First experience of selpercatinib (LOXO-292) in the management of pediatric patients with RET-altered cancers

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Introduction

RET gene fusions and activating point mutations are primary oncogenic drivers that show a predominantly mutually exclusive pattern of occurrence with driver alterations in other oncogenes.1-12

- Activating point mutations of RET have been detected in ~65% of sporadic medullary thyroid carcinomas (MTCs), and in ~90% of hereditary MTCs.
- RET fusions have been reported in 10-20% of sporadic papillary thyroid carcinomas. 1-2% of non-small cell lung cancers, and at a lower frequency (~1%) in other tumor types including breast, colorectal and pancreatic cancers.
- Papillary thyroid cancers in children and adolescents are more likely to harbor RET fusions than those in older patients.

In infants and young children, RET fusions have been predominantly reported in patients with various sarcoma subtypes.

To date, no specific RET inhibitor has received regulatory approval for the treatment of RET-altered cancers.

Selpercatinib

Selpercatinib is a novel, highly selective, small molecule inhibitor of RET currently in clinical development for patients with advanced cancers harboring oncogenic RET alterations.13

Selpercatinib has nanomolar potency against activating RET alterations in RET fusion- or point mutation-positive (including the gatekeeper residue) preclinical cell-based cancer models.13

Selpercatinib is clinically active in patients with RET-altered solid tumors, including those that have metastasized to the central nervous system (CNS). (Figure 1).14,15

Figure 1. Antitumor activity in RET-altered lung and thyroid cancers in the LIBRETTO-001 study.16

Patient 1 with a CCDC6-RET fusion-positive papillary thyroid cancer

An 8-year-old girl presented with a CCDC6-RET fusion-positive diffuse-sclerosing variant papillary thyroid cancer and progressive locoregional lymph node and lung metastases.

Prior therapies included total thyroidectomy and bilateral radical neck dissection, and 6 months of radionuclide therapy. Post-operative complications of anterior neck abscess and esophageal stenosis with diverticulum had occurred.

Selpercatinib was initiated at 80 mg BID.

After 2 cycles of treatment, a partial response was observed with 65% tumor reduction.

Patient 2 with a MYH10-RET fusion-positive infiltrative myofibromatous hemangiopericytoma

A previously healthy 7-month-old girl presented with lower extremity paraesthesia and lumbosacral, pelvic and retroperitoneal infiltrative myofibromatous hemangiopericytoma harboring a MYH10-RET fusion.

Prior therapies included cyclophosphamide and topotecan chemotherapy and vandetanib.

Selpercatinib was initiated at 48 mg BID.

After 1 cycle of selpercatinib, a partial response was observed with 32% tumor reduction, which deepened to continued treatment.

After 7 cycles of selpercatinib, the paraspinal mass had completely resolved, and the patient had regained lower extremity neurologic function.

Patient 4 with an NCOA4-RET fusion-positive lipofibromatosis

An otherwise healthy 21-month old girl presented with an NCOA4-RET fusion-positive lipofibromatosis on her left foot affecting her gait.

Amputation or surgery that would have resulted in significant functional impairment was recommended.

Selpercatinib was initiated at 48 mg BID.

After 2 cycles of selpercatinib, a partial response was observed with 59% tumor reduction.

Tumor infiltration between the metastasals has completely disappeared.

References

Table 1. Patient characteristics and clinical outcome

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
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<td>2 months</td>
<td>At birth</td>
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<td>Infantile myofibromatous hemangiopericytoma</td>
<td>Congenital mesoblastic nephroma, infantile fibrosarcoma</td>
<td>Lipofibromatosis</td>
<td>Medullary thyroid cancer (MEN 2B)</td>
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<td>Paraspinal and retroperitoneal</td>
<td>Kidney, lung</td>
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<td>RET alteration</td>
<td>CCDC6-RET fusion</td>
<td>MYH10-RET fusion</td>
<td>SPECCL-RET fusion</td>
<td>NCOA4-RET fusion</td>
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</table>

Patient 3 with a RET-codon 918 mutant MTC

A 19-month-old girl presented with mesoblastic nephroma, left-sided cerebrovascular accident, and multifocal masses in the brain, lungs and left kidney.

Lung masses were diagnosed as pulmonary infantile fibrosarcoma; both the nephroma and the sarcoma harbored a SPECCL-RET fusion.

Prior therapies included a nephrectomy and 3 lines of chemotherapy (actinomycin and vincristine; vincristine, dacarbazine and cyclophosphamide; topotecan and cyclophosphamide).

Selpercatinib was initiated at 42 mg BID.

A selpercatinib concentration of 4.5 ng/ml was achieved in cerebrospinal fluid at a dose level of 48 mg BID, increasing to 16 ng/ml after dose escalation to 94 mg BID.

After 2 cycles of selpercatinib, a partial response was observed with 41% tumor reduction, which deepened to 66% tumor reduction by cycle 8.

Patient 5 with a RET codon 918 mutant MTC

A 7-year-old boy presented with an MEN 2B-associated RET codon 918 mutation-positive MTC.

The patient had a thyrotoxicosis with tracheo-earthy, followed by vandetanib therapy. Vandetanib was discontinued due to grade 3 colitis.

Selpercatinib was initiated at 90 mg BID.

After 2 cycles of selpercatinib, stable disease was observed.

Conclusion

- These preliminary data from 5 patients in a real-world setting suggest that selpercatinib is effective and safe in pediatric patients whose tumors harbor RET alterations.

- A phase 1/2 trial (LIBRETTO-121, NCT03899782) is now open to evaluate patients with RET-altered advanced solid or primary CNS tumors.

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