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Written By: Joshua Nubla, PharmD
NCODA

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) *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.

PQI Process:

- Determine if a patient is eligible for selpercatinib
  - Review potential patients for presence of a *RET* gene fusion in NSCLC or thyroid cancer 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		

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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/; resume at a reduced dose
	Grade 4	Discontinue selpercatinib
Hemorrhagic Events	Grade 3/4	Hold selpercatinib until recovery to baseline or Grade 0/1 Discontinue selpercatinib for severe or 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
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 at 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).