First experience of LOXO-292 in the management of pediatric patients with *RET*-altered cancers

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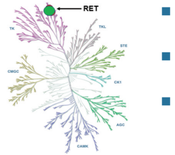
Abstract 10045

Background

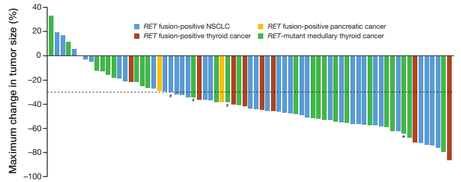
- *RET* fusions and RET-activating point mutations are primary oncogenic drivers that show predominantly mutual exclusivity with driver alterations in other oncogenes:[1-12]
  - Activating point mutations have been detected in ~65% of sporadic medullary thyroid carcinomas (MTC), and in >90% of hereditary MTC
  - *RET* fusions have been reported in 10–20% of sporadic papillary thyroid carcinomas, approximately 2% of non-small cell lung cancers, and at a lower frequency (≤1%) in other tumor types, including breast, colorectal and pancreatic cancers
  - Children and adolescents with papillary thyroid cancer and MEN 2B medullary thyroid cancer are more likely to harbor *RET* fusions than older patients with those malignancies
  - In infants and young children, *RET* fusions have been predominantly reported in patients with various sarcoma subtypes
- No agents are currently approved by the U.S. Food and Drug Administration (FDA) for adult and pediatric patients with *RET*-altered cancers.

LOXO-292



- LOXO-292 is a novel, highly selective, small molecule inhibitor of RET currently in clinical development for patients with advanced cancers harboring oncogenic *RET* alterations.[13]
- LOXO-292 has nanomolar potency against activating *RET* alterations in *RET* fusion- or point mutation-positive (including the gatekeeper residue) preclinical cell-based cancer models.[13]
- LOXO-292 is clinically active in patients with *RET*-altered solid tumors, including those that have metastasized to the central nervous system (CNS) (**Figure 1**).[14-16]

Figure 1. Antitumor activity in *RET*-altered cancers in the LIBRETTO-001 study



Patients shown were enrolled as of April 2, 2018 with a data cutoff July 19, 2018.
Note: 7 patients not displayed; 4 due to treatment discontinuation prior to first post-baseline response assessment, 3 due to nonmeasurable disease at baseline (2 stable disease, and 1 complete response). *Complete response; †Unconfirmed response awaiting confirmatory response assessment. NSCLC, non-small cell lung cancer.

LOXO-292 in pediatric patients with *RET* fusion-positive tumors

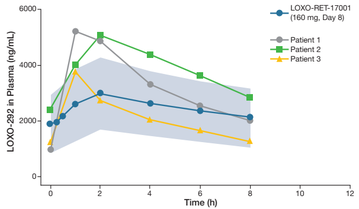
- As of April 5, 2019, 4 pediatric patients with tumors harboring *RET* gene fusions (**Table 1**) received LOXO-292; these patients had no other viable treatment options and were ineligible for the ongoing LOXO-292 phase 1/2 clinical trial (NCT03157128) due to their age (<12 years).
- Access to LOXO-292 was granted using FDA-allowed, institutional review board-approved single patient protocols.
- Patients received LOXO-292 (capsule or liquid formulation) orally, continuously, at a starting dose of 90 mg/m^2 twice daily (BID). Each treatment cycle consisted of 28 days. Response to treatment was assessed by local investigators.

Table 1. Patient characteristics and clinical outcome

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Country	Republic of Korea	USA	USA	USA
Gender	Female	Female	Female	Female
Age at diagnosis	7 years	7 months	2 months	At birth
Age at enrollment	8 years	13 months	21 months	21 months
Diagnosis	Papillary thyroid cancer	Infantile myofibroma/ hemangiopericytoma	Congenital mesoblastic nephroma, infantile fibrosarcoma	Lipofibromatosis
Primary tumor location	Thyroid	Paraspinal and retroperitoneal	Kidney, lung	Left foot
Presence of metastases	Lymph node, lung	–	Lung, brain	None
***RET* fusion**	*CCDC6-RET*	*MYH10-RET*	*SPECC1L-RET*	*NCOA4-RET*
Dose	80 mg BID	44 mg BID	42 mg BID	48 mg BID
Prior therapy				
Chemotherapy	No	Yes	Yes	No
Surgery	Yes	No	Yes	No
Radiotherapy	Yes	No	No	No
MKI	No	Yes	No	No
Best RECIST response to LOXO-292	PR	PR	PR	PR
Duration of treatment with LOXO-292 (months)	5+	6+	2+	2+
Treatment ongoing	Yes	Yes	Yes	Yes
AE ≥grade 3	None	None	None	None
Dose modification/ discontinuation due to an AE	None	None	None	None

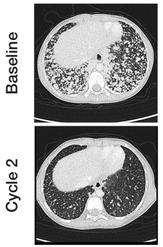
AE, adverse event; MKI, multikinase inhibitor; PR, partial response.
Data cutoff April 5, 2019

LOXO-292 pharmacokinetics



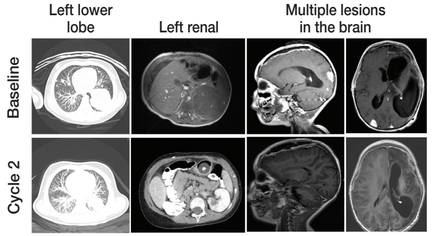
- Plasma concentrations of LOXO-292 in pediatric patients enrolled in this study were similar to those of adult patients enrolled in the LIBRETTO-001 study.

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



- An 8-year-old girl presented with *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 radioiodine therapy. Post-operative complications of anterior neck abscess and esophageal stricture with diverticulum had occurred.
- LOXO-292 was initiated at 80 mg BID.
- After 2 cycles of LOXO-292, a partial response was observed with 60% tumor reduction.

Patient 3 with *SPECC1L-RET* fusion-positive mesoblastic nephroma and infantile fibrosarcoma



- A 19-month-old girl presented with mesoblastic nephroma, left-sided cerebrovascular accident, and multifocal masses in the brain, lungs and left kidney.
- Lung lesions were diagnosed as pulmonary infantile fibrosarcoma; both the nephroma and the sarcoma harbored a *SPECC1L-RET* fusion.
- Prior therapies included a nephrectomy and 3 lines of chemotherapy (actinomycin and vincristine; vincristine, dactinomycin and cyclophosphamide; topotecan and cyclophosphamide).
- LOXO-292 was initiated at 42 mg BID.
- After 2 cycles of LOXO-292, a partial response was observed with 41% tumor reduction.

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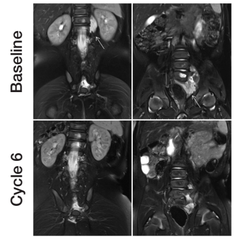
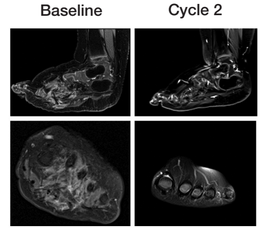
Patient 2 with *MYH10-RET* fusion-positive infantile myofibroma/ hemangiopericytoma



- A previously healthy 7-month-old girl presented with lower extremity paraplegia and lumbosacaral, pelvic and retroperitoneal infantile myofibroma/hemangiopericytoma harboring *MYH10-RET* fusion.
- Prior therapies included cyclophosphamide and topotecan chemotherapy and vandetanib.
- LOXO-292 was initiated at 44 mg BID.
- After 1 cycle of LOXO-292, a partial response was observed with 32% tumor reduction, which has deepened with continued treatment.
- After 7 cycles of LOXO-292, the paraspinal mass has completely resolved, and the patient has regained lower extremity neurologic function.

Patient 4 with *NCOA4-RET* fusion-positive lipofibromatosis



- An otherwise healthy 21-month-old girl presented with *NCOA4-RET* fusion-positive lipofibromatosis on her left foot affecting her gait.
- Amputation or surgery that would result in significant functional impairment was recommended.
- LOXO-292 was initiated at 48 mg BID.
- After 2 cycles of LOXO-292, a partial response was observed with 59% tumor reduction.
- Tumor infiltration between the metatarsals had completely disappeared.

Conclusions

- These preliminary data from 4 patients in a real-world setting suggest that LOXO-292 is effective and safe in pediatric patients whose tumors harbor *RET* gene fusions.
- A phase 1/2 trial (LIBRETTO-121, NCT03899792) is now open to pediatric patients with *RET*-altered advanced solid or primary CNS tumors.

Acknowledgements

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