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Positive Quality Intervention: Selpercatinib (Retevmo®) Management

Description: This PQI is developed to provide guidance for management of patients treated with selpercatinib.

Background: Selpercatinib is a kinase inhibitor indicated for the treatment of:

- Adult patients with metastatic *RET* fusion-positive non-small cell lung cancer (NSCLC)
- Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant medullary thyroid cancer (MTC) who require systemic therapy*
- Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory (if radioactive iodine is appropriate)*
- Adult patients with advanced or metastatic *RET* fusion-positive solid tumors who have progressed on or following prior systemic therapy or who have no satisfactory alterative treatment options*

*This indication is approved under accelerated approval based on overall response rate and duration of response.[1]

A multicohort study was conducted in patients with *RET* fusion-positive metastatic NSCLC, advanced or metastatic MTC, and *RET* point-mutation advanced or metastatic MTC. The major efficacy outcome, objective response rate (ORR) to selpercatinib was 64% in previously treated NSCLC. Median duration of response was 17.5 months and 63% of the responses were ongoing at a median follow-up of 12.1 months. For those who were previously untreated, ORR was measured at 85% (n=39).[2] Efficacy in patients with *RET*-mutant MTC who were previously treated with cabozantinib and/or vandetanib was studied and ORR was 69% (n=55) and median duration of response was not reached despite a median follow-up of 14.8 months. In this same study, cabozantinib or vandetanib-naive patients had an ORR of 73% (n=88). *RET* fusion-positive thyroid cancer patients who were radioactive iodine (RAI)-refractory and were systemic therapy naïve had an ORR of 100% (CR 12.5%, PR 74%, n=8). Those thyroid patients previously treated with sorafenib, lenvatinib, or both had an ORR of 79% (CR 5.3%, PR 74%, n=19).[3] Permanent discontinuation due to adverse reactions occurred in 5% of patients who have received selpercatinib. Dosage reductions due to an adverse reaction occurred in 31% of patients and the reactions where at least 2% or more of patients required reduction included increased AST/ALT, QT prolongation and fatigue.

In September 2022, selpercatinib gained accelerated approval for its use in *RET* fusion-positive locally advanced or metastatic solid tumors. LIBRETTO-001 is a multicenter, open-label study which evaluated patients with *RET* fusion-positive tumors (other than NSCLC and MTC) who progressed on or following standard of care or have no satisfactory alternative treatment options.[4] Tumor types included in the study were pancreatic adenocarcinoma, colorectal, salivary, unknown primary, breast, soft tissue sarcoma, bronchial carcinoid, ovarian, small intestine, and cholangiocarcinoma.[5] Primary efficacy measures demonstrated ORR of 44% (n=41) with a duration of response (DOR) of 24.5 months. Efficacy evaluation was supported by data in 343 patients with *RET* fusion-positive NSCLC and MTC. Most common adverse reactions (≥25%) were edema, diarrhea, fatigue, dry mouth, hypertension, abdominal pain, constipation, rash, nausea, and headache. Patients received selpercatinib until disease progression or unacceptable toxicity.

PQI Process:

- Determine if a patient is eligible for selpercatinib
  - Review potential patients for presence of a *RET* gene fusion in NSCLC, thyroid cancer, or solid tumors or presence of a *RET* gene mutation in MTC
  - Review the **Selpercatinib (Retevmo®) Genomic Testing Management** PQI

Upon prescription of selpercatinib:

- Confirm Correct Dosing

- Recommended dosage in adults and pediatric patients 12 years of age or older is based on weight
  - Less than 50 kg: 120 mg orally twice daily
  - 50 kg or greater: 160 mg orally twice daily
- Dosing considerations for Adverse Reactions

Recommended Selpercatinib Dose Reductions for Adverse Reactions[1]

Dose Reduction	**Patients Weighing Less Than 50 kg**	**Patients Weighing 50 kg or Greater**
First	80 mg orally twice daily	120 mg orally twice daily
Second	40 mg orally twice daily	80 mg orally twice daily
Third	40 mg orally once daily	40 mg orally twice daily
Permanently discontinue if patient is unable to tolerate three dose reductions		

Adverse Reaction	**Severity**	**Dosage Modification**
Hepatotoxicity	Grade 3/4	Hold selpercatinib and monitor AST/ALT once weekly until resolution to Grade 1 or baseline Resume at reduced dose by 2 dose levels and monitor AST/ALT once weekly until 4 weeks after reaching dose taken prior to the onset of Grade 3/4 increased AST/ALT Increase dose by 1 dose level after a minimum of 2 weeks without recurrence and then increase to dose taken prior to the onset of Grade 3 or 4 increased AST or ALT after a minimum of 4 weeks without recurrence
Hypertension	Grade 3	Hold selpercatinib for Grade 3 hypertension that persists despite optimal antihypertensive therapy; resume at a reduced dose when hypertension is controlled
	Grade 4	Discontinue selpercatinib
QT Interval Prolongation	Grade 3	Hold selpercatinib until recovery to baseline or Grade 0/1; resume at a reduced dose
	Grade 4	Discontinue selpercatinib permanently
Hemorrhagic Events	Grade 3/4	Hold selpercatinib until recovery to baseline or Grade 0/1 Discontinue selpercatinib permanently for severe/life-threatening hemorrhagic events
Hypersensitivity Reactions	All Grades	Hold selpercatinib until resolution of the event and initiate corticosteroids Resume at a reduced dose by 3 dose levels while continuing corticosteroids Increase dose by 1 dose level each week until the dose taken prior to the onset of hypersensitivity is reached, then taper corticosteroids Discontinue permanently for recurrent hypersensitivity
Other Adverse Reactions	Grade 3/4	Hold selpercatinib until recovery to baseline or Grade 0/1 Resume at a reduced dose

Recommended Dosage for Concomitant Use of Strong and Moderate CYP3A Inhibitors

	Recommended Dosage	
Current Dosage	**Moderate CYP3A Inhibitor**	**Strong CYP3A Inhibitor**
120 mg orally twice daily	80 mg orally twice daily	40 mg orally twice daily
160 mg orally twice daily	120 mg orally twice daily	80 mg orally twice daily

Recommended Dosage for Severe Hepatic Impairment

Current Dosage	**Recommended Dosage**
120 mg orally twice daily	80 mg orally twice daily
160 mg orally twice daily	80 mg orally twice daily

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) sheet
- Counsel patient to swallow the capsules whole with or without food and to not crush/chew the capsules

- Counsel patient to report adverse events related to high blood pressure, liver problems, heart rhythm changes, signs of bleeding or tumor lysis syndrome, allergic reactions, and lack of wound healing
- Ensure proper contraception during therapy and for 1 week after final dose

References:

1. RETEVMO ® (selpercatinib) [package insert].
2. Drilon A, Oxnard GR, et al. Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer. *N Engl J Med*. 2020; 383:813-824.
3. Shah MH, Sherman EJ, et al. Selpercatinib (LOXO-292) in patients with *RET*-mutant medullary thyroid cancer. J Clin Oncol. 2020; 38 (15).
4. ClinicalTrials.gov. A study of selpercatinib (LOXO-292) in participants with advanced solid tumors, RET fusion-positive solid tumors, and medullary thyroid cancer. *National Institute of Health U.S. National Library of Medicine*. 2022.
5. Food and Drug Administration. FDA approves selpercatinib for locally advanced or metastatic RET fusion-positive solid tumors. *FDA.* 2022.