



Positive Quality Intervention: Regorafenib (Stivarga®) in Metastatic Colorectal Cancer

Description: Management of adverse effects related to regorafenib treatment in metastatic colorectal cancer. Optimal dosing and follow up are essential to help patients benefit fully while taking this medication.

Background: Regorafenib is indicated in Metastatic colorectal cancer (CRC) who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an antiVEGF therapy, and, if RAS wild-type, an anti-EGFR therapy. Regorafenib is a multikinase inhibitor that has shown an overall survival (OS) benefit (6.4 months, regorafenib + supportive care versus 5.0 months, placebo + supportive care; CORRECT Trial) in the third line setting. Keeping patients on therapy can be challenging due to the adverse effect profile* of multikinase inhibitors. The ReDOS trial evaluated the dose escalation strategy in regorafenib patients and efficacy. A strategy with weekly dose escalation of regorafenib from 80 mg to 160 mg/day (Arm A) was found to be superior to a starting dose of 160 mg/day (Arm B). A trend for improved OS was seen in the dose escalation arm. The dose escalation strategy did not appear to compromise QOL. Patients started on 80 mg for the first week with weekly dose escalations in the absence of significant drug-related toxicities. Median OS was improved in Arm A vs. Arm B (9.8 months vs. 6.0 months; HR 0.72, 95% CI, p=0.12). Median Progression Free Survival was 2.8 months for Arm A vs. 2.0 months for Arm B (HR 0.84, CI 95%, p=0.38).

PQI Process: Upon receipt of a new prescription for regorafenib

- If the starting dose of 160 mg by mouth once daily is written, exercise clinical judgement and contact prescriber to discuss potentially starting with dose escalation schedule (ReDOS trial strategy⁴):
 - Document follow up schedule and dose escalation in EMR
 - Initiate patient at 80 mg for the first week of cycle 1
 - If no significant drug-related toxicities, escalate to 120 mg for the second week of cycle 1, otherwise keep therapy at current dose
 - If no significant drug-related toxicities, escalate to 160 mg for the third week of cycle 1, otherwise keep therapy at current dose
 - For following cycles, start therapy at current tolerated dose (no dose escalation)
- Avoid use with strong CYP3A4 inducers/inhibitors
- Monitor patients closely if using with BCRP substrates
- Coordinate and establish a weekly follow up call with the patient or caregiver for the first 8 weeks
- Monitor baseline LFTs before initiation, every 2 weeks during the first two months of therapy and at least monthly thereafter
- CBC with differential and platelets and serum electrolytes at baseline and monthly
- Monitor blood pressure weekly for the first 6 weeks of therapy, then every cycle
- Monitor for hand-foot skin reaction (HFSR) weekly for 2 cycles, then every cycle
- Monitor for signs/symptoms of cardiac issues, bleeding, GI perforation or fistula, infection, and/or neurological symptoms
- Monitor for impaired wound healing; hold medication for 2 weeks prior to surgery
- Consider providing urea base moisturizer and anti-diarrheals

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Patient-Centered Activities:

- Provide [Oncology Chemotherapy Education \(OCE\)](#) sheet
- Consider providing [Treatment Support Kit \(TSK\)](#)
- Provide patient starter kit and consider antidiarrheal and moisturizing cream
- Educate patient on dosing schedule (once daily for 3 weeks on and 1 week off)
- Ensure patient knows to take dose with a low-fat meal (< 600 calories and 30% fat)
- Only open 1 bottle of regorafenib at a time ***medication expires 7 weeks after bottle is opened**
 - **Packaging now available in 21 count bottle**
 - Store tablets in original container and DO NOT remove desiccant
 - Discard any unused tablets after 7 weeks
- Ensure patient or caregiver is able to take and record blood pressure at home weekly
- Patient Assistance: [NCODA Financial Assistance Tool](#)
- Take dosage with low fat meal (< 600 calories)
 - Examples of [Low Fat food choices](#)⁵
 - Dairy and dairy-like products
 - Low-fat (1%) or fat-free (skim) yogurt, cottage cheese, or milk
 - Fat-free American cheese or other types of fat-free cheeses
 - Fish, meat, poultry, and other protein
 - Egg whites or egg substitutes
 - Crab, white fish, shrimp, and light tuna (packed in water)
 - Chicken and turkey breast (without skin), or ground turkey breast
 - Beans, peas, and lentils, cooked (or canned) without added fats
 - Grains, cereals, and pastas
 - Hot (oatmeal or grits) and cold cereals (except granola types)
 - Whole grain brown rice or noodles (watch out for fat in added sauces)
 - Whole grain bagels, pita bread, or English muffins
 - Low-fat crackers and breads
 - Soft tortillas – corn or whole wheat
 - Fruits- including fresh, frozen, or canned (in their own juice)
 - Vegetables- including fresh, frozen, or canned (choose lower-sodium varieties)
 - Other foods
 - Broth type soups with a vegetable base
 - Sauces, pudding, or shakes made with skim milk

Supplemental Information:

*Dose limiting side effects include (percentage refers to all grades)¹: Skin and subcutaneous tissue adverse events, including palmar-plantar erythrodysesthesia (Hand and Foot syndrome) 72%, diarrhea 43%, hypertension 30%, fatigue 64%, increased LFTs (AST-65%, ALT-45%, Bilirubin-45%). The median time to first adverse event was 2 weeks with worst incidences occurring at 3 weeks. The worst severity of diarrhea occurred at 4 weeks. Increases in LFTs usually occur within the first 8 weeks of therapy.

References:

1. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013;381(9863):303-312.
2. [NCCN Clinical Practice Guidelines in Oncology \(NCCN guidelines®\) for colon cancer.](#)
3. [STIVARGA® \(Regorafenib\) \[Prescribing Information\].](#)
4. Bekaii-Saab TS, Ou F-S, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study [published online June 28, 2019]. *Lancet Oncol.* doi: 10.1016/S1470-2045(19)30272-4.
5. <https://www.cancer.org/healthy/eat-healthy-get-active/take-control-your-weight/low-fat-foods.html>.