

**Positive Quality Intervention: Regorafenib (Stivarga®) In the Treatment of Hepatocellular Carcinoma**

Description: Understand how to identify eligible patients and manage adverse effects of regorafenib treatment in hepatocellular carcinoma.

Background: Regorafenib is a multi-kinase inhibitor indicated for the treatment of patients (Childs Pugh A) with Hepatocellular Carcinoma (HCC) who have been previously treated with sorafenib.¹ Designated by NCCN as category 1 in this distinction.² In the phase III – RESORCE Trial, regorafenib was assessed in patients with HCC who have progressed on sorafenib and concluded that there was an improved overall survival compared to placebo (10.6 months vs. 7.8 months).³ This study also portrayed the difficulties of maintaining therapy, as the discontinuation rate due to adverse events within the treatment arm was observed at 25% and 43% due to progression. The most common grade (all grade) adverse events occurring more frequently in the regorafenib group included: Hand-foot skin reaction (51%), asthenia/ fatigue (42%), diarrhea (41%), and hypertension Grade 3 or 4 (31%).

PQI Process: Consider reviewing all current HCC patient in EMR for appropriateness of regorafenib therapy
Upon receipt of a new prescription for regorafenib:

- If the typical starting dose of 160 mg by mouth once a day 3 weeks on, 1 week off is written, *consider* initiating dose titration based on the mCRC ReDos trial in metastatic colorectal cancer (mCRC)⁴
 - 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)
- 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

Patient-Centered Activities:

- Provide [Oral Chemotherapy Education \(OCE\)](#) Sheet
- Consider providing [Treatment Support Kit \(TSK\)](#)
- Emphasize counseling on side effects
- Educate patients on side effects and report adverse effects to prescriber and recommend dose adjustments in 40 mg increments as tolerated
- Dosing is once daily for 3 weeks on therapy then 1 week off therapy per cycle

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- 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
- 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

References:

1. [STIVARGA® \(Regorafenib\) \[Prescribing Information\]](#).
2. NCCN Clinical Practice Guidelines in Oncology (NCCN guidelines®) for hepatobiliary cancers. All rights reserved.
3. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Bruix, Jordi et al. The Lancet, Volume 389 , Issue 10064 , 56 – 66.
4. Bekaii-Saab T, Ou FS, Ciombor KK, et al. Regorafenib dose optimization study (ReDOS): A phase II randomized study of lower starting dose regorafenib compared to standard dose regorafenib in patients with refractory metastatic colorectal cancer (mCRC). Journal of Clinical Oncology 2016 34:15_suppl, TPS3630-TPS3630.
5. <https://www.cancer.org/healthy/eat-healthy-get-active/take-control-your-weight/low-fat-foods.html>.