Regimen Reference Order

LYMP – Dose Adjusted R-EPOCH (*CYCLE 2 and Onwards*)

ARIA: LYMP – [R-EPOCH – predniSONE 4]
LYMP – [R-EPOCH(Dose Lvl -2) pred 9]
LYMP – [R-EPOCH(Dose Lvl -1) pred 9]
LYMP – [R-EPOCH(Dose Lvl +1) pred 9]
LYMP – [R-EPOCH(Dose Lvl +2) pred 9]
LYMP – [R-EPOCH(Dose Lvl +3) pred 9]
LYMP – [R-EPOCH(Dose Lvl +4) pred 9]
LYMP – [R-EPOCH(Dose Lvl +5) pred 9]
LYMP – [R-EPOCH(Dose Lvl +6) pred 9]

This RRO is for Cycles 2 to 6 of regimen LYMP – Dose Adjusted R-EPOCH
For Cycle 1, see RRO LYMP – Dose Adjusted R-EPOCH (CYCLE 1 ONLY)

Planned Course: **Every 21 days for 6 cycles**
Indication for Use: **Aggressive B Cell Lymphoma**

CVAD: PICC Required (double lumen preferred)

Proceed with treatment if:
ANC equal to or greater than 1 x 10^9/L AND Platelets equal to or greater than 75 x 10^9/L
- **Contact Hematologist if parameters not met**

SEQUENCE OF MEDICATION ADMINISTRATION

Pre-treatment Requirements

Drug	Dose	CCMB Administration Guideline
Instruct patient to start vigorous oral pre-hydration (600-900 mL) the morning of cyclophosphamide treatment **(Self-administered at home)**		

Treatment Regimen – Dose-Adjusted R-EPOCH (CYCLE 2 and Onwards)

Establish primary solution 500 mL of: normal saline

Drug	Dose	CCMB Administration Guideline
Cycle 2 and Onwards		
Days 1 to 5 (HIV serology negative) or Days 2 to 5 (HIV serology positive)		
predniSONE	60 mg/m^2	*For HIV serology negative patients*: Orally at supper on **Day 1** and then twice daily on **Days 2 to 5** inclusively (9 doses total) *For HIV serology positive patients*: Orally once daily at breakfast on **Days 2 to 5** inclusively (4 doses total) **(Self-administered at home)**

Day 1		
cetirizine	10 mg	Orally 30 minutes prior to riTUXimab
acetaminophen	650 mg	Orally 30 minutes prior to riTUXimab
dexamethasone	12 mg	IV in normal saline 50 mL over 15 minutes
Wait 30 minutes after completion of IV pre-medication(s) before starting riTUXimab		
riTUXimab (Subcutaneous)	1400 mg (1400 mg = 11.7 mL)	**Subcutaneous**: Administer over 5 minutes into abdomen Syringe should be held in hand for 5 minutes to warm up and decrease viscosity Use 25G needle **Nursing Alert: Ensure subcutaneous riTUXimab formulation is used (riTUXimab-hyaluronidase, human)*
	OR	
riTUXimab (IV brand name specific)	375 mg/m^2	**Rapid infusion:** IV in normal saline over 90 minutes: Infuse 50 mL of a 250 mL bag (or 100 mL of a 500 mL bag) over 30 minutes, then infuse the remaining 200 mL (or 400 mL of a 500 mL bag) over 60 minutes **Nursing Alert: IV tubing is primed with riTUXimab* **Alert: Ensure brand name on prescription label (indicated in brackets on prescription label) matches prescribed order* **Alert: riTUXimab infusion must be complete prior to CADD-Solis VIP ambulatory pump connect* **Alert: Pharmacy to ensure final volume on label*
		OR
		Slow infusion: IV made up to a final concentration of 1 mg/mL in normal saline. Start at 100 mg/hr for 30 minutes and escalate infusion rate in 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr **Nursing Alert: IV tubing is primed with riTUXimab* **Alert: Ensure brand name on prescription label (indicated in brackets on prescription label) matches prescribed order* **Alert: riTUXimab infusion must be complete prior to CADD-Solis VIP ambulatory pump connect* **Alert: Pharmacy to ensure final volume on label*
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
DOXOrubicin + vinCRIStine + etoposide	See *Appendix A* for Drug Dosing	**If dose of etoposide is equal to or less than 150 mg:** IV over 24 hours via CADD-Solis VIP ambulatory pump DOXOrubicin, vinCRIStine and etoposide will be admixed in normal saline 500 mL bag with CADD-Solis VIP pump programmed as follows: **Reservoir Volume = 552 mL; Rate = 23 mL/hour** *Use non-DEHP bags and non-DEHP administration sets* ****Alert: DOXOrubicin, vinCRIStine and etoposide are compounded in same bag***

DOXOrubicin + vinCRIStine + etoposide	See *Appendix A* for Drug Dosing	**OR** **If dose of etoposide is greater than 150 mg:** IV over 24 hours via CADD-Solis VIP ambulatory pump DOXOrubicin, vinCRIStine and etoposide will be admixed in normal saline 1000 mL bag with CADD-Solis VIP pump programmed as follows: **Reservoir Volume = 1056 mL; Rate = 44 mL/hour** *Use non-DEHP bags and non-DEHP administration sets* **Alert:* ***DOXOrubicin, vinCRIStine and etoposide are compounded in same bag***
Days 2, 3 and 4		
DOXOrubicin + vinCRIStine + etoposide	See *Appendix A* for Drug Dosing	**If dose of etoposide is equal to or less than 150 mg:** IV over 24 hours via CADD-Solis VIP ambulatory pump DOXOrubicin, vinCRIStine and etoposide will be admixed in normal saline 500 mL bag with CADD-Solis VIP pump programmed as follows: **Reservoir Volume = 552 mL; Rate = 23 mL/hour** *Use non-DEHP bags and non-DEHP administration sets* **Alert:* ***DOXOrubicin, vinCRIStine and etoposide are compounded in same bag***
		OR **If dose of etoposide is greater than 150 mg**: IV over 24 hours via CADD-Solis VIP ambulatory pump DOXOrubicin, vinCRIStine and etoposide will be admixed in normal saline 1000 mL bag with CADD-Solis VIP pump programmed as follows: **Reservoir Volume = 1056 mL; Rate = 44 mL/hour** *Use non-DEHP bags and non-DEHP administration sets* **Alert:* ***DOXOrubicin, vinCRIStine and etoposide are compounded in same bag***
Day 5 (for patients who receive Dose Level -2, -1, 1, 2 or 3)		
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
cyclophosphamide	See *Appendix A* for Drug Dosing	IV in normal saline 500 mL over 2 hours
OR		
Day 5 (for patients who receive Dose Level 4, 5 or 6)		
normal saline	500 mL	IV over 1 hour (Pre hydration)
ondansetron	16 mg	Orally 30 minutes pre-chemotherapy
mesna	See *Appendix A* for Drug Dosing	IV in normal saline 50 mL over 15 minutes immediately prior to cyclophosphamide
cyclophosphamide	See *Appendix A* for Drug Dosing	IV in normal saline 500 mL over 2 hours **Alert: start of cyclophosphamide infusion will be considered "Hour 0"*

normal saline	500 mL	IV over 2 hours from "Hour 2" to "Hour 4"
mesna	See *Appendix A* for Drug Dosing	IV in normal saline 50 mL over 15 minutes at "Hour 4"
mesna	See *Appendix A* for Drug Dosing	Orally with juice or soft drink at "Hour 6" **(Self-administered at home)** **Nursing Alert: Inform patient time to take dose*
Patients will receive methotrexate Intrathecal Therapy with this regimen **(See *Appendix B* – Intrathecal Therapy (IT) For CNS Negative Lymphoma)** **OR** **(See *Appendix B* – Intrathecal Therapy (IT) For CNS Positive Lymphoma)**		
All doses will be automatically rounded that fall within the DSG Approved Dose Bands. See LYMP DSG – Dose Banding document for more information		

In the event of an infusion-related hypersensitivity reaction, refer to the **'Hypersensitivity Reaction Standing Order'**

REQUIRED MONITORING

Cardiac Monitoring

- Left Ventricular Ejection Fraction (LVEF) monitoring is recommended at baseline at physician's discretion and as clinically indicated

All Cycles

Day 1

- CBC, serum creatinine, urea, electrolytes, liver enzymes, LDH, total bilirubin, uric acid, glucose and albumin as per Physician Orders

Days 8 to 21

- CBC, serum creatinine, urea, electrolytes, liver enzymes, LDH, total bilirubin, uric acid, glucose and albumin as per Physician Orders twice weekly beginning Day 8
- INR on Day 15 (or later, prior to Lumbar Puncture (LP))

Transfusion parameters

- Hemoglobin: Transfuse 1 unit packed red blood cells for hemoglobin less than 80 g/L
- Platelets: Transfuse platelets if platelets less than 10 x 10^9/L or if platelets are between 10 to 20 x 10^9/L and patient is febrile. If the platelets are between 10 to 50 x 10^9/L and there are symptoms of bleeding, then the hematologist should be notified to discuss platelet transfusion

INTRAVENOUS riTUXimab

- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O_2 saturation) prior to each dose and as clinically indicated
- No observation period is required. Patient can be discharged from treatment room if stable whether they had a reaction or not

SUBCUTANEOUS riTUXimab

- Full vital signs (temperature, heart rate, respiratory rate, blood pressure and O_2 saturation) prior to each dose, at discharge and as clinically indicated
- **15 minute observation period required after each dose**

Recommended Support Medications

Drug	Dose	CCMB Administration Guideline
filgrastim (brand name specific) *(See Filgrastim Clinical Guide)*	5 mcg/kg (rounded to nearest 300 mcg or 480 mcg)	Subcutaneously once daily until ANC greater than 5 x 10^9/L post nadir to start on Day 8
omeprazole	20 mg	Orally once daily for 21 days as needed
Senokot-S	2 tablets	Orally twice daily as needed for constipation
ondansetron	8 mg	Orally every 12 hours as needed for nausea and vomiting
sulfamethoxazole-trimethoprim	800/160 mg	Orally twice daily on Saturdays and Sundays only
zopiclone	7.5 mg	Orally at bedtime as needed for sleep

DISCHARGE INSTRUCTIONS

- Patients should be instructed to contact their cancer team immediately if symptoms of hypersensitivity reactions occur after discharge
- Ensure patient has the correct time to come for replacement of intravenous bag and pump disconnect/reconnect on Days 2, 3, 4 and 5
- Instruct patient to keep infusion bag upright at all times to prevent air in line
- Nurse to provide patient with container to place infusion bag in overnight. Place container on table or chair next to bed
- Instruct patient to check ambulatory pump 4 times per day to ensure drug is infusing
- Clinic nurse to provide patient with blood work and intrathecal appointments
- Instruct patient to:
    - Continue taking anti-emetic(s) at home
    - Maintain oral intake of 2000 mL (8 glasses) of fluid daily at home
    - Empty bladder every 2 hours while awake and at bedtime for 24 hours after each dose of cyclophosphamide
    - Obtain immediate assistance as per your clinic's contact instructions if:
        - Symptoms of hemorrhagic cystitis (e.g. dysuria, hematuria)
        - Unable to drink recommended amount of fluid
    - For patients who receive Dose Level 4, 5 or 6: Self-administer "Hour 6" of mesna by mixing the contents of the mesna syringe in juice or soft drink. If patient vomits within 2 hours of taking "Hour 6" mesna, they should be advised to contact their cancer team. Patient may require intravenous hydration
- predniSONE is a cancer therapy in this treatment regimen. Remind patient to take predniSONE at home
- Remind patient to take sulfamethoxazole-trimethoprim (*Pneumocystis jirovecii* pneumonia prophylaxis) at home
- Reinforce applicable safe handling precautions of medications, blood and body fluids for 48 hours after completion of chemotherapy

ADDITIONAL INFORMATION

- DOXOrubicin is cardiotoxic
- Cumulative DOXOrubicin dose should be calculated and should not exceed 450 mg/m^2
- Administering nurse must document any infusion-related reactions with any dose of riTUXimab
- Ensure there were **no Grade 3 or 4** infusion-related reactions with any previous dose prior to administering riTUXimab via subcutaneous injection or rapid infusion
- Intravenous riTUXimab formulation is available from more than one manufacturer and uses several different brand names. Brand name will be indicated in brackets after riTUXimab. **Ensure prescription label matches the brand name on prescribed order for intravenous riTUXimab**
- Preference is given to a Monday start for each cycle. If treatment begins on Tuesday, then Day 5 cyclophosphamide must be administered at CCMB MacCharles on Saturday
- Beginning Cycle 4 onwards: Notify treatment room if patient will receive Dose Levels 4, 5 or 6 to ensure adequate treatment time is booked for patient

Appendix A

Drug Dosing – HIV serology negative patients

For **HIV serology negative patients**, physician to use the following tables for doses:

Drugs	Drug Doses per Dose Levels							
	-2	**-1**	**1**	**2**	**3**	**4**	**5**	**6**
DOXOrubicin (mg/m^2/day)	10	10	10	12	14.4	17.3	20.7	24.8
vinCRIStine (mg/m^2/day) (no cap)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
etoposide (mg/m^2/day)	50	50	50	60	72	86.4	103.7	124.4
cyclophosphamide (mg/m^2)	480	600	750	900	1080	1296	1555	1866
mesna IV prior to cyclophosphamide and "Hour 4" (mg/m^2/dose)						260	310	370
mesna PO "Hour 6" (mg/m^2)						520	620	740

Dose Escalation

- The doses are escalated 20% above last cycle. The 20% dose escalation is based on the previous dose received (i.e. compounded dose escalation)
- Dose adjustments above level 1 apply to DOXOrubicin, etoposide and cyclophosphamide
- Dose adjustments below level 1 apply to cyclophosphamide **ONLY**
- Drug doses are based on previous cycle ANC and platelet nadir, as follows:

Drug doses based on previous cycle ANC and platelet nadir

Nadir blood counts	**Dose adjustments**
If nadir ANC equal to or greater than 0.5 x 10^9/L	Increase 1 dose level above last cycle
If nadir ANC less than 0.5 x 10^9/L	Same dose level as last cycle
If nadir platelets less than 25 x 10^9/L	Decrease 1 dose level below last cycle

Drug Dosing – HIV serology positive patients

For **HIV serology positive patients**, physician to use the following tables for doses:

Drugs	Initial Dose (Dose Level 1)
DOXOrubicin	10 mg/m^2/day
vinCRIStine	0.4 mg/m^2/day (no cap)
etoposide	50 mg/m^2/day
cyclophosphamide	750 mg/m^2

Dose Escalation

- DOXOrubicin, vinCRIStine and etoposide doses do not increase (remain at Dose Level 1)
- cyclophosphamide doses are based on previous cycle blood work, as follows:

cyclophosphamide dose based on previous cycle blood work*

Blood counts (based on twice weekly blood counts)	cyclophosphamide dose adjustments
If nadir ANC less than 0.5 x 10^9/L lasting 2 to 4 days	Reduce cyclophosphamide dose by 25% of initial dose (Reduce by 187 mg/m^2)
If nadir platelets less than 25 x 10^9/L lasting 2 to 4 days	Reduce cyclophosphamide dose by 25% of initial dose (Reduce by 187 mg/m^2)
If nadir ANC less than 0.5 x 10^9/L lasting 5 or more days	Reduce cyclophosphamide dose by 50% of initial dose (Reduce by 375 mg/m^2)
If nadir platelets less than 25 x 10^9/L lasting 5 or more days	Reduce cyclophosphamide dose by 50% of initial dose (Reduce by 375 mg/m^2)

***Note:** In the event that the cyclophosphamide dose had been reduced on the previous cycle, it may be increased on the next cycle if the following criteria are met: If nadir ANC greater than 0.5 x 10^9/L and nadir platelets greater than 25 x 10^9/L, then increase cyclophosphamide dose by 187 mg/m^2 each cycle (up to a maximum of full dose (750 mg/m^2)).

Appendix B

Initial lumbar puncture (LP)

- Most patients should have an initial diagnostic lumbar puncture prior to initiation of Cycle 1
- If using this regimen for Primary Mediastinal Lymphoma, CNS investigation/prophylaxis is only required if high risk
- The initial lumbar puncture specimen needs to be sent for cell count with differential, protein, glucose, flow cytometry (must ensure sample received by lab no later than 14:00 Monday to Thursday and prior to 11:00 a.m. Friday)
- No need for cytology on CSF sample
- Tube 1 = 2 mL for protein and glucose
- Tube 2 = 2 mL for cell count with differential
- All patients with neurological symptoms (or abnormal initial lumbar puncture) should have MRI brain/spine in addition to initial lumbar puncture

Intrathecal Therapy (IT) – For Central Nervous System (CNS) Negative Lymphoma

Proceed with treatment if:

- ***Platelets equal to or greater than 50 x 10^9/L AND INR is less than 1.5***

Note: CBC and INR results must be within 1 week of intrathecal administration

A total of 6 intrathecal methotrexate doses will be given to CNS Negative Lymphoma patients (diagnostic lumbar puncture counts as one of the six intrathecal treatments)

Drug	Dose	CCMB Administration Guideline
methotrexate	12 mg	Intrathecal in 6 mL preservative free normal saline administered in Lymphoma Clinic

Note: Intrathecal is ordered as a separate support regimen

CNS negative patients

- A total of 6 prophylactic treatments is recommended with methotrexate 12 mg. The diagnostic lumbar puncture counts as one of the six intrathecal treatments that are required
- Hematologist may give IT once every cycle for 6 cycles
- With 2nd to 6th lumbar punctures, specimens should be sent for (unless instructed otherwise by hematologist) protein, glucose and cell count with differential. Do not send 2nd to 6th lumbar punctures for flow cytometry or microbiology
- Tube 1 = 2 mL for protein and glucose
- Tube 2 = 2 mL for cell count with differential

Intrathecal Therapy (IT) – For Central Nervous System (CNS) Positive Lymphoma

Proceed with treatment if:

- ***Platelets equal to or greater than 50 x 10^9/L AND INR is less than 1.5***

Note: CBC and INR results must be within 1 week of intrathecal administration

Intrathecal methotrexate given:

- **Twice weekly for 2 weeks past the first negative cytology** (with a minimum of 4 weeks of intrathecal treatment (minimum 8 doses)), then
- **Weekly for 6 weeks**, then
- **Every 4 weeks for 6 months**

Drug	Dose	CCMB Administration Guideline
methotrexate	12 mg	Intrathecal in 6 mL preservative free normal saline administered in Lymphoma Clinic

Note: Intrathecal is ordered as a separate support regimen

CNS positive patients

- Intrathecal methotrexate twice weekly for 2 weeks past the first negative cytology with a minimum of 4 weeks of intrathecal treatment (minimum 8 doses). Then, intrathecal methotrexate weekly for 6 weeks and then every 4 weeks for 6 months
- Depending on clinical circumstance, an alternative regimen may be considered
- Tube 1 = 2 mL for protein and glucose
- Tube 2 = 2 mL for cell count with differential