Activity of larotrectinib in children with TRK fusion thyroid cancer

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TRK fusion cancer

- Somatic oncogenic fusions involving the NTRK1, NTRK2, and NTRK3 genes (NTRK gene fusions), which encode the TRKA, TRKB, and TRKC receptor tyrosine kinases, occur in a broad range of solid tumors
- Beyond embryogenesis, TRK proteins are primarily expressed in the nervous system
- The 3 neurotrophin receptors regulate specific normal functions
- NTRK1 encodes TRKA
- NTRK2 encodes TRKB
- NTRK3 encodes TRKC
- NTRK gene fusions are generally rare, but are recurrent oncogenic drivers

NTRK1/2/3

- LBD, ligand binding domain
- NTRK gene fusions are found at high frequencies in certain rare tumor types and may be oncogenic drivers in up to 1% of all solid tumors
- The incidence of TRK fusions in pediatric thyroid cancer has been reported to be as high as 27%, especially in tumors with papillary histology

TRK Fusion

- Larotrectinib is a highly potent, small-molecule inhibitor of TRKA, TRKB, and TRKC (5-11 nm IC50 in cellular assays)
- Larotrectinib is highly active in children and adults with TRK fusion solid tumors, eliciting durable responses in both

Larotrectinib

- Larotrectinib is a highly potent, small-molecule inhibitor of TRKA, TRKB, and TRKC
- Liquid formulation allows dosing of children as young as 1 month of age and delivers equivalent pharmacokinetics to capsules
- Larotrectinib is highly active in children and adults with TRK fusion solid tumors, eliciting durable responses in both

Efficacy in TRK fusion tumors

- Larotrectinib is the first selectivity TRK inhibitor in clinical development
- Reductions in tumor burden among patients in the dose escalation phase of the larotrectinib pediatric clinical trial as assessed by investigators are shown in the waterfall plot below

Larotrectinib in pediatric TRK fusion papillary thyroid carcinoma (PTC)

- Five children with TRK fusion metastatic PTC were enrolled across 2 clinical trials: NCT02637687 and NCT02578431
- Prior to enrollment all patients had
  - Undergone thyroidectomy and lymph node dissection due to extensive lymph node metastases
  - Received 2 to 3 courses of I-131 therapy
- Date of data cutoff: February 19, 2018

Patient

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>Age at first dose (yrs)</td>
<td>15</td>
<td>18</td>
<td>7</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
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<td>Female</td>
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<tr>
<td>Gene fusion</td>
<td>TRKA-TPM3</td>
<td>TRKB-TPM3</td>
<td>SQS281-TRK1</td>
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<td>Dose (mg)</td>
<td>150 BID</td>
<td>100 BID</td>
<td>75 BID (100 mg/m2)</td>
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<tr>
<td>Metastases</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>RECIST measurable PTC</td>
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<td>Best RECIST response</td>
<td>SD</td>
<td>SD</td>
<td>SD</td>
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<td>PR</td>
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<td>Radiographic resolution of non-target lesions</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>
| RR, partial response; SD, stable disease.

Adverse events (AEs) with larotrectinib

- AEs related to larotrectinib in these 5 patients were mainly Grade 1 and included
  - Abnormal amine transferase (ALT) increase, aspartate aminotransferase (AST) increase, creatinine increase, changes in weight (gain/loss)
  - Nausea, vomiting, diarrhea, rash, hypothyroidism, alopecia, fatigue, and anorexia

Conclusions

- TRK fusions can occur in PTC
- Children and adolescents with TRK fusion metastatic thyroid carcinoma have meaningful clinical benefit when treated with larotrectinib
- Adverse events with larotrectinib were mainly Grade 1 and easily managed
- Molecular profiling capable of identifying NTRK gene fusions should strongly be considered in patients with advanced pediatric thyroid carcinoma

References


Acknowledgments

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