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Encorafenib (Braftovi®) + Cetuximab (Erbitux®) + mFOLFOX6 for BRAF V600E-Positive Metastatic Colorectal Cancer

Description: The purpose of this PQI is to review clinical considerations related to the use of encorafenib combined with cetuximab and mFOLFOX6 (EC + mFOLFOX6) in patients with BRAF V600E-mutated metastatic colorectal cancer (mCRC).

Background: Encorafenib, a selective ATP-competitive inhibitor of BRAF, in combination with cetuximab—an epidermal growth factor receptor (EGFR) inhibitor—and the chemotherapy regimen mFOLFOX6 (folinic acid, fluorouracil, and oxaliplatin), has been granted accelerated FDA approval for the treatment of adult patients with BRAF V600E-mutated mCRC. This approval was based on findings from the BREAKWATER trial.

Below are the most common adverse reactions associated with the regimen (≥ 25%):

- Peripheral neuropathy, nausea, fatigue, rash, diarrhea, decreased appetite, vomiting, hemorrhage, abdominal pain, and pyrexia

PQI Process:

- Verify correct dosing

Medication	Dose	Route of Administration	Frequency*
Encorafenib (Braftovi®)	300 mg (4 x 75 mg capsules)	Oral	Daily
Cetuximab (Erbitux®)	500 mg/m^2	IV over 120 minutes	Every 14 days
Folinic Acid/Leucovorin	400 mg/m^2	IV over 120 minutes	Every 14 days
Oxaliplatin	85 mg/m^2	IV over 120 minutes	Every 14 days
5-fluorouracil (5FU)	400 mg/m^2 IV bolus x1, then 2400 mg/m^2 IVCI	IVCI over 46-48 hours	Every 14 days

*28-day cycle

- Verify appropriate pre-medications have been ordered
  - Cetuximab: H1-antagonist prior to first dose; may omit for subsequent infusions if no HSR
  - Oxaliplatin: Moderately emetogenic – ensure antiemetic prophylaxis
    - 5HT3 RA + dexamethasone, OR
    - Olanzapine + palonosetron + dexamethasone, OR
    - NK1 RA + 5HT3 RA + dexamethasone
  - Encorafenib: Moderately–highly emetogenic. Ensure PRN oral antiemetics; consider scheduled dosing if poorly tolerated.
- Genetic & Cardiac Risk Evaluation
  - DPYD testing: Consider prior to 5-FU initiation per institutional protocols.
    - See: DPYD Testing Prior to Fluoropyrimidine Treatment - NCODA

- QTc Monitoring: Baseline and periodic ECGs for those on or with:
  - QT-prolonging meds
  - Known long QT syndrome
  - Bradyarrhythmias or heart failure
- Assessment of potential drug-drug interactions:
  - Encorafenib is a substrate and strong inducer of CYP3A4
    - Also inhibits the drug transporters BCRP/ABCG2, OATP1B1/1B3
- Labs Prior to Each Cycle:
  - CBC, CMP, bilirubin
  - Monitor and replete magnesium, potassium, calcium
  - Evaluate renal function and adjust oxaliplatin dosing as needed
  - Hold if ANC $\geq$ 1,500/mm^3 and/or platelets $\geq$ 75,000/mm^3
- Supportive Care and Monitoring:
  - Skin exams prior to encorafenib, every 2 months during therapy, and up to 6 months after
  - Prophylactic acneiform rash management (oral antibiotics +/- low/moderate topical steroids)
    - Managing EGFR Inhibitor Induced Rash - NCODA
  - Urea cream for hand-foot syndrome
    - Medication Induced Hand-Foot Syndrome - NCODA
  - For additional details regarding AE management with EC, see: Management of adverse events from EC: insights from BEACON trial
- Potential Alternative Regimen
  - Note: mFOLFOX6 is the only FDA-approved chemotherapy backbone for use in combination with EC. However, BREAKWATER also evaluated FOLFIRI + EC with promising efficacy and safety results.
- Anti-EGFR Agent Selection:
  - While cetuximab was used in BREAKWATER, panitumumab (Vectibix®) is considered clinically interchangeable with cetuximab, and may carry a lower risk of HSR
  - May consider substitution with panitumumab in patients with:
    - History of HSR to cetuximab, Alpha-gal syndrome, tick bite exposure, residing/living in the southeastern U.S., or history of Lyme disease

Patient-Centered Activities:[2]

- Discuss financial support resources
  - Commercially insured patients:
    - 30-day trial voucher
    - Co-pay assistance
  - Medicare/Medicaid and uninsured patients:
    - Pfizer Oncology Together
    - Medicare Prescription Payment Plan via part D insurer
  - Pfizer Access & patient support services available
- Provide patient with Patient Education Sheets
  - Encorafenib, Cetuximab, and FOLFOX
- Educate on common side effects and proactive symptom management strategies. Highlight when to contact the oncology team.
  - GI and Dermatologic toxicities (see additional education sheets linked below)
    - Nausea/vomiting:https://www.oralchemoedsheets.com/index.php/supplement-library/27-supplemental-available/495-nauseaandvomiting
    - Diarrhea: https://www.oralchemoedsheets.com/index.php/supplement-library/27-supplemental-available/497-diarrhea

- Acneiform rash (EGFR-related): https://www.oralchemoedsheets.com/index.php/supplement-library/27-supplemental-available/595-acneiform-rash
- Stomatitis/mucositis: https://www.oralchemoedsheets.com/index.php/supplement-library/27-supplemental-available/560-mucositis-stomatitis
- Hand-foot syndrome: https://www.oralchemoedsheets.com/index.php/supplement-library/27-supplemental-available/509-managing-hand-foot-reaction

- Arthralgia
  - Bilateral joint pain (small/large joints)
  - Supportive care: rest, gentle stretching, OTC oral/topical analgesics (acetaminophen, NSAIDs) as needed
  - Consider steroids for refractory pain
- Neuropathy
  - Acute (cold-sensitive)
    - Onset during or after infusion; symptoms include cold-induced tingling, pharyngolaryngeal dysesthesia, and first-bite jaw pain
    - Management
      - Avoid cold exposure post-infusion
      - Use room-temp food/drinks
      - Bundle exposed skin
      - Eat slowly to reduce first-bite pain
    - Contact clinic if symptoms persist or impact nutrition/function
  - Chronic (cumulative exposure > 780 mg/m^2)
    - Persistent tingling/numbness (stocking-glove distribution)
    - Symptoms may take 6-18 months to resolve
    - Monitor for “coasting” (worsening neuropathy 2-3 months post-treatment)
    - Notify care team for possible dose adjustments or discontinuation
- Monitoring for unique toxicities:
  - QTc prolongation (ECG as needed)
  - Ocular toxicities (baseline and symptom-driven assessment)
  - Secondary skin malignancies (derm evaluation every 2 months during treatment and 6 months post therapy)

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