Larotrectinib is highly active in patients with advanced recurrent TRK fusion thyroid (TC) and salivary gland cancers (SGC)


Abstract # 20570

Introduction

- TRK fusions, involving the genes NTRK1, NTRK2, and NTRK3, occur in a broad range of solid tumors and are oncogenic.
- Targeted inhibition of TRK can be an effective antitumor approach.
- Larotrectinib is the first selective pan-TRK inhibitor in clinical development and has demonstrated an overall response rate of 76% by investigator assessment.
- The incidence of TRK fusions in TC has been reported to be as high as 27% in pediatric patients and 12% in adult patients, especially in tumors with papillary histology.
- In SGCs, TRK fusions define mammalian analog secretory cancers (MASC).
- Here we provide the first report summarizing the activity and safety of TRK-directed therapy with larotrectinib in the treatment of advanced, recurrent TRK-fusion TCs and SGCs including non-papillary and non-MASC histologies.

TRK fusions are rare but recurring oncogenic drivers

- Beyond embryogenesis, tropomyosin receptor kinase (TRK) protein expression is primarily limited to the nervous system.
- Three neurotrophin receptors encoded by 3 distinct genes that regulate specific normal functions:
  - NTRK1 encodes TRKA - Pain, thermoregulation
  - NTRK2 encodes TRKB - Movement, memory, mood, appetite, body weight
  - NTRK3 encodes TRKC - Proprioception
- Recurrent chromosomal fusion events have been identified across diverse pediatric and adult cancers.

TRK fusions are found in diverse cancer histologies

- NTRK1/2/3 encode TRK kinase domain
- 5' partner: ADAM family member, EGR family members, PDGFRB
- Local promoter
- LBD
- NTRK1/2/3

Larotrectinib is highly effective in TRK fusion TC and SGC

- Larotrectinib is the first and only selective pan-TRK inhibitor.

- Larotrectinib is highly potent small-molecule inhibitor of TRKA/B/C.
- Larotrectinib is highly active against TRK fusion cancers with durable responses in both children and adults.
- Larotrectinib targets TRK fusions occurring in non-papillary TC and non-MASC SGC.

Patient and disease characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N=19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>59 (16-75)</td>
</tr>
<tr>
<td>Female, n</td>
<td>7 (37%)</td>
</tr>
<tr>
<td>ECOG 0-1</td>
<td>19 (100%)</td>
</tr>
<tr>
<td>Tumor type/histology, n (%)</td>
<td>19 (100%)</td>
</tr>
<tr>
<td>Thyroid</td>
<td>6 (31.6%)</td>
</tr>
<tr>
<td>Papillary</td>
<td>6 (31.6%)</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>6 (31.6%)</td>
</tr>
<tr>
<td>Anaplastic/MASC</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Mucoepidermoid</td>
<td>1 (5.3%)</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>1 (5.3%)</td>
</tr>
</tbody>
</table>

Disease status at enrollment

- Metastatic: 18
- Locally advanced: 1

Median number of prior systemic therapies, n=19

- TC, n=7
  - SGC, n=12
  - 0.5

Previously treated

- Previous treatment type (n=19)
  - Surgery | 18 (94.7%)
  - External beam radiation | 18 (94.7%)
  - Systemic treatment | 12 (63.2%)

TC specific therapy (n=7)

- Noc 10.5%
- Yes 89.5%

Best overall response for patients with measurable disease, n=19

- Complete response: 17.6%
- Partial response: 70.6%

Progressive disease: 11.8%

Larotrectinib is highly active in TRK fusion TC and SGC

- Larotrectinib efficacy regardless of tumor type (INV)
- Larotrectinib efficacy regardless of NTRK fusion (INV)

Adverse events with larotrectinib: ≥15% in safety database (n=125)

- Fatigue | 15 (18%)
- Anemia | 2 (2%)
- Anorexia | 3 (10%)
- Constipation | 2 (2%)
- Dizziness | 2 (2%)
- Nausea | 14 (15%)
- Diarrhea | 1 (1%)

Durable response in ETv6-NTRK3 fusion papillary TC

- Larotrectinib is highly effective in TRK fusion TC and SGC

Durable response in ETv6-NTRK3 fusion MASC of the salivary gland

- Larotrectinib is highly active in patients with advanced recurrent TRK fusion thyroid (TC) and salivary gland cancers (SGC)

Conclusions

- TRK fusions can occur in non-papillary TC, and non-MASC SGC.
- TRK inhibition with larotrectinib yields high response rates, including complete responses, in adolescents and adults with recurrent pre-treated TRK fusion TC and SGC.
- Responses with larotrectinib therapy are generally durable.
- Prolonged larotrectinib therapy is associated with minimal toxicity and no drug discontinuations for TEAEs.
- Genomic profiling with assays capable of identifying TRK fusions should be strongly considered in patients with TC and SGC of all histologies when determining systemic treatment options, especially in the setting of recurrence.

References


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.