Regimen Monograph

A - Regimen Name

IDEL+RITU Regimen

Idelalisib-rituximab

IDEL(MNT) Regimen

Idelalisib

Disease Site

Hematologic
Leukemia - Chronic Lymphocytic (CLL)

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 relapsed chronic lymphocytic leukemia (CLL) who are not fit to receive cytotoxic treatment. Idelalisib is contraindicated for first line treatment of CLL as clinical trials have shown shorter survival and increased adverse effects.

Rituximab is only funded by NDFP if used in combination with idelalisib. Rituximab-idelalisib is not funded for patients whose disease has progressed on ibrutinib in the relapsed setting (and vice-versa). See the NDFP and EAP funding criteria for details.

Supplementary Public Funding

idelalisib
Exceptional Access Program (idelalisib - For the treatment of relapsed chronic lymphocytic leukemia, in combination with rituximab, according to specific clinical criteria) (EAP Website)

riTUXimab
New Drug Funding Program (Rituximab (Biosimilar IV) - In Combination with Idelalisib - Relapsed Chronic Lymphocytic Leukemia) (NDFP Website)

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B - Drug Regimen

Note: Different rituximab products are NOT INTERCHANGEABLE.

idelalisib	150 mg	PO	BID
riTUXimab[1]	375 mg /m²	IV	Day 1, Week 1
THEN			
riTUXimab[1]	500 mg /m²	IV	Day 1, Weeks 3, 5, 7, 9, 13, 17, 21 (total 8 infusions)

(1) Consider slower infusion rate or split dosing over days 1-2 (± corticosteroids) for any cycle where high tumour load or WBC > 25 x 10^9/L

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C - Cycle Frequency

Rituximab is given for a total of 8 doses as per the above schedule.

Idelalisib should be given continuously until disease progression. (Use regimen code IDEL(MNT) for single-agent idelalisib post-IDEL+RITU combination treatment).

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Other Supportive Care:

- **Screen for hepatitis B virus in all cancer patients starting systemic treatment.** Refer to the hepatitis B virus screening and management guideline.
- If high volume disease, consider steroids and prophylaxis for tumour lysis.

For idelalisib:

- A supply of loperamide should be provided for diarrhea.
- Advise patients to avoid sun exposure or use sufficient sun protection.
- Antibiotic prophylaxis for PCP/PJP is required during treatment and for 2 to 6 months after discontinuation of treatment.

Premedication (prophylaxis for infusion reactions):

Administer at least 30 minutes prior to rituximab:

- Oral antipyretic (e.g. acetaminophen)
- H1-receptor antagonist (e.g. diphenhydramine)
- Corticosteroid (e.g. methylprednisolone 80 mg IV) in patients with high bulk disease or pulmonary involvement if no corticosteroids are already being given as part of the chemotherapy regimen.

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E - Dose Modifications

Refer to protocol by which patient is being treated. Rituximab infusion should be administered in a setting where full resuscitation facilities are immediately available, and under the close supervision of someone experienced and capable of dealing with severe infusion-related reactions. **Rituximab must not be administered as an IV bolus or push.**

See premedication and monitoring sections for supportive care, screening and monitoring recommendations.

Dosage with toxicity

Dose levels for idelalisib: 150 mg twice daily, 100 mg twice daily, if further dose reductions are required, discontinue.

Dose modifications should be made for the drug thought to be causally related.

Toxicity	Grade	Idelalisib	Rituximab
Neutropenia	3	Maintain dose. Consider G-CSF support.	Maintain dose.
	4 for ≥ 14 days or febrile neutropenia or infection	Consider G-CSF support. If G-CSF used may hold or continue at same dose or reduce 1 dose level. If not used, hold until ANC ≥ 0.5 x 10^9/L then restart with a 1 dose level reduction.	May hold for up to 4 weeks
Thrombocytopenia or thrombocytopenic bleeding	4	Hold until ≤ grade 3. Restart with a 1 dose level reduction	Hold until platelets ≥ 25 x 10^9/L. Restart at previous dose. If delay is > 4 weeks, discontinue.
Rash	2	Hold until < grade 1. Restart at same dose.	Hold until < grade 1. Restart at same dose.
	3 or 4	Hold until < grade 1. Restart with 1 dose level reduction Discontinue if severe cutaneous reactions or SJS/TEN confirmed and treat appropriately.	Hold until < grade 1. Restart at previous dose Discontinue for severe mucocutaneous reactions and treat appropriately.
Diarrhea	1	Provide supportive care (e.g. loperamide) and maintain dose.	Maintain dose
	2	Provide supportive care (e.g. loperamide) and hold until ≤ grade 1. Restart at same dose.	Maintain dose

	3 or 4	Hold until ≤ grade 1 then restart with a 1 dose level reduction. Provide supportive care (e.g. loperamide). Consider adding anti-inflammatory (e.g. budesonide, sulfasalazine)	Grade 3: hold until stable. Restart at previous dose. Grade 4: discontinue
AST/ALT elevation	1-2	Maintain dose	Maintain dose
	3-4	Hold until ≤ grade 1 then restart with a 1 dose level reduction. Discontinue for recurrent hepatotoxicity.	Grade 3: hold until stable. Restart at previous dose. Discontinue if grade 4 or signs of hepatitis.
Pneumonitis / organizing pneumonia	any grade	Hold and evaluate for respiratory symptoms. • If no infectious origin found and pneumonitis is likely drug-related, discontinue idelalisib. Consider steroids especially if severe • If infectious origin found, monitor/treat until resolved. Restart at 1 dose level reduction.	Grade 1-2: Hold until stable. Restart at previous dose. Grade 3-4: discontinue
CMV infection/viremia		Discontinuation if evidence of CMV infection or viremia (positive PCR or antigen test)	Discontinue
Signs and symptoms of PML	Any	Hold and investigate; refer to neurologist. Discontinue if confirmed.	
Signs and symptoms of PCP/PJP		Discontinue	Discontinue
Serious/life-threatening cardiopulmonary events; Reactivation of tuberculosis or hepatitis B; PRES		Discontinue	Discontinue

Other non-hematological toxicity	3 or 4	Hold until ≤ grade 1 then restart with a 1 dose level reduction.	Hold until ≤ grade 2, then restart at the previous dose. Grade 4: discontinue

Management of Infusion-Related Reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

IV rituximab:

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion. • Manage the symptoms. **Restart:** • Once symptoms have resolved, restart at 50% of the rate at which the IR occurred.	• Re-challenge at 50% of the administration rate at which the IR occurred and with pre-medications. • Consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Consider clinical benefit and risks of further treatment. Consider patient factors, severity and nature of the IR and availability of suitable alternative treatment. • Consider desensitization for patients with recurrent reactions despite pre-medications and a slower infusion rate.

Hepatic Impairment

No dosage adjustment is required for idelalisib in mild to moderate hepatic impairment. Insufficient data for patients with severe hepatic impairment. No dosage adjustment required for rituximab. Discontinue if evidence of hepatitis.

Renal Impairment

No dosage adjustment is required for idelalisib or rituximab.

Dosage in the Elderly

No dosage adjustment is required for elderly patients. The incidence of severe adverse events with idelalisib was higher among patients aged 65 and older compared to younger patients, but age had no clinically relevant effect on drug exposure. Older patients are more likely to experience serious adverse events (including cardiac, pulmonary, or other grade 3/4 toxicity) with rituximab.

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F - Adverse Effects

Refer to idelalisib, riTUXimab 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
• Hypersensitivity (with rituximab; may be severe) • Increased triglycerides • Increased LFTs (may be severe)	• Diarrhea (may be severe) • Fatigue • Cough, dyspnea (may be severe) • Nausea, vomiting • Fever • Abdominal pain • Myelosuppression	• Rash (may be severe) • Anorexia • Headache • Insomnia • Edema • Hypotension (with rituximab)	• Venous thromboembolism • Arterial thromboembolism • Arrhythmia • Cardiotoxicity • GI obstruction/perforation • Hemolysis

	+/- infection (including atypical, viral reactivation), bleeding (may be severe)	• Flu-like symptoms (with rituximab)	• Vasculitis • Nephrotoxicity • PRES • PML • Tumour lysis syndrome • Pneumonitis (including organizing pneumonia)

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G - Interactions

Refer to idelalisib, riTUXimab drug monograph(s) for additional details

- Antihypertensive agents may potentiate hypotension with rituximab; consider withholding 12 hours before and during the infusion.
- Use with caution with cisplatin; monitor renal function closely
- Idelalisib is a substrate for CYP3A4 and is susceptible to drugs interactions with inducers and inhibitors of this isoenzyme. Avoid strong CYP3A4 inducers and inhibitors where possible.
- Idelalisib is also a CYP3A4 inhibitor. Caution and monitor with substrates that have a narrow therapeutic index.
- Idelalisib may reduce the effectiveness of oral contraceptives. Caution and consider an alternative method of contraception.

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H - Drug Administration and Special Precautions

Refer to idelalisib, riTUXimab drug monograph(s) for additional details

Administration

Note: Different rituximab products are NOT INTERCHANGEABLE.

Rituximab IV and subcutaneous formulations are not interchangeable. The dosing and concentrations of these products are different.

Rituximab should be administered in a setting where full resuscitation facilities are immediately available, and under the close supervision of someone experienced and capable of dealing with severe infusion-related reactions.

Rituximab (IV)

- DO NOT administer as an IV push or bolus.
- Dilute to a final concentration of 1-4 mg/mL in normal saline or D5W.
- To avoid foaming, gently invert the bag to mix the solution.
- Do not admix with other drugs.
- Administer rituximab through a dedicated line.
- Compatible with PVC or polyethylene bags.

Infusion rates:

First infusion:

- Recommended to be administered over a graduated rate: initial rate of 50 mg/h, then escalate rate in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h (about 4.25 hours in total).

Subsequent infusions:

- If no severe infusion reaction (grade 3 or 4) occurred with the first cycle, a rapid infusion of IV rituximab over a total of 90 minutes can be initiated with cycle 2 (20% of the dose in the first 30 min then the remaining 80% over 60 min).
- OR initial rate of 100 mg/h, then escalate rate in 100 mg/h increments every 30 minutes, to a maximum of 400 mg/h as tolerated (about 3.25 hours in total).
- Alternatively, subcutaneous administration of rituximab can be considered starting with cycle 2.

When bulky disease present or WBC > 25-50 x 10^9/L, consider:

- A slower infusion rate, or
- Split dosing over days 1-2, or
- Delaying rituximab treatment until chemotherapy has reduced the lymphocyte count

Idelalisib:

- May be administered with or without food
- If a dose is missed, it may be taken within 6 hours of the missed dose. If a dose is missed by more than 6 hours, it should not be taken; the next dose should be taken as scheduled.

- Dispense only in original container with intact seal and store below 30^{o}C.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications

- Idelalisib is contraindicated in first-line CLL outside of a clinical trial and in patients with hypersensitivity to the drug or its components.
- Rituximab is contraindicated in patients with known hypersensitivity and anaphylactic reactions to proteins of similar mouse or human origin, to Chinese Hamster Ovary (CHO) cell proteins or to any component of this product.

Warnings/precautions

- Idelalisib should not be started in patients with any evidence of ongoing systemic bacterial, fungal or viral infections.
- Idelalisib is not recommended in patients with ongoing inflammatory bowel disease, active hepatitis or liver disease.
- Exercise caution with rituximab in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection.
- Prior to starting rituximab in HBV seropositive patients, consultation with a liver disease expert is recommended to determine ongoing monitoring of HBV reactivation and its management.
- Exercise caution in patients with neutrophil counts < 1.5 x 10^{9}/L and/or platelets < 75 x 10^{9}/L due to limited experience in this patient group.
- Use with extreme caution in patients with pre-existing cardiovascular disease or in patients with high tumour burden.
- Use with caution in patients with pulmonary insufficiency or lung tumour infiltration, and in patients with myelosuppression.

Pregnancy & lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).

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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.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; baseline, every 2 weeks for the first 6 months, and at least weekly in patients with grade 3 or 4 ANC or platelets
- Liver function tests; baseline, every 2 weeks for the first 3 months, thereafter every 1 to 3 months, and as clinically indicated. At least weekly with hepatotoxicity.
- CMV serology (PCR and antigen); baseline and regular
- Renal function tests; baseline and at each visit
- Clinical assessment of infusion reactions with rituximab, hypersensitivity, infection (including opportunistic, CMV), bleeding, GI, pulmonary, skin, CNS, cardiovascular and respiratory toxicity, tumour lysis syndrome; at each visit

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

Suggested Clinical Monitoring

Monitor cardiovascular symptoms in patients who have cardiac conditions or recurrent cardiac events with rituximab; at each visit

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J - Administrative Information

Outpatient prescription for home administration (idelalisib)

Approximate Patient Visit
IDEL+RITU 3 to 5 hours

Pharmacy Workload **(average time per visit)**
IDEL+RITU 20.946 minutes

Nursing Workload **(average time per visit)**
IDEL+RITU 69.167 minutes

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K - References

Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014 Mar 13;370(11):997-1007.

Idelalisib and rituximab drug monographs, Cancer Care Ontario.

PEBC Advice Documents or Guidelines

- Rituximab in Lymphoma and Chronic Lymphocytic Leukemia

November 2023 Modified Pregnancy/lactation section

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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.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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