Written By: Jeff Engle, PharmD, MS
University of Minnesota Masonic Cancer Clinic
Updated 10.7.21

Positive Quality Intervention: Sorafenib (Nexavar®) for the Treatment of Hepatocellular Carcinoma and Transition to Second-line Regorafenib (Stivarga®)

Description: This PQI will discuss effective management of adverse effects of sorafenib in the treatment of hepatocellular carcinoma and discuss data supporting the sequencing of patients to second-line therapy with regorafenib for increased survival benefit.

Background: Hepatocellular carcinoma (HCC) is associated with a high mortality rate and historically the treatment options have been limited. Prior to 2018, sorafenib was the only Food and Drug Administration approved targeted therapy for the initial treatment of unresectable HCC in patients diagnosed with late stage or metastatic disease.[7] Second-line treatment options, though growing in number, have limited and at times conflicting survival data; and all factors of options should be considered.[14, 18] A retrospective study of the RESORCE trial ascertained median time from start of sorafenib to death in patients receiving sequential therapy to regorafenib. Exploratory analysis revealed time from sorafenib initiation to death as 26 months for regorafenib patients vs. 19.2 months for placebo patients.[16]

PQI Process: Upon receipt of a prescription for sorafenib:

- Obtain CBC with differential, metabolic panel including magnesium and phosphorus, liver function tests, lipase and amylase prior to starting therapy and then monthly until labs have stabilized
- Consider obtaining thyroid stimulating hormone level at baseline, every 4 weeks for 4 months, and then every 2-3 months thereafter
- Monitor blood pressure at baseline and weekly during the first 6 weeks of sorafenib, and then monitor blood pressure, utilizing clinic appointments and treatment any developing hypertension as needed
- Treatment associated hypertension and dermatologic toxicity are managed with dose interruptions and reductions.[8] Grade 1 dermatologic toxicity may not require dosage adjustments (see table 3 for dose reductions due to toxicity)
- Consider proactively discussing 2nd line treatment options following progression or intolerance

If regorafenib is considered for 2nd line tyrosine kinase inhibitor transitioning

- Ensure recovery from sorafenib mediated adverse effects and that patient did not permanently discontinue sorafenib due to toxicity or inability to tolerate doses
    - RESORCE trial required that patients be able to tolerate at least 400 mg a day of sorafenib for 20 days of the last 28 days prior to withdrawal to be eligible
- Determine Child-Pugh Class status and make appropriate recommendation for therapy
- If underlying hypertension exists or developed while on sorafenib, ensure appropriate blood pressure control prior to starting regorafenib
- Refer to **Regorafenib (Stivarga®) In the Treatment of Hepatocellular Carcinoma** PQI for managing adverse effects

Written By: Jeff Engle, PharmD, MS
University of Minnesota Masonic Cancer Clinic
Updated 10.7.21

Patient Centered Activities:

Counseling for sorafenib

- Provide patient Oral Chemotherapy Education (OCE) sheet and Oral Chemotherapy Education Supplemental sheets
- Counsel patient on the signs and symptoms of hand-foot syndrome and other dermatologic side effects
  - Refer to **Medication Induced Hand-Foot Syndrome** PQI
- Counsel on appropriate management of chemotherapy induced diarrhea
  - Refer to **Oncolytic Induced Diarrhea** PQI
- Counsel on measuring blood pressure weekly at home (first 6 weeks) and instruct to report blood pressures > 140/90 mmHg
- Dose adjustments for baseline hepatic and renal dysfunction have been recommended based on a phase I pharmacokinetic study and are included in Table 1 and 2[15]

Counseling for regorafenib

- Provide patient Oral Chemotherapy Education (OCE) sheet and Oral Chemotherapy Education Supplemental sheet
- Utilize principles within **Regorafenib (Stivarga®) In the Treatment of Hepatocellular Carcinoma** PQI
- Counsel patient on the signs and symptoms of hand-foot syndrome and other dermatologic side effects
  - Refer to **Medication Induced Hand-Foot Syndrome** PQI

Supplemental Information:

Table 1: Dose Adjustments for Baseline Hepatic Dysfunction[15]*

Degree of Hepatic Impairment	Criteria	Sorafenib Dose
Mild	Bilirubin >1 to ≤1.5 times ULN and/or AST >ULN	400 mg twice daily
Moderate	Bilirubin >1.5 to ≤3 times ULN; any AST	200 mg twice daily
Severe	Albumin <2.5 g/dL with any bilirubin/AST	200 mg once daily
	Bilirubin >3 to 10 x ULN with any AST	No tolerable dose identified

*Reference used differs slightly from sorafenib prescribing information reference

Table 2: Dose Adjustments for Baseline Renal Dysfunction[15]

Baseline Creatinine Clearance	Sorafenib Dose
40-59 mL/min	400 mg twice daily
20-39 mL/min	200 mg twice daily
< 20 mL/min	Unable to define dose
Hemodialysis	200 mg once daily

Table 3: Dose Reduction Levels for Adverse Effects*

Dose Reduction	Sorafenib Dose
Starting	400 mg twice daily
1	200 mg twice daily
2	200 mg once daily or 400 mg every other day
3	Discontinue

Written By: Jeff Engle, PharmD, MS
University of Minnesota Masonic Cancer Clinic
Updated 10.7.21

Patient Assistance

Sorafenib patients can utilize the REACH support program while on therapy

- Nurse counselors are available for answering questions and providing patient education including Patient Starter Kits
- Service counselors are available to discuss patient access services including co-pay assistance

References:

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019 Jan;69(1):7-34.
2. Cronin KA, Lake AJ, Scott S, et al. Annual report to the nation on the status of cancer, part I: National cancer statistics. Cancer. 2018 Jul 1;124(13):2785-2800.
3. Morgan TR, Mandayam S, Jamal MM. Alcohol and hepatocellular carcinoma. Gastroenterology. 2004; 127: S87–96.
4. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology. 2012;142:1264–73.e1.
5. Marrero JA, Kulik LM, Sirlin CB, et al. Diagnosis, staging, and management of hepatocellular carcinoma: 2018 practice guidance by the American Association for the Study of Liver Diseases. Hepatology. 2018 Aug;68(2):723-750.
6. National Comprehensive Cancer Network. Hepatobiliary cancers version 1.2019. https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf.
7. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359:378-390.
8. Nexavar® (sorafenib) [prescribing information]. Wayne, NJ: Bayer Healthcare Pharmaceuticals Inc.
9. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib (RESORCE): a randomized, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389:56-66.
10. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMat 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet. 2017;389:2492-2502.
11. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol. 2018;19(7):940-952.
12. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med. 2018;379:54-63.
13. Zhu AX, Kang YK, Yen CJ, et al. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α-fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2019 Feb;20(2):282-296.
14. Merck Provides Update on KEYNOTE-240, a Phase 3 Study of KEYTRUDA® (pembrolizumab) in Previously Treated Patients with Advanced Hepatocellular Carcinoma. Merck. Published February 19, 2019. https://bit.ly/2SQ6J45.
15. Miller AA, Murry DJ, Owzar K, et al. Phase I and pharmacokinetic study of sorafenib in patients with hepatic or renal dysfunction: CALGB 60301. J Clin Oncol. 2009 Apr 10;27(11):1800-5.
16. Finn RS et. Al Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC. J Hepatol. 2018 Aug;69(2):353-358. doi: 10.1016/j.jhep.2018.04.010.