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Positive Quality Intervention: Ripretinib (Qinlock®) for Treatment of Adults with Advanced Gastrointestinal Stromal Tumors

Description: The purpose of this PQI is to summarize the process for initiating and monitoring ripretinib therapy in patients with advanced gastrointestinal stromal tumor (GIST) who have received 3 or more prior kinase inhibitors including imatinib.

Background: Ripretinib is a tyrosine kinase inhibitor (TKI) which inhibits KIT proto-oncogene tyrosine kinase (KIT) and platelet derived growth factor receptor A (PDGFRA) kinases. Ripretinib also inhibits PDGFRB, TIE2, VEGFR2, and BRAF. Ripretinib was approved for the treatment of metastatic GIST in May of 2020. The efficacy of ripretinib in advanced GIST, after 3 prior TKIs, was demonstrated in the INVICTUS trial (supplemental section). Ripretinib is a switch control tyrosine kinase inhibitor specifically designed to broadly inhibit KIT and PDGFRA mutated kinases with a unique dual mechanism of action. Ripretinib binds to both the switch pocket region and the activation loop securing the target kinase into an inactive conformation, resulting in the inhibition of downstream signaling and cell proliferation. It represents a new opportunity for patient benefit after treatment with 3 or more prior therapies in advanced, unresectable GIST.

PQI Process: Identify patients with advanced, unresectable metastatic GIST progressing after at least imatinib, plus 2 other TKIs. Upon receipt of a prescription for ripretinib:

- Initial dose 150 mg daily - available as 50 mg tablets
- Drug interactions
  - If concurrent strong CYP3A4 inhibitor monitor more frequently for adverse reactions
  - Avoid concurrent strong CYP3A4 inducers, try to replace with alternate therapy
  - Avoid concomitant use of with moderate CYP3A inducers *If a moderate CYP3A inducer cannot be avoided, increase dosing frequency to 150 mg twice daily
- Monitor blood pressure (BP) at baseline and as clinically indicated throughout therapy
- Monitor for palmar plantar erythrodysesthesia (PPE) and arthralgias/myalgias during therapy
  - See Drug Induced Hand-Foot Syndrome PQI
- Assess cardiac ejection fraction at baseline and then during treatment if clinically indicated
- Perform dermatologic evaluations when initiating and routinely during treatment
- Dose modifications for adverse effects – See Supplemental Section
- Hold for at least 1 week prior to elective surgeries and for at least 2 weeks following major surgery and until adequate wound healing

Patient Centered Activities:

- Provide Oral Chemotherapy Education (OCE) and Oral Chemotherapy Education Supplemental Sheet
- Administration: Can be taken with or without food, with the same time each day preferred
  - Take a missed dose if remembered within 8 hours of the due time
  - Do not take an additional dose if one is vomited up
- Females of childbearing potential or female partners of males should use birth control measures to prevent pregnancy until 1 week post treatment

References:

1. Qinlock (ripretinib) [prescribing information] Waltham, MA Deciphera Pharmaceuticals, LLC 2021.
2. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomized, placebo-controlled, phase 3 trial.*Lancet Oncol.* **2020;**21:923-934.

Supplemental Information: Table 1: Adverse Reaction and Dose Modification

Dose reduction for adverse reactions: 100 mg orally once daily. Permanently discontinue in patients who are unable to tolerate 100 mg orally once daily.

Adverse Reaction	Severity	Dose Modification
Palmar-Plantar Erythrodysesthesia	Grade 2	• Withhold until Grade ≤1 or baseline. If recovered within 7 days, resume at same dose; otherwise resume at reduced dose. • Consider re-escalating if maintained at Grade ≤1 or baseline for at least 28 days. • If PPE recurs, withhold until Grade ≤1 or baseline and then resume at a reduced dose regardless of time to improvement.
	Grade 3	• Withhold for at least 7 days or until Grade ≤1 or baseline (max 28 days). Resume at a reduced dose. • Consider re-escalating if maintained at Grade ≤1 or baseline for at least 28 days.
Hypertension	Grade 3	• If symptomatic, withhold until symptoms have resolved and BP is controlled. • If BP is controlled to Grade ≤1 or baseline, resume at the same dose; otherwise, resume at reduced dose. • If Grade 3 hypertension recurs, withhold until symptoms have resolved and BP is controlled. Resume at a reduced dose.
	Grade 4	Permanently discontinue
Left Ventricular Systolic Dysfunction	Grade 3/4	Permanently discontinue
Arthralgia/Myalgia	Grade 2	• Withhold until Grade ≤1 or baseline. If recovered within 7 days, resume at same dose; otherwise resume at reduced dose. • Consider re-escalating if maintained at Grade ≤1 or baseline for at least 28 days. • If arthralgia or myalgia recurs, withhold until Grade ≤1 or baseline and then resume at a reduced dose regardless of time to improvement.
	Grade 3	• Withhold for at least 7 days or until Grade ≤1 or baseline (max of 28 days). Resume at a reduced dose. • Consider re-escalating if maintained at Grade ≤1 or baseline for at least 28 days.
Other	Grade 3/4	• Withhold until Grade ≤1 or baseline (maximum 28 days), and then resume at a reduced dose; otherwise permanently discontinue. • Consider re-escalating if no recurrence of the adverse reaction for at least 28 days. • If Grade 3 or 4 recurs, permanently discontinue.

Table 2: Clinical Trial Information

Invictus Study	
Patient population	Adults with advanced GIST progressing after at least 3 TKIs including imatinib
Study design	Double blind, randomized (2:1) controlled trial of ripretinib (R) vs placebo (P), placebo-treated patients were allowed to crossover after progression
Outcomes	Median progression free survival (mPFS) R - 6.3 months, P – 1 month (P<0.0001) Objective response rate (ORR) R – 9%, P – 0% (P=0.0504) Median overall survival* (mOS) R – 15.1 months, P – 6.6 months *Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints of ORR and OS