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Positive Quality Intervention: Fruquintinib (Fruzaqla®)

Description: The purpose of this PQI is to review clinical information regarding fruquintinib (Fruzaqla®) treatment of metastatic colorectal cancer and to provide insights into best practices and treatment optimization.

Background:
Fruquintinib is a selective, small-molecule kinase inhibitor of all 3 vascular endothelial growth factor receptors (VEGFR) comprehensively inhibiting the VEGF pathway. This activity restricts tumor growth and progression and potentially inhibits lymphangiogenesis.[1-3] Its selectivity minimizes off-target kinase activity.[3]Fruquintinib is indicated for adult patients with metastatic colorectal cancer who have received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if RAS wild-type and medically appropriate, an anti-EGFR therapy.[4] Approval was based on the results of two phase III, randomized (2:1), placebo-controlled trials: FRESCO and FRESCO-2. FRESCO, conducted in China with 416 patients, showed a median overall survival (OS) of 9.3 months with fruquintinib + best supportive care (BSC) versus 6.6 months with placebo + BSC (HR = 0.65, $p < 0.001$).[5] FRESCO-2 involved 691 patients internationally, showing an OS of 7.4 months with fruquintinib + BSC versus 4.8 months with placebo + BCS (HR = 0.66, $p < 0.001$).[6] Both trials demonstrated improved progression-free survival (FRESCO: 3.7 months vs. 1.8 months, HR = 0.26, $p < 0.001$; FRESCO-2: 3.7 months vs. 1.8 months, HR = 0.32, $p < 0.001$) and disease control rate (FRESCO: 62% vs. 12%; FRESCO-2: 56% vs. 16%) with fruquintinib + BSC compared to placebo + BSC.[5,6] The most common adverse reactions (incidence ≥20%) seen with fruquintinib are hypertension, palmar-plantar erythrodysesthesia (hand-foot syndrome), proteinuria, dysphonia, abdominal pain, diarrhea, and asthenia.[4]

PQI Process:

1. **Eligibility Assessment and Clinical Criteria Confirmation:**
    - **Provider:** Confirm the diagnosis of mCRC and that the patient has previously received:
        - Fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.
        - Anti-VEGF therapy (i.e., bevacizumab in the first/second line setting).
        - If RAS wild-type and clinically indicated, anti-EGFR therapy.
    - Assess ECOG performance status to ensure appropriateness for fruquintinib initiation.
2. **Dosage Determination and Prescription Order:**
    - **Provider:** Determine the appropriate starting dose
        - 5 mg orally once daily for 21 days, followed by 7 days off
        - No dosage adjustment is recommended for patients with mild hepatic impairment; has not been sufficiently studied in patients with moderate hepatic impairment; not recommended for use in patients with severe hepatic impairment.
    - **Pharmacist:** Verify dose accuracy in the electronic health record and confirm consistency with clinical guidelines.
3. **Patient Education and Counseling:**
    - **Pharmacist/Provider:** Provide comprehensive education on fruquintinib, emphasizing:
        - The correct dosing regimen and adherence to the 21-day on, 7-day off cycle.
        - Instructions on administration with or without food.
        - The recognition and reporting of adverse events such as hypertension, hand-foot syndrome, and fatigue.
    - Reinforce the importance of follow-up visits and routine lab monitoring.
4. **Drug Interaction Evaluation:**
    - **Pharmacist:** Conduct a complete medication reconciliation to identify potential interactions, particularly with CYP3A4 or inhibitors/inducers of CYP1A2, CYP2C19, CYP2C8, and CYP2C9

- **Technician:** Assist with reviewing flagged medications for high-risk interactions and alert the pharmacist for further assessment.

5. **Prescription Review and Dispensing:**
   - **Provider:** Electronically prescribe fruquintinib with the correct regimen, including treatment duration and any necessary dose adjustments.
   - **Pharmacist:** Validate the prescription against clinical standards and ensure that all necessary documentation is completed.
   - **Technician:** Prepare, label, and package the medication accurately, adhering to pharmacy protocols.
6. **Lab Monitoring and Follow-Up Scheduling:**
   - **Provider:** Establish a follow-up plan for regular assessment of blood pressure, liver function tests (LFTs), proteinuria, and therapeutic response.
   - **Pharmacist:** Schedule follow-up calls to monitor adherence and assess for potential adverse effects.
   - **Technician:** Document and track lab results and escalate abnormal findings for review by the pharmacist and provider.
7. **Adverse Event Management and Escalation:**
   - **Provider:** During follow-up visits, actively monitor patients for key adverse events such as hypertension, hand-foot syndrome, and LFT abnormalities.
   - **Pharmacist:** Educate patients on identifying and reporting adverse events early and provide supportive care recommendations as needed. Recommend dose adjustments to provider as appropriate based on assessment of patient therapy tolerance including labs.
   - **Technician:** Maintain accurate records of reported adverse events and communicate these to the pharmacist for further intervention.

   Additional Considerations for the Healthcare Team:
   - **Provider:** Maintain vigilance for necessary dose adjustments based on emerging clinical information and lab findings.
   - **Pharmacist:** Facilitate collaboration with providers to enhance medication management and resolve drug interaction issues.
   - **Technician:** Ensure accurate and up-to-date records of patient information, medication inventory, and timely reordering of fruquintinib.

Patient-Centered Activities:
Provide Patient Education Materials:
Supply the patient with an Oral Chemotherapy Education (OCE) Sheet or equivalent educational material that explains fruquintinib's purpose, dosing regimen, potential side effects, and important safety information.
Counseling Pearls:

- **Administration Instructions:**
  Instruct the patient to swallow tablets whole without crushing, chewing, or splitting them. If a dose is missed, it is ok to administer the dose if <12 hours have passed since scheduled dose but never take 2 doses on the same day to make up for missed dose.
- **If Vomiting Occurs:**
  Advise the patient not to take an additional dose if vomiting occurs. They should continue with the next scheduled dose.
- **Hypertension Management:**
  Educate the patient on regularly monitoring their blood pressure and reporting any increases to their healthcare team. Reinforce the importance of adhering to antihypertensive medications if prescribed.
- **Gastrointestinal Toxicity:**
  Recommend taking fruquintinib with or without food as directed. For gastrointestinal symptoms such as nausea or diarrhea, suggest the use of prophylactic or as needed antiemetics and over-the-counter antidiarrheal agents like loperamide, as needed.

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- **Potential for Significant Drug Interactions:**
  Encourage the patient to notify their healthcare team of any new medications, over-the-counter products, or herbal supplements they intend to use to avoid harmful drug interactions.
- **Hand-Foot Syndrome Precautions:**
  Advise patients on preventive measures like using emollient creams, wearing comfortable shoes, and avoiding exposure to excessive heat or pressure on the palms and soles.
- **Photosensitivity Precautions:**
  Recommend the use of sunscreen and protective clothing to minimize the risk of photosensitivity.
- **May Cause Reproductive Effects:**
  Inform patients of child-bearing potential about the potential risks of infertility and the need for appropriate contraceptive measures during treatment.

References:

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6. Dasari A, Lonardi S, Garcia-Carbonero R, et al; FRESCO-2 Study Investigators. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. *Lancet*. 2023;402(10395):41-53. doi:10.1016/S0140-6736(23)00772-9

Supplemental Information:

Table 1. Recommended Dose Reductions for fruquintinib[4]

Dose Level	Fruquintinib dose
First dose reduction	4 mg orally once daily
Second dose reduction	3 mg orally once daily

Permanently discontinue fruquintinib in patients unable to tolerate 3 mg orally once daily

Table 2. Recommended Dosage Modifications for fruquintinib[4]

Adverse Reaction	Severity	Fruquintinib Dosage Modification
Hypertension (HTN)	Grade 3	Withold fruquintinib for persistent Grade 3 HTN despite optimal antihypertensive therapy If HTN fully resolves to ≤ Grade 1, resume at next lower dose level
	Grade 4	Permanently discontinue fruquintinib
Hemorrhagic Events	Grade 2	Withold fruquintinib until bleeding fully resolves or recovers to Grade 1 Resume at next lower dose level
	Grade 3 or 4	Permanently discontinue fruquintinib
Hepatotoxicity	ALT/AST > 3 x ULN or > 3 x baseline if baseline abnormal or total bilirubin (Tbili) > 1.5 x ULN or > 1.5 x baseline if baseline abnormal	Withold fruquintinib and monitor ALT/AST and Tbili until resolution to Grade 1 or baseline Resume at next lower dose level
	ALT/AST > 3 x ULN with concurrent Tbili > 2 x ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue fruquintinib
	AST or ALT > 20 x ULN if baseline was normal, or > 20 x baseline if baseline was abnormal or Tbili > 10 x ULN if baseline was normal, or > 10 x baseline if baseline was abnormal	Permanently discontinue fruquintinib
Proteinuria	≥ 2 grams proteinuria in 24 hours	Withhold fruquintinib until proteinuria fully resolves or is <1 gram/24 hours. Upon recovery, resume at the next lower dose level. Permanently discontinue fruquintinib for nephrotic syndrome or if proteinuria does not recover to <1 gram/24 hours.
Palmar-plantar erythrodysesthesia (PPE)	Grade 2	Withhold fruquintinib and initiate supportive treatment. If toxicity fully resolves or recovers to Grade 1, resume at the same dose level.
	Grade 3	Withhold FRUZAQLA and initiate supportive treatment. If toxicity fully resolves or recovers to Grade 1, resume at the next lower dose level.