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Positive Quality Intervention: Pralsetinib (Gavreto®) Management for Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer

Description: Pralsetinib is an oral rearranged during transfection (RET) tyrosine kinase inhibitor (TKI) that inhibits oncogenic RET fusions and mutations.[1] The purpose of this PQI is to review pralsetinibs role in therapy, management of adverse effects, potential drug interactions, and to recommend patient follow-up associated with pralsetinib treatment.

Background: The phase I/II ARROW trial examined pralsetinib for the treatment of RET fusion-positive metastatic non-small cell lung cancer (NSCLC).[1,2] In the dose expansion phase of the study, all patients received pralsetinib at a dose of 400 mg once daily. The trial included 87 patients who had previously undergone treatment with platinum chemotherapy. Overall response rate in these patients was 57% (95% CI: 46%, 68%) with 5.7% of patients achieving a complete response. Responses of 6 months or greater were seen in 75% of patients who responded to pralsetinib. The study population also included 27 patients who had not yet received any treatment. Overall response rate in these treatment-naïve patients was 70% (95% CI: 50%, 86%) with a complete response observed in 11% of patients. A duration of treatment response of 6 months or greater was seen in 58% of patients. Adverse effects seen in 25% or more of patients treated with pralsetinib include increase in liver enzymes, alkaline phosphatase and serum creatinine; decrease in hemoglobin, lymphocytes and neutrophils; fatigue, constipation, musculoskeletal pain, and hypertension.[1] Interstitial lung disease (ILD)/pneumonitis occurred in 10% of patients who received pralsetinib, including 2.7% with Grade 3-4, and 0.5% with fatal reactions.[1] Pralsetinib is also indicated in RET fusion-positive thyroid and RET-mutated medullary thyroid cancer.

PQI Process: Upon receipt of an order for pralsetinib:

- Ensure patient is an appropriate candidate based on diagnosis of RET fusion-positive metastatic NSCLC
  - FDA approved companion diagnostic test for RET fusion: Oncomine Dx Target (ODxT) Test
- Starting dose of pralsetinib is 400 mg by mouth once daily on an empty stomach
  - No food should be eaten for at least two hours prior to and at least one hour after pralsetinib
- Review patient's current prescriptions for potential drug interactions
  - Avoid P-gp substrates and strong CYP3A4 inhibitors and inducers
  - See package insert if interaction is unavoidable for specific dose recommendations[1]
- Verify monitoring parameters:
  - Baseline: AST, ALT, blood pressure, pregnancy status in females of reproductive potential
    - Do not initiate with uncontrolled hypertension
  - AST/ALT every 2 weeks for first 3 months of therapy, then monthly or as clinically indicated
  - Blood pressure after 1 week of therapy then at least monthly or as clinically indicated
  - Monitor for interstitial lung disease/pneumonitis, hemorrhage, and impaired wound healing
    - See ILD/PNEUMONITIS ASSESSMENT Tool

Recommended Pralsetinib Dose Reduction for Adverse Reactions

Dose reduction	Recommended dosage
Usual (initial dose)	400 mg once daily
First dose reduction level	300 mg once daily
Second dose reduction level	200 mg once daily
Third dose reduction level	100 mg once daily
Permanently discontinue pralsetinib if patient unable to tolerate 100 mg once daily	

Pralsetinib Dosage Adjustments for Toxicities

Toxicity	Severity	Pralsetinib dose adjustment
Hemorrhagic events	Grade 3/4	Hold until recovery to baseline or Grade 0 or 1 Discontinue for severe/life-threatening hemorrhagic events
Hypertension	Grade 3	Initiate or optimize hypertensive therapy and hold for Grade 3 hypertension that persists despite management with optimal antihypertensive therapy Resume at a reduced dose when hypertension is controlled
	Grade 4	Discontinue
Hepatotoxicity	Grade 3/4	Hold and monitor AST/ALT once weekly until ≤ Grade 1 or baseline Resume at reduced dose If hepatotoxicity recurs ≥ Grade 3, discontinue pralsetinib
Pulmonary toxicity (interstitial lung disease (ILD)/pneumonitis)	Grade 1/2	Hold until resolution, then resume pralsetinib at a reduced dose Permanently discontinue pralsetinib for recurrent ILD/pneumonitis
	Grade 3/4	Permanently discontinue pralsetinib for confirmed ILD/pneumonitis
Other adverse reactions	Grade 3/4	Hold until improvement to ≤ Grade 2, then resume pralsetinib at a reduced dose Permanently discontinue for recurrent Grade 4 adverse reactions

Patient-Centered Activities:

- Provide Oral Chemotherapy Education (OCE) sheet
- Counsel to administer orally and review the importance of taking on an empty stomach
- Review baseline labs and chronic medications
- Proper sign/symptom monitoring
- Evaluate if patients have missed any doses between cycles to determine if interventions are needed such as reminders, calendars, pill box, etc
- Ensure that the patient is aware that pralsetinib should be held for 5 days prior to elective surgery and 2 weeks following major surgery and until adequate wound healing
- Patient Assistance: NCODA Financial Assistance Tool

References:

1. Gavreto® (pralsitinib) package insert.
2. Gainor JF, Curigliano G, Kim D-W, et al. Registrational dataset from the phase I/II ARROW trial of pralsetinib (BLU-667) in patients with advanced RET fusion+ non-small cell lung cancer (NSCLC).[abstract]. JClin Oncol 2020;38:Abstract 9515.