Received: 20 August 2020 | Revised: 22 September 2020 | Accepted: 22 October 2020

DOI: 10.1002/hed.26527

CASE REPORT

WILEY

Neoadjuvant selpercatinib for advanced medullary thyroid cancer

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Abstract

Background: Targeted kinase inhibitors have been increasingly utilized in the treatment of advanced medullary thyroid cancer (MTC) over the last decade. Recently, highly potent next generation selective RET inhibitors have been clinically validated, and selpercatinib was recently Food and Drug Administration (FDA)-approved for advanced MTC. The advent of highly selective, potent RET inhibitors is broadening the treatment options for patients with *RET*-mutated cancers.

Methods: We report the first published case of neoadjuvant selpercatinib followed by surgery for a patient with initially unresectable, widely metastatic, *RET*-mutated MTC who was treated on a single patient protocol.

Results: After greater than 50% RECIST response, the patient underwent complete surgical resection followed by selpercatinib resumption. He remains locoregionally disease-free 21 months after starting therapy with stable metastatic disease (after initial partial response); and calcitonin/CEA continue to decline.

Conclusion: This novel treatment strategy for locoregionally advanced RET-mutated MTC warrants further study in clinical trials.

KEYWORDS

LOXO-292, medullary, neoadjuvant, selective RET inhibitor, selpercatinib

Yelda Jozaghi and Mark Zafereo are co-first authors.

This study was conducted through a single patient Investigational Drug Application (IND) approved by the United States Food and Drug Administration (FDA) and Loxo Oncology. Study drug was provided by Loxo Oncology.

1 | INTRODUCTION

Medullary thyroid cancer (MTC) is a neuroendocrine malignancy that arises from the parafollicular C-cells of

the thyroid gland, accounting for approximately 1%-2% of thyroid malignancies in the United States.[1] MTC can be either sporadic (80%) or hereditary (20%), with the inherited form associated with the multiple endocrine neoplasia (MEN) syndromes, MEN2A and MEN2B. Virtually all patients with hereditary MTC have a *RET* germline mutation. Sporadic MTC is associated with a somatic *RET* mutation in approximately 40%-50% of cases.[1-8] Duration of survival for patients with MTC is reasonably good, but rapidly declines in the metastatic setting. Ten-year survival rates have been quoted as 100%, 93%, 71%, and 21%, respectively, for stage 1, 2, 3, and 4 disease.[9]

Targeted drug therapies have been increasingly utilized in the treatment of MTC over the last decade. On the basis of phase-3 trials,[10,11] the Food and Drug Administration (FDA) approved the multikinase inhibitors (MKI) vandetanib in 2011 and cabozantinib in 2012, for the treatment of advanced progressive MTC. The response to these MKI is limited by suboptimal RET inhibition and inhibition of alternative targets.[10,11] The inhibition of alternative targets, specifically VEGFR2, creates off-target toxicities which limit the dose patients can tolerate,[12] as well as potentially increase perioperative surgical risk.[13]

In more recent years, highly potent selective RET inhibitors (selpercatinib/LOXO-292, pralsetinib/BLU667) have been discovered and subsequently clinically validated.[23] Their high selectivity and potent anti-RET activity has been demonstrated in various in vitro and in vivo models.[12] Registrational clinical trials have shown high response rate and favorable side-effect profile.[12,14] With less VEGFR activity compared with earlier generation MKIs, these selective RET inhibitors may have a safer perioperative profile. Selpercatinib was FDA approved as of May 2020 for the treatment of advanced *RET*-mutated MTC, advanced *RET* fusion-positive thyroid cancer requiring systemic therapy, and RET fusion-positive nonsmall cell lung cancer.

Herein, we report a case of a patient with initially unresectable, widely metastatic, *RET*-mutated medullary thyroid carcinoma treated on a single-patient clinical protocol with neoadjuvant selpercatinib/LOXO-292 followed by definitive surgery. The significant tumor response to neoadjuvant selpercatinib rendered his locoregional disease resectable, and he is now 21 months postinitiation of neoadjuvant treatment with stable distant disease (following partial response) on continued therapy. This is the first published case of a RET-specific tyrosine kinase inhibitor in the neoadjuvant setting for *RET*-mutant MTC.

2 | CASE

A 20-year-old men who went to an outside institution with persistent diarrhea and weight loss was ultimately diagnosed with widely metastatic disease involving his pituitary, neck, mediastinum, lungs, liver, and spine. He underwent a resection of the pituitary mass and core biopsy of a mediastinal mass, both of which were compatible with MTC. Germline testing did not reveal a *RET* mutation. The patient then sought medical care at the University of Texas M. D. Anderson Cancer Center. Pathology was confirmed as MTC and serum Carcinoembryonic antigen (CEA) and calcitonin levels were 886 ng/mL (normal reference: <3.8 ng/mL) and 12 356 pg/mL (normal reference: <14.3 pg/mL), respectively.

A contrast-enhanced CT neck and chest scan demonstrated an approximate 2 cm left thyroid tumor with very bulky (up to 5 cm) bilateral central, superior mediastinal, and lateral neck lymphadenopathy (Figure 1). CT scans of the chest, abdomen, and pelvis showed scattered pulmonary and liver metastases, in addition to sclerotic spinal metastases involving T2, T3, T5, T8, T11, and L4 vertebral bodies. Vocal fold function was intact on flexible laryngoscopy.

Genomic molecular testing indicated a somatic *RET* deletion Y900_S904delinsP. Following multidisciplinary assessment, it was concluded that the patient was not meaningfully surgically resectable; given that primary surgery would have significant morbidity including likely sacrifice of his left recurrent laryngeal nerve and phrenic nerve. Furthermore, gross complete resection could not be achieved given the significant encasement of the left subclavian artery, among other major neck/mediastinal vessels. Following FDA approval and Institutional Review Board (IRB) approval (The University of Texas M. D. Anderson Cancer Center), he was enrolled in a single-patient protocol with neoadjuvant oral selpercatinib, with intent for surgery dependent upon response. Dose modifications and interruptions followed a prescribed algorithm. Adverse events were graded using the Common Terminology Criteria for Adverse Events version 4.03. Response was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

A restaging CT following 4 cycles (~28 days each) of selpercatinib demonstrated marked interval improvement in multicompartmental nodal and visceral metastases in the neck, chest, and abdomen (Figure 1), while the multifocal osseous metastases were stable. He received almost six cycles (157 days) of neoadjuvant selpercatinib, 160 mg orally twice daily, which was well tolerated with

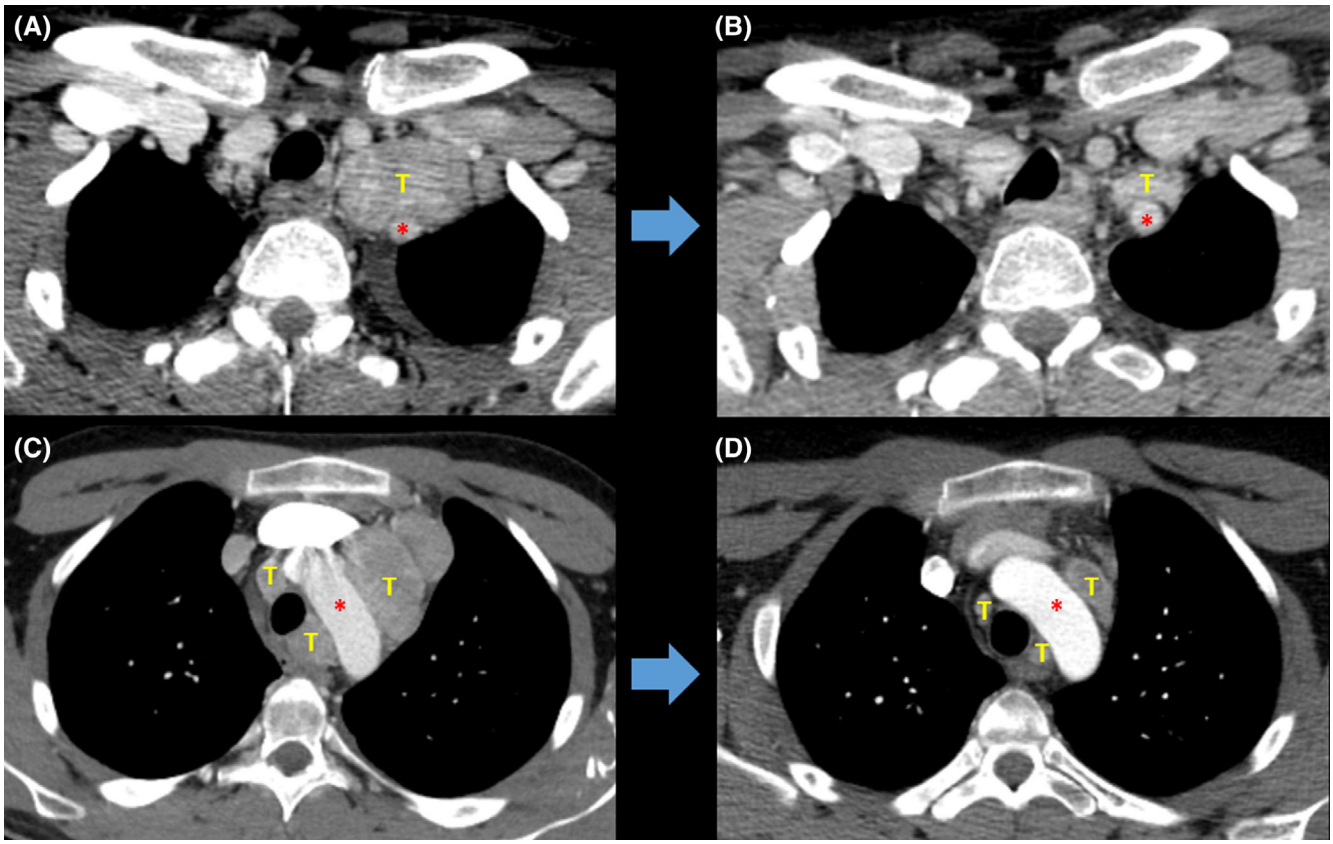

FIGURE 1 CT findings prior to and following neoadjuvant selpercatinib. Panels A and C depict the extent of neck and superior mediastinal lymph node prior to neoadjuvant treatment. Panels B and D depict the extent of neck and superior mediastinal disease following 3.6 months of neoadjuvant treatment. In panel A, the tumor (yellow letter T) is wrapped >180° around the subclavian artery (asterisk), while in panel B, the tumor has regressed considerably, with a better defined interface with the subclavian artery. In panel C, there is significant tumor (yellow letter T) wrapped around the aortic arch (red asterisk), such that both the left phrenic and recurrent laryngeal nerve would be at considerable risk with surgery, while in panel D, the tumor has regressed considerably, putting these nerves at much lower surgical risk. Overall response by RECIST 1.1 after 3.6 months of Selpercatinib was 51.5%

only mild transaminitis (Grade 1) not requiring dose reduction. This was the only adverse event observed. The patient was discussed at multidisciplinary tumor board, and the consensus was to offer the patient surgery in order to consolidate the effect of the neoadjuvant treatment, with a goal toward maximizing long-term locoregional control. After holding selpercatinib for 3 days, surgery was performed, including total thyroidectomy, bilateral central compartment dissection, bilateral lateral neck dissection (levels 2, 3, 4, and 5b), and median sternotomy with bilateral superior mediastinal dissection. Intraoperatively, significant tissue fibrosis was noted throughout the neck related to neoadjuvant therapy, along with residual nodal disease in the bilateral central compartments, lateral necks, and superior mediastinum. Gross removal of all disease (R1 resection) was achieved. Recurrent laryngeal nerves and parathyroid glands were preserved, and the patient recovered well from surgery with a 5-day hospital stay without complications. Surgical pathology is summarized in Table 1 and depicted in Figure 2.

Following surgery, treatment with selpercatinib was resumed 9 days following surgery. Serial imaging studies over the following 18 months have shown stability of distant metastatic sites while continuing selpercatinib, and he remains structurally without evidence of locoregional disease. Calcitonin and CEA levels have continued to decline, with calcitonin and CEA levels at 308 pg/mL and 106 ng/mL, respectively, at last follow-up (Figure 3).

3 | DISCUSSION

The advent of highly potent next generation selective RET inhibitors has altered the landscape of *RET*-altered cancers including RET translocated tumors.[15] While

TABLE 1 Surgical pathologic features following neoadjuvant selpercatinib

Features	Findings
Primary tumor focality	Unifocal
Primary tumor site	Right thyroid lobe
Primary tumor greatest dimension	1.5 cm
Histologic type	Medullary thyroid carcinoma
Margins of thyroid	Negative
Angioinvasion	Not identified
Lymphatic invasion	Not identified
Extrathyroidal extension (ETE)	No gross ETE identified, but multiple tumor deposits in perithyroidal fibroadipose tissue and muscles
Number of lymph nodes examined	104
Number of lymph nodes involved	36
Extranodal extension	Present
Size of largest nodal metastatic deposit	4.7 cm[a]
Pathologic stage classification	ypT1bN1bM1 (Stage IVC)

[a]in the superior mediastinum.

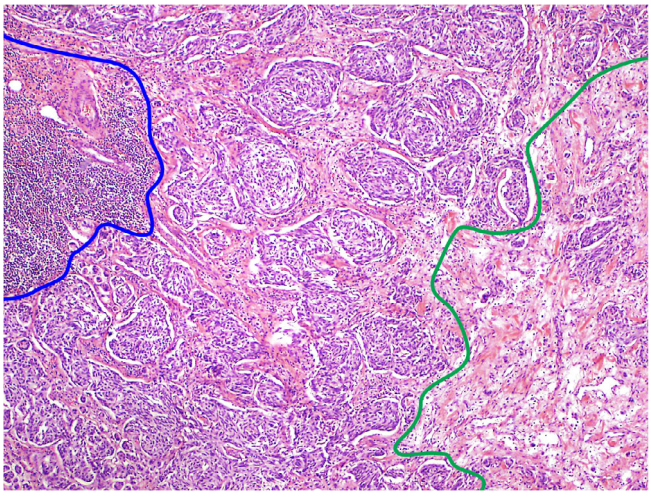

FIGURE 2 Surgical pathology following neoadjuvant selpercatinib. Lymph nodes showed variable cellular metastases with back-to-back tumor nests or admixed with amyloid and fibrosis between tumor clusters. This metastatic lymph node in the superior mediastinum shows minimal residual lymphoid tissue (left: blue region), and nests of spindled to epithelioid tumor cells admixed with areas of acellular, vascular stroma (right: green region), consistent with treatment effect

germline mutational testing has long been standard of care in medullary thyroid patients with cancer, in this new era of FDA-approved RET-specific inhibitors for MTC, somatic tumor mutational testing may also be considered in cases where systemic therapy is being evaluated. This single-patient protocol offered this patient with a guarded prognosis effective targeted treatment of his disease with minimal side effects. Given the bulky superior mediastinal disease with subclavian artery encasement, primary surgery would not have achieved an R1 resection. Alternatively, he would have been a candidate for a MKI. However the use of MKI's for advanced MTC have demonstrated activity but with associated treatment-related adverse events, which can be dose limiting.[10-12,16,17] The off-target effects of MKI's against other receptor tyrosine kinases, such as VEGFR2, limit both their efficacy, in terms of RET inhibition, and maximal tolerated dose. VEGFR2 regulates angiogenesis and vascular endothelial permeability.[14,18] The off-target effects can result in dose-limiting hypertension, thrombosis, hemorrhage, and fistula formation,[10,14,18] which in turn have the potential to increase perioperative and postoperative risk.

Selective RET inhibitors offer a promising avenue for patients with *RET*-mutated cancers, as they have been designed for potent inhibition of the most common *RET* activating mutations, fusions, and acquired resistance mutations.[14,19,23] Furthermore, they can be effective in gatekeeper RET V804 mutations that convey resistance to cabozantinib and vandetanib.[20,21] In addition to high selectivity for RET, selective RET inhibitors have demonstrated favorable bioavailability, predictable exposure, significant central nervous system penetration, and limited drug interactions.[12] Biochemical assays have shown that pralsetinib, another selective RET inhibitor, inhibits the wild type RET kinase activity with an 8- to 28-fold higher potency when compared with the MKI's cabozantinib, vandetanib, and RXDX-105.[14] A recently published phase 1-2 trial of selpercatinib for *RET*-altered thyroid cancer has shown a complete or partial response in 73% of patients with *RET*-mutant MTC who had not previously received multikinase therapy.[24] These patients had a 1-year progression-free survival of 92%.[24] This study further highlighted the adverse events associated with selpercatinib, including hypertension, transaminitis, hyponatremia, and diarrhea.[24]

The decision to operate on a patient with advanced disease and marked response to a RET tyrosine kinase specific inhibitor requires careful consideration after multidisciplinary input, weighing the benefit of surgery to limit potential future morbidity which may accompany tumor escape and locoregional progression, and the burden and aggressiveness of distant metastatic disease.

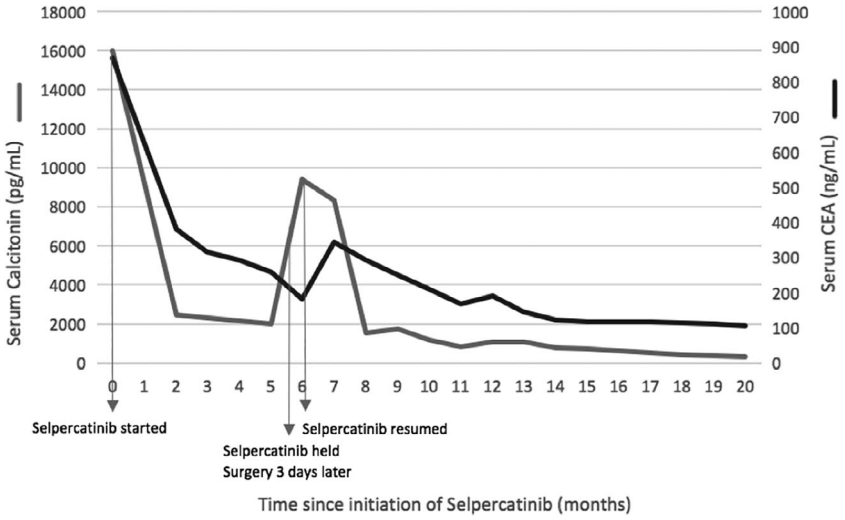

FIGURE 3 Serum calcitonin and CEA trend throughout treatment

Systemic therapy without surgical intervention is a reasonable approach, however, resistance to kinase inhibitors eventually ensues in most patients, potentially threatening critical structures in the neck including the trachea, esophagus, and major nerves and blood vessels.[22] Thus, upfront surgery is often considered in patients who present with distant metastatic disease. As demonstrated with this single patient protocol, an initial period of significant clinical response to RET specific inhibitor may provide a window of opportunity to surgically resect previously unresectable or bulky locoregional disease with decreased surgical morbidity. The short half-life of selpercatinib (32 hours) and limited antiangiogenic activity is a safer alternative to potent antiangiogenic drugs such as cabozantinib (120 hours) or vandetinib (19 days), in the surgical setting, where bleeding and wound healing may be compromised by systemic therapy.[15]

An alternative approach would be to continue selective RET inhibitor indefinitely with observation of locoregional disease. However, if such a patient were to ultimately develop drug resistance to selective RET inhibition with locoregional disease progression, the window of surgical resection may be missed. Progressive locoregional disease may become symptomatic more quickly than distant disease due to the preponderance of critical structures in the neck and superior mediastinum. Additionally, if such a patient is ultimately transitioned to broader MKI therapy with more significant antiangiogenic activity, then the timing of surgery also becomes more challenging. This approach of neoadjuvant RET-specific inhibitor followed by surgery for patients with locoregionally advanced MTC (with or without distant metastases) should continue to be studied in the context of clinical trials.

4 | CONCLUSION

This single patient protocol for locoregionally advanced and distantly metastatic *RET* mutated MTC with significant response to neoadjuvant selpercatinib followed by surgery highlights a potential new treatment paradigm in this disease. The greater than 50% RECIST response with minimal side effects over 5 months ultimately enabled both complete surgical resection and avoidance of significant upfront surgical morbidity. In this patient, the relative low morbidity and complete gross surgical resection has significantly reduced the risk of locoregional complications down the road which may have resulted from locoregional tumor escape and progression of unresected disease. Further clinical trials are required to establish safety, efficacy, and long-term outcomes with this approach.

ACKNOWLEDGMENTS

This work was not funded. Selpercatinib was provided to the patient by LOXO Oncology as per the clinical protocol agreement. This work has not been presented at any meetings or conferences.

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How to cite this article: Jozaghi Y, Zafereo M, Williams MD, et al. Neoadjuvant selpercatinib for advanced medullary thyroid cancer. *Head & Neck*. 2021;43:E7–E12. https://doi.org/10.1002/hed.26527