Regimen Monograph

A - Regimen Name

SORA Regimen

SORAfenib

Disease Site	Genitourinary - Renal Cell / Kidney
Intent	Palliative
Regimen Category	**Evidence-Informed :** Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.
Rationale and Uses	Treatment of locally advanced/metastatic renal cell carcinoma (clear cell) in patients, with low or intermediate risk factor, who have failed prior cytokine therapy.
Supplementary Public Funding	**SORAfenib** Exceptional Access Program (SORAfenib - Metastatic renal cell carcinoma of clear cell histology as second-line treatment, with specific criteria)

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B - Drug Regimen

SORAfenib	400 mg	PO	Twice Daily

(Outpatient prescription in 200mg tablets)

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C - Cycle Frequency

CONTINUOUS TREATMENT

Continue treatment until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal – No routine prophylaxis; PRN recommended

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and could be considered. See appendix 6 for general recommendations. Hypokalemia, hypomagnesemia and hypocalcemia should be corrected before sorafenib treatment.

Dosage with toxicity

Dose levels:

Dose level	Sorafenib dose

0	800mg daily dose (400mg bid)
-1	600mg daily dose (400mg and 200mg, 12 hours apart)
-2	400mg daily dose (200mg bid)
-3	200mg daily dose (200mg od)

Toxicity grade	**Occurrence**	**Dose modification**
Grade 1 skin	Any	Continue treatment with sorafenib and consider topical/supportive therapy for symptomatic relief.
Grade 2 skin	1st	Continue treatment, supportive care. Consider ↓ 2 dose levels for 28 days; if does not improve hold for at least 7 days until ≤ grade 1 and restart at 400mg daily. If ≤ grade 1 x 28 days, consider re-escalating to full dose.
	2nd or 3rd	As for 1st occurrence, but do no re-escalate if hold required.
	4th	Consider discontinuing sorafenib.
Grade 3 skin	1st	Supportive care and hold at least 7 days until ≤ grade 1, restart by ↓ 2 dose levels; if ≤ grade 1 x 28 days, consider re-escalating to full dose.
	2nd	As for 1st occurrence, but do not re-escalate.
	3rd	Consider discontinuing sorafenib.
Grade 3 non-hematological/related organ	1st	Hold until recovery to ≤ grade 2; ↓ 2 dose levels
	2nd	Discontinue
Cardiac ischemia and/or infarction	Any	Hold; consider discontinuing
↑LFTs	Any	Hold if severe and rule out other causes. Discontinue if drug-induced hepatitis.
GI perforation, severe hypertension despite treatment, cardiac failure, ≥ grade 3 bleeding, pneumonitis, SJS or TEN, Grade 4 non-	Any	Discontinue

hematological/related organ		

Hepatic Impairment

Patients with hepatocellular carcinoma (HCC) and Child-Pugh B hepatic impairment have greater systemic exposure than Child-Pugh A patients, although this difference is not seen in non-HCC patients. Exercise caution and monitor closely when treating Child-Pugh B patients with sorafenib, due to the heterogenous nature of this population. Sorafenib has not been studied in patients with Child Pugh C hepatic impairment.

Miller 2009 suggested the following dose modifications in patients **with HCC**:

Child-Pugh		Bilirubin	Albumin	Dose
A	AND	≤ 1.5 x ULN		400mg bid
B	AND/OR	> 1.5 - 3 x ULN		200mg bid
C	AND/OR	> 3 x ULN		Do not treat – severe toxicity likely
			≤ 25	200mg daily

Renal Impairment

Although the product monograph suggests that no dose adjustments are required in patients with mild, moderate, or severe renal impairment not requiring dialysis, a pharmacokinetic study (Miller 2009) suggested the following:

Creatinine clearance	Dose
> 40 mL/min	400mg BID
20-40 mL/min	200mg BID
< 20mL/min	No information; avoid or use with extreme caution

Dosage in the Elderly

Dosage adjustment is not necessary in elderly patients.

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F - Adverse Effects

Refer to SORAfenib drug monograph(s) for additional details of adverse effects.

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Abnormal electrolytes • Myelosuppression +/- infection, bleeding (may be severe) • Diarrhea • Increased amylase/lipase (may be severe) • Rash (may be severe) • Fatigue • Increased LFTs (may be severe) • Hand-foot syndrome • Alopecia	• Nausea, vomiting • Hypertension • Anorexia, weight loss • Hemorrhage (may be severe) • Cough, dyspnea (may be severe) • Neuropathy • Abdominal pain • Mucositis • Musculoskeletal pain • Headache	• Cholecystitis • Hypo/hyperthyroidism • Arterial thromboembolism • Venous thromboembolism • Artery aneurysm / dissection • Cardiotoxicity • Hypersensitivity • Pancreatitis • PRES • GI perforation • Osteonecrosis of the jaw • Renal failure • Rhabdomyolysis • Vasculitis • Secondary malignancy

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G - Interactions

Refer to SORAfenib drug monograph(s) for additional details

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H - Drug Administration and Special Precautions

Refer to SORAfenib drug monograph(s) for additional details

Administration

- Oral self-administration; drug available by outpatient prescription.
- Prescribed dose should be administered orally on an empty stomach, or with a low-fat or moderate-fat meal with a large glass of water
- Store at room temperature (15-30°C)

Contraindications

• Patients who have a hypersensitivity to this drug or any of its components

Warnings/Precautions

- Concomitant warfarin or antiplatelet agents should be used cautiously
- Temporary hold is recommended for patients undergoing major surgery
- Hypokalemia, hypomagnesemia and hypocalcemia should be corrected before treatment
- Due to the potential risk of bleeding, tracheal, bronchial, and esophageal infiltration should be treated with localized therapy before starting sorafenib in DTC patients.
- Sorafenib may impair exogenous thyroid suppression in DTC patients.
- Sorafenib should be administered with caution in patients who have bradycardia or with increased risk of developing prolongation of the QT interval/torsades de pointes (i.e. hypokalemia or hypomagnesemia, congenital long QT syndrome, history of cardiac disease or arrhythmias, concomitant anti-arrhythmic or other medications that may prolong QT interval). Patients with unstable coronary artery disease or recent MI (within 6 months) were excluded from clinical trials.

Pregnancy/Lactation

- Sorafenib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **2 weeks** after the last dose.
- Breastfeeding is not recommended.

- Sorafenib impairs male and female fertility.

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I - Recommended Clinical Monitoring

Recommended Clinical Monitoring

- Blood pressure; weekly for first 6 weeks of treatment, then periodically thereafter
- CBC; baseline and regular
- Thyroid function tests; baseline and regular
- ECG during therapy; baseline and periodic
- Electrolytes, including phosphate and calcium; baseline and regular
- INR, for patients on warfarin; regular, especially at initiation, or discontinuation or change of dose.
- Liver function tests, amylase and lipase; baseline and regular
- Clinical toxicity ratings (bleeding, hypertension, skin changes, diarrhea, pancreatitis, congestive heart failure, hepatitis, secondary malignancies); regular
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- LVEF, especially in patients with cardiac risk factors; baseline and periodic
- Dental evaluation before starting treatment with preventative dentistry as needed

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Escudier B, Eisen T, Stadler WM, et al. Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma. N Engl J Med 2007; 356:125-34.

Hollebecque A, Cattan S, Romano O, et al. Safety and efficacy of sorafenib in hepatocellular carcinoma: the impact of the Child-Pugh score. Aliment Pharmacol Ther 2011;34(10):1193-201.

Lencioni R, Kudo M, Ye SL, et al. First interim analysis of the GIDEON (Global Investigation of therapeutic decisions in hepatocellular carcinoma and of its treatment with sorafenib) non-interventional study. Int J Clin Pract 2012;66(7):675-83.

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;27(11):1800-5.

Pinter M, Sieghart W, Graziadel I, et al. Sorafenib in Unresectable Hepatocellular Carcinoma from Mild to Advanced Stage Liver Cirrhosis. Oncologist 2009;14(1):70-6.

Pressiani T, Boni C, Rimassa L, et al. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: a prospective feasibility analysis. Ann Oncol 2013;24(2):406-11.

Sorafenib drug monograph, Cancer Care Ontario.

Wörns MA, Weinmann A, Pfingst K, et al. Safety and efficacy of sorafenib in patients with advanced hepatocellular carcinoma in consideration of concomitant stage of liver cirrhosis. J Clin Gastroenterol 2009;43(5):489-95.

Zhu AX, Clark JW. Commentary: Sorafenib Use in Patients with Advanced Hepatocellular Carcinoma and Underlying Child-Pugh B Cirrhosis—Evidence and Controversy. Oncologist 2009;14(1):67-9.

PEBC Advice Documents or Guidelines

- The Use of Targeted Therapies in Patients with Inoperable Locally Advanced or Metastatic Renal Cell Cancer

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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