shown here. The patient discontinued treatment prior to any post-baseline tumor measurements.

CR, complete response; ORR, objective response rate; PR, partial response
Integrated dataset: Larotrectinib is efficacious regardless of tumor type

**Maximum change in tumor size (%)**

- Infantile fibrosarcoma
- Soft tissue sarcoma
- Thyroid
- Salivary gland
- Melanoma
- Breast
- Appendix
- Pancreas
- Gastrointestinal stromal tumor
- Colon
- Lung
- Cholangiocarcinoma
- Congenital mesoblastic nephroma
- Unknown primary
- Bone sarcoma

**Integrated‡ (n=109)**

<table>
<thead>
<tr>
<th>Best response</th>
<th>ORR (95% CI)†</th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>17%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ORR (95% CI)†: 81% (72–88%)

*Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment

*Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; #Surgical CR; †RECIST 1.1

Note: Two patients not shown here. These patients discontinued treatment prior to any post-baseline tumor measurements.

CR, complete response; ORR, objective response rate; PR, partial response
Integrated dataset: Larotrectinib is efficacious regardless of age

- Maximum change in tumor size (%)
  - Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment
  - Age <21 years
  - Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy
  - Surgical CR
  - RECIST 1.1

Note: Two patients not shown here. These patients discontinued treatment prior to any post-baseline tumor measurements.

**Investigator response assessments, as of 30 July 2018**

<table>
<thead>
<tr>
<th>Integrated‡ (n=109)</th>
<th>ORR (95% CI)†</th>
<th>81% (72–88%)</th>
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</thead>
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<td>63%</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>17%</td>
<td></td>
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</table>

‡Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment
†Age <21 years
*Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy
#Surgical CR
†RECIST 1.1

CR, complete response; ORR, objective response rate; PR, partial response
Integrated dataset (n=122): Duration of larotrectinib treatment

84% of responding patients and 73% of all patients remain on treatment or underwent surgery with curative intent.

Median time to response = 1.8 months

Overall treatment duration (months)

n=122 patients

Investigator response assessments, as of 30 July 2018
Sustained responses with larotrectinib (DOR)

Primary dataset*

- Median follow-up: 17.6 months
- Median DOR: not reached
- 88% probability at 0.5 months from start of response
- 75% probability at 1 month from start of response

Supplementary dataset*

- Median follow-up: 7.4 months
- Median DOR: not reached
- 93% probability at 0.5 months from start of response
- 81% probability at 1 month from start of response

Kaplan-Meier landmark analysis
- 17 Jul 2017
- 30 July 2018
- 6 months: 83% vs. 88%
- 12 months: 71% vs. 75%

*In patients with confirmed complete or partial responses
DOR, duration of response

Investigator response assessments, as of 30 July 2018
## Adverse events with larotrectinib: ≥15% in safety database (n=207)

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>15</td>
<td>3</td>
<td>–</td>
<td>36</td>
</tr>
<tr>
<td>Dizziness</td>
<td>25</td>
<td>3</td>
<td>1</td>
<td>–</td>
<td>29</td>
</tr>
<tr>
<td>Nausea</td>
<td>24</td>
<td>3</td>
<td>1</td>
<td>–</td>
<td>29</td>
</tr>
<tr>
<td>Constipation</td>
<td>22</td>
<td>5</td>
<td>&lt;1</td>
<td>–</td>
<td>27</td>
</tr>
<tr>
<td>Anemia</td>
<td>10</td>
<td>7</td>
<td>10</td>
<td>–</td>
<td>27</td>
</tr>
<tr>
<td>ALT increased</td>
<td>17</td>
<td>5</td>
<td>3</td>
<td>&lt;1</td>
<td>26</td>
</tr>
<tr>
<td>AST increased</td>
<td>18</td>
<td>5</td>
<td>3</td>
<td>–</td>
<td>26</td>
</tr>
<tr>
<td>Cough</td>
<td>23</td>
<td>3</td>
<td>&lt;1</td>
<td>–</td>
<td>26</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>6</td>
<td>1</td>
<td>–</td>
<td>23</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>6</td>
<td>&lt;1</td>
<td>–</td>
<td>23</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>12</td>
<td>5</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>18</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10</td>
<td>6</td>
<td>2</td>
<td>–</td>
<td>18</td>
</tr>
<tr>
<td>Headache</td>
<td>13</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>16</td>
</tr>
<tr>
<td>Myalgia</td>
<td>12</td>
<td>3</td>
<td>1</td>
<td>–</td>
<td>16</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>12</td>
<td>4</td>
<td>–</td>
<td>–</td>
<td>15</td>
</tr>
</tbody>
</table>

### Treatment-related AEs (%)

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>&lt;1</td>
<td>–</td>
<td>18</td>
</tr>
<tr>
<td>Dizziness</td>
<td>&lt;1</td>
<td>–</td>
<td>21</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>–</td>
<td>15</td>
</tr>
<tr>
<td>Constipation</td>
<td>–</td>
<td>–</td>
<td>12</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>–</td>
<td>11</td>
</tr>
<tr>
<td>ALT increased</td>
<td>2</td>
<td>&lt;1</td>
<td>21</td>
</tr>
<tr>
<td>AST increased</td>
<td>1</td>
<td>–</td>
<td>19</td>
</tr>
<tr>
<td>Cough</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>–</td>
<td>–</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>–</td>
<td>–</td>
<td>10</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>–</td>
<td>–</td>
<td>4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>&lt;1</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>–</td>
<td>–</td>
<td>7</td>
</tr>
</tbody>
</table>

- 11 (9%) of 122 patients with TRK fusion cancer required dose reductions – all maintained tumor regression on reduced dose
- 1 (<1%) of 122 patients with TRK fusion cancer discontinued larotrectinib due to an adverse event

**Notes:**
- AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase
- As of 30 July 2018
Patient with **EPS15-NTRK1** lung cancer and CNS metastases

77-year-old female with **EPS15-NTRK1** NSCLC diagnosed with stage IV disease with distant metastases to liver and brain

- Prior history of breast cancer
- Pre-existing symptoms of anorexia, fatigue, cough, hyperlipidemia
- ECOG 1
- No prior surgery, radiation or chemotherapy

Started on larotrectinib 100 mg BID and treatment ongoing

- Start of cycle 3:
  - PR in lung target lesions
  - CNS non-target lesion shows aggregate volume decrease of 95%

*BID, twice-daily; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; PR, partial response*

*Images courtesy of Rob Young and Ezra Rosen, Memorial Sloan Kettering Cancer Center*
Patient with *ETV6-NTRK3* infantile fibrosarcoma

8-month-old infant boy with congenital *ETV6-NTRK3* infantile fibrosarcoma

- Refractory to 2 prior lines of chemotherapy
  - Vincristine & actinomycin
  - Doxorubicin & ifosfamide

Started on larotrectinib 100 mg BID and treatment ongoing

- PR at cycle 3, day 1
Conclusions

- Larotrectinib continues to demonstrate robust tumor-agnostic and age-agnostic antitumor activity against TRK fusion cancer, regardless of \textit{NTRK} gene or fusion partner involved
  - ORR of 80\% (\(n=55\)) and 81\% (\(n=54\)) in primary and supplementary datasets, respectively, per investigator assessment
  - Demonstrated activity in CNS disease
- Duration of response has improved with additional follow-up
  - At a median follow-up of 17.6 months in the primary dataset, median DOR not reached
  - 12-month landmark DOR of 75\% and 81\% for the primary and supplementary datasets, respectively
- NDA on file with FDA (PDUFA date November 26, 2018) and MAA submitted to EMA in August 2018
- Genomic profiling with assays capable of identifying \textit{NTRK} gene fusions should be strongly considered in patients with solid tumors of all histologies when determining systemic treatment options.
Acknowledgments

- We thank the patients and their families, many of whom traveled long distances to participate in these studies.
- These studies are funded by Loxo Oncology, Inc and Bayer AG.