Regimen Monograph

A - Regimen Name

SORA Regimen

SORAfenib

Disease Site	Endocrine - Thyroid
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	For treatment of locally advanced or metastatic, progressive differentiated thyroid carcinoma (DTC) in patients refractory to radioactive iodine.

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B - Drug Regimen

SORAfenib	400* mg	PO	BID

(This drug is not currently publicly funded for this regimen and intent)

*(outpatient prescription in 200 mg tablets)

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C - Cycle Frequency

CONTINUOUS 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.

Electrolyte abnormalities should be corrected before starting treatment.

Patients with DTC should have esophageal and upper airway infiltration controlled with local measures prior to starting treatment to reduce the risk of bleeding.

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 ↓1 dose level. If no improvement within 7 days, hold until ≤ grade 1, then ↓ 1 dose level.
	2nd	hold until resolved to ≤ grade 1. Resume by ↓ 1 dose level.
	3rd	Hold until resolved to ≤ grade 1. Resume by↓ 2 dose levels.
	4th	Discontinue
Grade 3 skin	1st	Hold until resolved to ≤ grade 1. Resume by ↓ 1 dose level
	2nd	Hold until resolved to ≤ grade 1. Resume by ↓ 2 dose levels.
	3rd	Discontinue
Grade 3 non hematological/organ	1st	Hold until recovery to ≤ grade 2, Resume by ↓ 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 / TEN; Grade 4 non-hematological/organ	Any	Discontinue
*For patients who require a dose reduction for Grade 2 or 3 skin toxicity, dose may be increased if improved to ≤ grade 1 after 28 days of treatment at reduced dose.		

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 hepatocellular carcinoma:

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

The product monograph states that no dose adjustments are required in patients with mild, moderate, or severe renal impairment not requiring dialysis. 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

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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.

- Sorafenib inhibits CYP2B6 and 2C8 and is a substrate for CYP3A4
- Avoid use with strong CYP3A4 inducers; use with caution with CYP3A4 inhibitors
- Avoid use with neomycin given risk of reduced sorafenib exposure
- Avoid use with paclitaxel/carboplatin given increased risk of toxicity
- Avoid use with drugs that may prolong the QT interval
- Caution and monitor INR in patients receiving warfarin
- Sorfenib may impair exogenous thyroid suppression. Caution and monitor TSH levels. Thyroid replacement may need dosage adjustment.

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H - Drug Administration and Special Precautions

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

Administration:

- Administer on an empty stomach, or with a low-fat or moderate-fat meal and 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

Other Warnings/Precautions:

- Concomitant warfarin or antiplatelet agents should be used cautiously
- Temporary hold is recommended for patients undergoing major surgery
- Electrolyte abnormalities 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 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 and 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

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- Blood pressure; weekly for first 6 weeks of treatment, then periodically thereafter
- CBC; baseline and at each visit
- Close monitoring of blood calcium and TSH levels; baseline, monthly and as clinically indicated
- ECG during therapy; baseline and periodic
- Electrolytes, including phosphate and calcium; baseline and at each visit
- INR, for patients on warfarin; regular, especially at initiation, or discontinuation or change of dose.
- Liver function tests, amylase and lipase; baseline and at each visit
- Clinical toxicity assessment of bleeding, hypertension, skin changes, diarrhea, pancreatitis, congestive heart failure, hepatitis, secondary malignancies; at each visit

- 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

Brose MS, Nutting CM, Jarzab B, et al; DECISION investigators. Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet. 2014 Jul 26;384(9940):319-28.

Sorafenib drug monograph, Cancer Care Ontario.

PEBC Advice Documents or Guidelines

- CCO Thyroid Cancer Guideline: An Endorsement of the 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

October 2020 Updated uncommon adverse effects

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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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