Regimen Monograph

A - Regimen Name

IRINTMZL Regimen

IRINTMZL

Disease Site	Sarcoma - Ewing's
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 advanced Ewing's sarcoma, who have relapsed after standard therapies.
Supplementary Public Funding	**temozolomide** ODB - General Benefit (temozolomide)

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B - Drug Regimen

irinotecan	10 to 20* mg /m²/day	IV	Days 1 to 5 and 8 to 12

*pediatric phase I studies used 20mg/m^2 but subsequent studies used 10mg/m^2 because of the lower incidence of dose-limiting diarrhea

temozolomide	100 mg /m²/day	PO	Days 1 to 5

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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

Irinotecan - Cholinergic adverse effects (early diarrhea): Prophylactic atropine may be considered in patients experiencing cholinergic symptoms. Diarrhea (abdominal cramp = diarrhea) may be severe and delayed with Irinotecan; use loperamide 4mg at the onset of diarrhea, then 2mg q2h until patient is diarrhea-free for 12 hours

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

Patients should not be re-treated until recovery from GI toxicity to baseline (without loperamide for at least 24 hours) has occurred, platelets ≥ 100 x 10^9/L, and ANC ≥ 1.5 x 10^9/L.

Dose levels:

irinotecan: 20 mg/m^2, 10 mg/m^2, 5 mg/m^2

temozolomide: 100 mg/m^2, 50 mg/m^2

Dose modifications for worst toxicity in previous cycle		
Grade **(hematologic or non-hematologic toxicity*)**	**Dose during cycle**	**Irinotecan/temozolomide dose for next cycle****
1	No change	No change
2	No change	Reduce by 1 dose level
3 (including febrile neutroprenia, neutropenia or thrombocytopenia) (except rash, pneumonitis)	Omit	Reduce by 1 dose level
any grade 4, recurrent Grade 3, pneumonitis, OR severe rash	Discontinue	Discontinue
Hepatotoxicity	Omit	Assess risk/benefit before continuing treatment. Consider dose reduction.
Hepatitis B	Discontinue	Discontinue if active disease or reactivation.
*Except for alopecia, nausea, vomiting ** New cycles should not be started until ANC is ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L and GI toxicity resolved to baseline (without loperamide for at least 24 h)		

Hepatic Impairment

Irinotecan elimination is decreased in hepatic impairment with increased exposure to the SN-38 metabolite. Patients with bilirubin 1-1.5 x ULN or Gilbert's syndrome are at an increased risk of myelosuppression.

Bilirubin [1]		**Transaminases (AST/ALT)**	**Irinotecan**	**Temozolomide**
22-35 µmoL/L (1-1.5 x ULN) or with Gilbert's syndrome			Monitor closely; may consider dose reduction	No studies performed; monitor
> 35 µmoL/L	OR	>3 x ULN (without liver metastases) or >5 x ULN (with liver metastases)	Usage not recommended.	No studies performed; monitor closely and consider dose modification
[1]Consider investigating for reversible causes such as biliary obstruction and re-evaluate after stent				

Renal Impairment

No studies performed for either irinotecan or temozolomide. No dosage adjustment recommended for mild to moderate renal impairment. Monitor closely with severe renal impairment and consider temozolomide dose modification.

Dosage in the elderly

Monitor patients ≥ 65 years closely for increased risk of diarrhea and myelosuppression.

Dosage based on gender

Decreased clearance of temozolomide and a higher incidence of grade 4 thrombocytopenia or neutropenia may occur in females, especially in the first cycle. Monitor for toxicity.

Children

Use of temozolomide in children has not been approved in North America. Doses used in children are similar to doses used in adults, although the AUC appears to be higher compared to adults. Pediatric patients appeared to tolerate higher plasma concentrations of temozolomide before reaching dose-limiting toxicity, which may likely be due to increased bone marrow reserves. Safety and efficacy of irinotecan have not been established in pediatric patients.

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F - Adverse Effects

Refer to irinotecan, temozolomide drug monograph(s) for additional details of adverse effects

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Increased LFTs (may be severe) • Nausea, vomiting • Fatigue • Alopecia • Abdominal pain • Anorexia, weight loss • Diarrhea (may be severe) • Constipation • Myelosuppression +/- infection (including opportunistic and viral reactivation), bleeding (may be severe) • Headache • Cholinergic symptoms (warmth, rhinitis, lacrimation, increased salivation, diaphoresis or flushing, abdominal cramping and sudden diarrhea) • Cough, dyspnea • Insomnia, somnolence • Dizziness • Rash (may be severe) • Mucositis • Dyspepsia • Edema	• Hypersensitivity • Venous thromboembolism • Arterial thromboembolism • GI obstruction, perforation • Pancreatitis • Pneumonitis • Renal failure • Tumour lysis syndrome • Secondary malignancy • Delayed wound healing

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G - Interactions

Refer to irinotecan, temozolomide drug monograph(s) for additional details

- Monitor carefully with drugs associated with aplastic anemia (e.g. cotrimoxazole, phenytoin)
- Azole antifungals are contraindicated with irinotecan (discontinue at least one week before the first dose)
- Avoid prochlorperazine on the same day as irinotecan given increased risk of akathesia
- Avoid strong inihibitors of CYP3A4 (e.g. macrolide antibiotics, Grapefruit juice)
- Avoid strong inducers of CYP3A4 (e.g. phenytoin, rifampin, St. John's wort - discontinue St. John's wort at least a week prior to irinotecan dose)
- Avoid use with atazanavir and UGT1A1 inhibitors (e.g. sorafenib)
- Use with caution with neuromuscular blockers (e.g. succinylcholine) given risk of prolonged effects

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H - Drug Administration and Special Precautions

Refer to irinotecan, temozolomide drug monograph(s) for additional details

Administration

Irinotecan:

- Mix in D5W (preferred) or NS in a concentration range between 0.12 to 3 mg/mL; some centres give this infusion IV over 60 minutes.
- Do not refrigerate admixtures in NS (may result in precipitation)
- Avoid freezing irinotecan and its admixtures since this may result in drug precipitation.
- Do not admix with other drugs
- Protect from light
- Prior to the initial irinotecan treatment, patients should be given a sufficient supply of loperamide and instructed on its appropriate use.

Temozolomide:

- It is preferable to give temozolomide on an empty stomach, at least one hour before or at least 2 hours after a meal, as this may help reduce nausea and vomiting. Alternatively, it may be given with food; however, administration timing relative to meals should be consistent.
- Capsules must not be opened or chewed, but are to be swallowed whole with a glass of water.

- If vomiting occurs after the dose is administered, do not administer a second dose.
- Store capsules at room temperature (15 to 30°C).

Contraindications

- Patients with a known hypersensitivity to irinotecan, temozolomide or dacarbazine
- Patients with severe myelosuppression
- Patients with active hepatitis B infection
- Patients with ECOG performance status of 3 or 4
- Patients with moderate to severe hepatic dysfunction
- Irinotecan should not be co-administered with azole antifungals (ketoconazole etc, see Interactions section)
- Avoid in patients with hereditary fructose intolerance since the product contains sorbitol
- Avoid the use of live or live attenuated vaccines

Other warnings/precautions

- Elderly patients, patients with poor performance status (= 2), limited marrow reserve, 3rd space accumulation, Gilbert's syndrome and patients with reduced UGT1A1 activity may be more susceptible to the toxic effects of irinotecan; they should be carefully monitored and dose reduction considered.
- The concurrent administration of irinotecan with irradiation is not recommended. Patients with prior pelvic or abdominal irradiation are at an increased risk of severe myelosuppression following irinotecan therapy.
- Temozolomide and irinotecan are not recommended for use in pregnancy. Adequate contraception should beused by both sexes during treatment, and for at least 6 months after the last dose.
- Impaired fertility in males was observed in animals (temozolomide); advice on cryoconservation of sperm should be sought.

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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 and at least weekly
- Liver and renal function tests; baseline and before each cycle
- Hepatitis B screening; baseline. If active, do not treat with temozolomide. If not active, monitor every 1-2 cycles for reactivation & continue for 6 months after treatment discontinuation.
- Clinical toxicity assessment including fatigue, diarrhea and other GI effects, cholinergic effects, infections (including opportunistic (PCP) and viral reactivation

(Hepatitis B)), bleeding, nausea and vomiting, pneumonitis, hypersensitivity, thromboembolism, skin and respiratory toxicity; at each visit

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

Suggested Clinical Monitoring

Blood glucose, especially in patients with diabetes; baseline and regular

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J - Administrative Information

Temozolomide: outpatient administration

Approximate Patient Visit	2.5 hours
Pharmacy Workload (average time per visit)	8.162 minutes
Nursing Workload (average time per visit)	41.667 minutes

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K - References

Irinotecan and temozolomide drug monographs, Cancer Care Ontario.

Blanchette PS, Lo A, Ng P. Irinotecan and temozolomide in adults with recurrent Sarcoma. Journal of Solid Tumors. 2015 July; 5(2): 105-11.

Casey DA, Wexler LH, Merchant MS, et al. Irinotecan and temozolomide for Ewing sarcoma: the Memorial Sloan-Kettering experience. Pediatr Blood Cancer. 2009 Dec;53(6):1029-34.

Ewing sarcoma recurrent or metastatic irinotecan and temozolomide. eviQ (Cancer Institute NSW) Australia, May 2021.

Regimen reference order - Irinotecan + temozolomide. Cancer Care Manitoba, July 2018.

Wagner LM, McAllister N, Goldsby RE, et al. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. Pediatr Blood Cancer. 2007 Feb;48(2):132-9.

August 2021 Modified Drug Administration section (irinotecan)

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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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