Regimen Monograph

A - Regimen Name

PAZO Regimen

Pazopanib

Disease Site	Sarcoma - Soft Tissue
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 adult patients with selective subtypes* of advanced soft tissue sarcoma who have received prior chemotherapy for metastatic disease or who have progressed within 12 months after (neo)adjuvant therapy. Patients were required to have disease progression on or after, or be intolerant to, anthracycline-based regimen in the pivotal phase III study in STS. *the pivotal trial excluded adipocytic sarcoma, GIST, rhabdomyosarcoma that was not alveolar or pleomorphic, chondrosarcoma, osteosarcoma, Ewing's sarcoma, primitive neuroectodermal tumours, DFSP, inflammatory myofibroblastic sarcoma, malignant mesothelioma and mixed mesodermal tumours of the uterus.

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B - Drug Regimen

pazopanib	800 mg	PO	Daily

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

(Outpatient prescription in multiples of 200mg 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.

Patients at risk of tumour lysis syndrome should have appropriate prophylaxis and be monitored closely.

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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. Do not use in patients with uncontrolled hypertension, who have had arterial thromboembolism within the past 6 months, or in patients who have moderate or severe hepatic impairment (Child-Pugh B or C). Also see "Dosage with toxicity" tables below.

Dosage with toxicity

Dose levels: 800mg, 600mg, 400mg, (200mg can be considered if benefit outweighs risk). Doses reduced for toxicity should not be re-escalated.

Toxicity / Event	Action
Mild myelosuppression	Hold until ANC ≥ 1.5 x 10^9/L and Platelets ≥ 100 x 10^9/L
Persistent hypertension despite anti-hypertensive therapy	Reduce dose; see Management of Angiogenesis Inhibitor-Induced Hypertension
Urine protein ≥ 3 grams/24h	Hold until urine protein < 3 grams/24h; restart with ↓ 1 dose level. Discontinue if recurs or develops severe nephrotic syndrome.
Hepatotoxicity	See table below
Serious infections	Consider hold or discontinuing pazopanib
Planned surgery	Hold for at least 7 days pre-surgery
Pnuemonitis/ILD	Hold and investigate. If confirmed, discontinue
Retinal detachment	Hold and refer to ophthalmologist for treatment.* Once resolved, consider risk vs. benefit of restarting. Discontinue if recurs.
Wound dehiscence	Discontinue
Nephrotic syndrome, arterial thromboembolism, significant bleeding, grade 4 related organ toxicity, perforation, fistula, RPLS/PRES, thrombotic microangiopathy	
Uncontrollable or malignant hypertension	

*Recommendation for ocular toxicity with VEGF inhibitors (Renouf 2012)

Hepatic Impairment During Treatment

Patients with baseline bilirubin > 1.5 x ULN and AST/ALT> 2 x ULN or moderate-severe hepatic dysfunction should not start treatment with pazopanib. Avoid concomitant statins.

Bilirubin during treatment		ALT / AST during treatment	Action
		3 – 8 x ULN (isolated ↑)	Continue treatment; LFTs weekly until ≤ grade 1 or baseline
		> 8 X ULN	Hold until ≤ grade 1. May restart if appropriate, ↓ to 400mg once daily; LFTs weekly x 8. Discontinue permanently if LFTs > 3 x ULN recurs.
>2 x ULN*	AND	> 3 x ULN	Discontinue permanently. Monitor liver function until recovery to grade 1 or baseline.
> ULN (isolated ↑) AND no signs and symptoms of liver injury	AND	< ULN	Caution; no dose adjustment needed. Investigate underlying cause.

* if mild and related to Gilbert's syndrome may treat as if isolated AST/ALT elevations.

Hepatic Impairment

Clearance decreased by 50% in patients with moderate hepatic impairment and dose-limiting toxicity was observed at 400mg. Do not start pazopanib in patients with baseline bilirubin > 1.5 x ULN and ALT > 2 x ULN or who have moderate or severe hepatic impairment (Child Pugh B or C). Use caution in patients with mild hepatic impairment.

Patients over age 60 may be at greater risk of elevated liver enzymes (ALT > 3 x ULN).

Renal Impairment

No dose adjustments are recommended for patients with mild or moderate renal impairment. Not recommended for use in patients with severe renal impairment (< 30 mL/min) as it has not been studied in this patient population.

Dosage in the elderly:

No dose adjustment required. Patients over age 60 may be at greater risk of elevated liver enzymes (ALT > 3 x ULN). Although no other differences in response were found between older and younger patients, older patients may be more sensitive to adverse effects.

Dosage based on ethnicity:

Myelosuppression and hand-foot syndrome were observed more frequently in East Asian patients.

Children:

Not recommended for use in children less than 18 years of age. Contraindicated in patients under 2 years of age. Epiphyseal and dental growth abnormalities, severe effects on body weight gain, organ growth and maturation have been observed in animal studies.

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F - Adverse Effects

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

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Diarrhea	• Hyper- / hypoglycemia • Hypertension (may be severe) • Hair or skin colour changes • Abnormal electrolytes • ↑ amylase/ lipase (may be severe) • Nausea, vomiting • Hypothyroidism (biochemical)	• Musculoskeletal pain • Anorexia • Cough/dyspnea • Fatigue • ↑ LFTs (may be severe) • Hemorrhage (may be severe) • Abdominal pain • Headache • Dizziness	• Cardiotoxicity • Venous thromboembolism • Arterial thromboembolism • Artery aneurysm /dissection • ↑QT interval, bradycardia • GI, GU fistula, perforation • RPLS/PRES • Pneumothorax • ILD; Pneumonitis

			• Proteinuria • Thrombotic microangiopathy • Retinal detachment • Pancreatitis • Myelosuppression +/- infection • Tumour lysis syndrome

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G - Interactions

Refer to pazopanib drug monograph(s) for additional details

- Co-administration with inhibitors that simultaneously target PgP, BCRP and/or CYP3A4 (e.g. lapatinib) should be avoided (increased pazopanib exposure)
- Avoid inducers, strong inhibitors, and substrates (especially those with a narrow therapeutic range) of CYP3A4
- Avoid substrates of CYP2C8 and CYP2D6 (especially those with a narrow therapeutic range)
- Avoid inducers and strong inhibitors of PGP and BCRP
- Additive effects are possilbe with drugs that ↑ QT interval, ↑ risk of bleeding, ↑ risk of hepatotoxicity, and those that decrease heart rate
- Avoid drugs that increase the gastric pH (e.g. PPI's) due to decreased pazopanib absorption and exposure

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H - Drug Administration and Special Precautions

Refer to pazopanib drug monograph(s) for additional details

Administration

- Avoid grapefruit, starfruit, Seville oranges, their juices or products during treatment. (See Interactions).
- A missed dose may be taken if there are more than 12 hours until the next dose.
- Swallow tablet(s) whole with a glass of water.
- Do not cut, crush or chew tablets, as this may increase drug exposure and side effects.

- Take each dose on an empty stomach, at least 1 hour before or 2 hours after a meal. Administration with meals doubles exposure

Contraindications:

- Patients who are hypersensitive to the drug or its components
- Patients who have uncontrolled hypertension or have had an arterial thromboembolism within the past 6 months
- Patients who have baseline bilirubin > 1.5 x ULN or AST/ALT > 2 x ULN and/or moderate-severe hepatic impairment
- Patients who have severe renal impairment
- Patients who have had a thrombotic event, history of hemoptysis, cerebral or significant GI bleeding within the past 6 months
- In combination with other anticancer agents (increased toxicity and/or mortality has been observed in combination with pemetrexed or lapatinib)
- Patients less than 2 years of age

Other Warnings/Precautions:

- Patients with risk factors for Torsades de Pointes (history of QT prolongation, antiarrhythmics, medications that prolong the QT interval, cardiac disease, electrolyte disturbances, diabetes or autonomic neuropathy)
- Patients with bradycardia, at increased risk of or a history of thrombotic events or hemorrhage
- Patients at risk of GI perforation or fistula
- Patients with hypothyroidism
- Patients on medications that can lead to bradycardia or which are hepatotoxic
- VEGF inhibitors may impair wound healing; pazopanib should be stopped at least 7 days prior to planned surgery
- Patients over 60 years of age may be at greater risk for ALT >3 X ULN.

Pregnancy & lactation

- Pazopanib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 8 weeks after the last dose for women of childbearing potential.
- Male patients, including those who have had vasectomies, should use condoms during intercourse with female partners who are pregnant or of childbearing potential during treatment and for at least 2 weeks after the last dose.
- Breastfeeding is not recommended.

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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

- 24 hour urine protein in patients with worsening proteinuria; as clinically indicated
- Blood glucose, lipase and amylase; baseline and at each visit
- Blood pressure; 2 readings separated by 24 hours at baseline, within one week after starting pazopanib and at each visit
- CBC; baseline and as clinically indicated
- ECG; baseline and periodic
- Electrolytes, including magnesium, calcium, phosphate; baseline and at each visit
- Liver function tests; baseline, at weeks 2, 4, 6, 8, at months 3 and 4, then periodically as clinically indicated; monitor more frequently in patients with known HLA-B*57-01 allele
- LVEF in patients at risk (including those who have received prior anthracyclines); baseline and periodic
- Renal function tests; baseline and at each visit
- Thyroid function tests; baseline and as clinically indicated
- Urinalysis; baseline and at each visit
- Signs and symptoms of tumour lysis syndrome in patients at risk; baseline and as clinically indicated
- Clinical toxicity assessment of hypertension, pneumonitis, thromboembolism, diarrhea, bleeding, infection, wound healing, fatigue, GI fistula/perforation, lung, neurologic or ocular effects; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Outpatient prescription for home administration

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K - References

Pazopanib drug monograph, Cancer Care Ontario.

Renouf DJ, Velazquez-Martin JP, Simpson R, Siu LL, Bedard PL. Ocular toxicity of targeted therapies. J Clin Oncol. 2012 Sep 10;30(26):3277-86.

Van der Graaf WTA, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2012;

379(9829):1879-86.

October 2020 Updated supportive measures, clinical monitoring and uncommon adverse effects sections

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M - Disclaimer

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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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