Regimen Monograph

A - Regimen Name

TRBC Regimen

Trabectedin

Disease Site	Gynecologic - Uterine Sarcoma Sarcoma - Uterine
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 the treatment of patients with metastatic leiomyosarcoma after failure of prior anthracycline and ifosfamide chemotherapy.

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B - Drug Regimen

trabectedin	1.5 mg /m²	IV over 24 hours	Day 1

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

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:

Also refer to CCO Antiemetic Summary

Premedication with corticosteroids (i.e. dexamethasone 20mg) IV 30 minutes before each trabectedin dose is required, for hepatoprotective and anti-emetic effects.

Consider supportive care/colony stimulating factors for myelosuppression per institutional guidelines.

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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.

Dosage with toxicity

List A

The following criteria must be met before EACH trabectedin treatment.

- ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hemoglobin ≥ 90 g/L
- Bilirubin ≤ ULN, AST and ALT ≤ 2.5 x ULN
- Albumin ≥ 25 g/L
- Creatinine clearance ≥ 30 mL/min (monotherapy)
- ALP (of non-osseous origin) ≤ 2.5 x ULN (consider hepatic isoenzymes 5' nucleotidase or GGT, to distinguish elevations that can be osseous in origin)
- CPK ≤ 2.5 x ULN

Table A - Dose Levels: Reduced doses are not re-escalated. Discontinue if toxicity recurs after 2 dose reductions.

Dose	Trabectedin
Starting dose	1.5 mg/m^2
First reduction	1.2 mg/m^2
Second reduction	1 mg/m^2

Table B - Dose Modifications for Toxicity:

Counts / Toxicity (worst in previous cycles)	Trabectedin Dose**
Grade 4 ANC≥ 5 days or Febrile neutropenia or Platelets < 25 x 10^9/L	↓ 1 dose level
Alkaline phosphatase > 2.5 x ULN (non-osseous)	↓ 1 dose level
AST/ALT > 2.5 x ULN and not recovered by Day 21 or bilirubin > ULN***	↓ 1 dose level
≥ grade 3 non-hematological/organ toxicity	↓ 1 dose level
Any grade rhabdomyolysis or CPK > 2.5 ULN	Hold until recovery, consider discontinuing
Severe hypersensitivity	Discontinue
Capillary leak syndrome	Hold if suspected; discontinue if confirmed and treat according to institutional practice
**Do not treat until laboratory values meet conditions listed in List A and organ/non-hematologic toxicities have recovered to ≤ grade 2. Delay for a maximum of 3 weeks – if not recovered, discontinue. ***Hold trabectedin until normalizes and restart at reduced dose. If not recovered by day 21, discontinue.	

Hepatic Impairment

At baseline:*

Parameter	≥ ULN - < 2.5 x ULN	≥ 2.5 ULN
Bilirubin	Do not treat	Do not treat
AST/ALT	No change	Do not treat
Alkaline Phosphatase	No Change	Do not treat

*Refer to Table B for dose modifications during treatment.

Renal Impairment

CrCl (ml/min)	Trabectedin
30-60	No change
< 30	Discontinue

Dosage in the Elderly

No dose adjustment needed. No differences in safety or effectiveness were seen in patients > 65 years of age versus younger patients.

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F - Adverse Effects

Refer to trabectedin 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
• Nausea and vomiting • Fatigue	• Increased LFTs (may be severe) • Myelosuppression +/- infection, bleeding (may be severe) • Increased CPK	• Anorexia • Constipation • Diarrhea • Headache • Musculoskeletal pain • Phlebitis	• Venous thromboembolism • Cardiotoxicity • Hypersensitivity • Capillary leak syndrome • Hypotension • Rhabdomyolysis • Renal failure

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G - Interactions

Refer to trabectedin drug monograph(s) for additional details

- Trabectedin does not appear to induce or inhibit major CYP450 enzymes, but is metabolized by CYP3A4 and susceptible to inducers or inhibitors.
- Avoid strong CYP3A4 inhibitors if possible, or consider a trabectedin dosage reduction.
- Avoid strong CYP3A4 inducers if possible, or monitor closely for reduced efficacy.
- Avoid high dose phenytoin; monitor for trabectedin toxicity and risk of seizures if used together.
- Avoid alcohol intake while on trabectedin treatment to prevent hepatotoxicity.
- Avoid hepatotoxic drugs and use with caution along with drugs that may cause muscle damage.

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H - Drug Administration and Special Precautions

Refer to trabectedin drug monograph(s) for additional details

Administration:

- Avoid grapefruit, starfruit, Seville oranges, their juices or products (as well as other inhibitors of CYP3A4) during treatment (see Interactions section)
- MUST be administered via central intravenous line.
- Patients must receive corticosteroid premedication 30 minutes before each trabectedin dose (i.e. dexamethasone 20mg IV), as an antiemetic and to protect the liver.
- Reconstitute with sterile water for injection as directed.
- Further dilute in 500mL Normal Saline or D5W.
- Compatible with PVC, glass, polyethylene (PE) containers and tubing.
- Do not mix or dilute with other drugs or solutions.
- Refrigerate unopened vials at 2-8°C.

Contraindications:

- patients who have a hypersensitivity to trabectedin or any of its components
- patients who have active, serious or uncontrolled infections
- patients who have left ventricular injection fraction below the lower limit of normal
- patients with active hepatitis, elevated bilirubin, or who have CPK > 2.5 times the upper limit of normal.

Warnings/precautions:

- Exercise caution in patients with a history of ischemic heart disease or tachyarrhythmia, as trabectedin has been associated with transient heart rate increases
- Avoid live vaccines
- Avoid alcohol, concomitant use of other hepatotoxic drugs or drugs known to cause rhabdomyolysis.

Pregnancy and Lactation:

- Trabectedin is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 3 months after the last dose for females (5 months for males)
- Breastfeeding is not recommended during treatment and for 3 months after the last dose.
- Fertility effects: Probable

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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

- CBC; baseline, prior to each cycle, and weekly for first 2 cycles, then once between cycles
- Liver function tests and CPK; baseline and prior to each cycle, and weekly for the first 2 cycles, then once between cycles
- Renal function tests; baseline and regular
- LVEF; baseline and periodic (especially in patients at risk of cardiac dysfunction)
- Albumin; if capillary leak syndrome suspected
- Assess for cardiac, musculoskeletal, GI, hepatic and local toxicity, as well as VTE, infection and bleeding; at each visit

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

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J - Administrative Information

Pharmacy Workload (average time per visit)	27.855 minutes
Nursing Workload (average time per visit)	76.667 minutes

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K - References

Monk BJ, Blessing JA, Street DG, et al. A phase II evaluation of trabectedin in the treatment of advanced, persistent, or recurrent uterine leiomyosarcoma: a gynecologic oncology group study. Gynecol Oncol. 2012 Jan;124(1):48-52.

Sanfilippo R, Grosso F, Jones RL, et al. Trabectedin in advanced uterine leiomyosarcomas: a retrospective case series analysis from two reference centers. Gynecol Oncol. 2011 Dec;123(3):553-6.

Trabectedin drug monograph, Cancer Care Ontario.

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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.

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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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