UKALL14v12 Consolidation Phase Cycle 1

This is a clinical trial protocol intended for off-trial use.

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Treatment of adult patients** (aged 25–65 years)*** with newly diagnosed, previously untreated acute lymphoblastic leukaemia (ALL) treated on UKALL14-protocol who are in remission but not eligible for allogeneic transplantation following treatment with Intensification/CNS Prophylaxis regimen	C91	00877a	Imatinib – CDS Other drugs - N/A

* This applies to post 2012 indications

**** riTUXimab[i] to be included in CD20 positive patients (in general >20% positivity)**

TREATMENT:

Table 1: UKALL14 treatment schedule

Phase 1 Standard induction	Phase 2 Standard induction	Intensification / CNS Prophylaxis	Consolidation Phase Cycle 1	Consolidation Phase Cycle 2	Consolidation Phase Cycle 3	Consolidation Phase Cycle 4	Maintenance

***It may sometimes be used in patients ≥ 19 years with Philadelphia Chromosome positive acute lymphoblastic leukaemia.

Patients being treated for ALL require complex inpatient care in a designated cancer centre with comprehensive multidisciplinary team (MDT) availability.

The consolidation phase consists of 4 cycles. This regimen contains details for cycle 1 only (Cycle is 21 days).

- Cycle 1 consolidation typically begins after intensification therapy, when ANC >0.75 x 10^9/L and platelets >75 x 10^9/L **(Refer to NCCP regimen 00876 UKALL 14v12 Intensification/CNS Prophylaxis Therapy)**

Note: Patients with central nervous system involvement

- Cranial irradiation typically will be considered before consolidation begins.
- Maintenance therapy with 6-mercaptopurine should be given throughout the period of CNS irradiation
  - In the event of cytopenias, 6-mercaptopurine should be reduced or omitted rather than radiotherapy being delayed
  - The dose of 6-mercaptopurine should not be increased as per the maintenance protocol but should be continued at 75mg/m^2 in the absence of cytopenias

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Day	Drug	Dose	Route	Diluent & Rate
1, 8[a]	riTUXimab (**CD20 positive patients** ONLY)	375mg/m^2	IV infusion[b] Observe post infusion[b]	500mL NaCl 0.9% at a maximum rate of 400mg/hour
1-5	Cytarabine	75mg/m^2	IV infusion	100mL NaCl 0.9% over 30 minutes[c]
1-5	Etoposide	100mg/m^2	IV infusion	1000mL NaCl 0.9% over 60 minutes[d]
1	Methotrexate	12.5mg	Intrathecal[e]	n/a
5 only	PEG-asparaginase **(Philadelphia negative patients ONLY) Patients >40 years old, use with caution**	1000 IU/m^2	IV infusion	100mL NaCl 0.9% over 2 hours
1-21	Imatinib **(Philadelphia positive patients ONLY)**	600mg[f]	PO	n/a
[a] Administration day may be amended at the discretion of the prescribing Consultant				
[b] See Table 2: Guidance for riTUXimab administration				
[c] May also be given by slow IV bolus (concentration of 20mg/mL)				
[d] Etoposide final concentration 0.2-0.4 mg/mL				
[e] Refer to **NCCP Guidance on the Safe Use of Intrathecal Chemotherapy in the Treatment of Cancer** -available on the NCCP website Timing of intrathecal therapy can be moved +/- 3 days**.**				
[f] Patient may require 400mg dose if 600mg not tolerated				

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

Table 2: Guidance for riTUXimab administration

The recommended initial rate for infusion is 50 mg/hour; after the first 30 minutes, it can be escalated in 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour. Subsequent infusions can be infused at an initial rate of 100 mg/hour, and increased by 100 mg/hour increments at 30 minute intervals, to a maximum of 400 mg/hour. Development of an allergic reaction may require a slower infusion rate. Any deviation from the advised infusion rate should be noted in local policies
Recommended observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies.
riTUXimab should be diluted to a final concentration of 1-4mg/mL.
Rapid rate infusion schedule[ii] See NCCP guidance Available on the NCCP website If patients did **not** experience a serious infusion related reaction with their first or subsequent infusions of a dose of riTUXimab administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions. Initiate at a rate of 20% of the total dose for the first 30 minutes and then 80% of the dose for the next 60 minutes (total infusion time of 90 minutes). If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions. Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious reactions to any prior biologic therapy or to riTUXimab, should not be administered the more rapid infusion.

ELIGIBILITY:

- Indication as above
- Aged ≥ 25 and ≤ 65 years old with acute lymphoblastic leukaemia **OR** ≥ 19 and ≤ 65 years old with Philadelphia Chromosome positive acute lymphoblastic leukaemia.

EXCLUSIONS:

- Hypersensitivity to riTUXimab, cytarabine, etoposide, PEG-asparaginase, methotrexate, imatinib, or any of the excipients
- Refer to NCCP Regimen 00874 UKALL14 Phase 1 Standard Induction Therapy for exclusions

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Haematologist working in the area of haematological malignancies

TESTS:

Baseline tests:

- Refer to UKALL14 v12 trial protocol for full details
- Ensure all previous pre-assessments as per Phase 1 Standard Induction have been completed
- FBC, liver and renal profile
- Amylase, blood glucose, coagulation screen including fibrinogen

Regular tests:

- Refer to UKALL14 v12 trial protocol for full details
- FBC, renal and liver profile as required
- Amylase, blood glucose
- Coagulation screen as per local policy

Disease monitoring:

Disease monitoring (including MRD by flow and molecular methods) should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.
- Further detailed information on managing dose modifications can be found in the UKALL14 v12 trial protocol

Renal and Hepatic Impairment:

Table 3: Dose modifications in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal impairment</th><th colspan="2">Hepatic impairment</th></tr>
<tr><td>riTUXimab</td><td colspan="2">No need for dose adjustment is expected

Haemodialysis: no need for dose adjustment is needed</td><td colspan="2">No need for dose adjustment is expected</td></tr>
<tr><td rowspan="6">Cytarabine</td><td colspan="2" rowspan="6">No dose adjustments are needed</td><td>Bilirubin (micromol/L)</td><td>Dose</td></tr>
<tr><td><50</td><td>100%</td></tr>
<tr><td>≥50 but <90</td><td>50%</td></tr>
<tr><td>≥90 but <120</td><td>25%</td></tr>
<tr><td>≥120</td><td>Omit dose</td></tr>
<tr><td colspan="2">Do not alter dose for abnormal transaminases</td></tr>
<tr><td rowspan="4">Etoposide</td><td>CrCl (mL/min)</td><td>Dose</td><td colspan="2" rowspan="4">Bilirubin < 50 micromol/L and normal albumin and normal renal function:
No need for dose adjustment is expected

Bilirubin ≥ 50 micromol/L or decreased albumin levels:
Consider 50% of the dose, increase if tolerated</td></tr>
<tr><td>>50</td><td>No dose adjustment is needed</td></tr>
<tr><td>10-50</td><td>75% of the original dose, increase if tolerated</td></tr>
<tr><td>Haemodialysis</td><td>Not dialysed, consider 75% of the original dose</td></tr>
<tr><td>PEG-asparaginase</td><td colspan="2">No dose adjustment is needed

Haemodialysis: no need for dose adjustment is expected</td><td colspan="2">Consider withholding if rising total bilirubin. Definitely withhold if total bilirubin > 50.

For severely abnormal transaminases, discuss with treating clinician.</td></tr>
<tr><td>Imatinib</td><td colspan="2">Patients with renal dysfunction or on dialysis should be given the minimum recommended dose of 400 mg daily as starting dose. However, in these patients caution is recommended.

The dose can be reduced if not tolerated. If tolerated, the dose can be increased for lack of efficacy</td><td colspan="2">Patients with mild, moderate or severe liver dysfunction should be given the minimum recommended dose of 400 mg daily. The dose can be reduced if not tolerated</td></tr>
<tr><td colspan="5">riTUXimab: Renal and hepatic – Giraud et al, 2023
Cytarabine: Renal – Giraud et al 2023, hepatic – UKALL14 v12
Etoposide: Renal and hepatic – Giraud et al, 2023
PEG-asparaginase: Renal - Giraud et al 2023, hepatic - UKALL14v12 and as agreed with clinical reviewer/clinical advisory group
Imatinib: Renal and hepatic – Product SmPC</td></tr>
</table>

Management of adverse events:

Table 4: Dose modification schedule based on adverse events

Drug	Adverse reactions			Recommended dose modification
riTUXimab	Severe infusion related reaction (e.g. dyspnoea, bronchospasm, hypotension or hypoxia) First occurrence			Interrupt infusion immediately. Evaluate for cytokine release/tumour lysis syndrome (appropriate laboratory tests) and pulmonary infiltration (chest x -ray). Infusion may be restarted on resolution of all symptoms, normalisation of laboratory values and chest x-ray findings at no more than one-half the previous rate.
	Second occurrence			Consider coverage with steroids for those who are not already receiving steroids. Consider discontinuing treatment.
	Mild or moderate infusion-related reaction			Reduce rate of infusion. The infusion rate may be increased upon improvement of symptoms.
Imatinib	**Bilirubin**		**Liver Transaminases**	Hold until bilirubin < 1.5 x ULN and transaminase levels < 2.5 x ULN and then resume at reduced dose: • 400mg to 300mg or • 600mg to 400mg
	> 3 x ULN	or	> 5 x ULN	
	Severe non-haematological toxicity			Withhold treatment until resolved. Resume treatment depending on the initial severity of the event.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

- As outlined in NCCP Classification Document for Systemic AntiCancer Therapy (SACT) Induced Nausea and Vomiting available on the NCCP website

riTUXimab: Minimal **(Refer to local policy).**
Cytarabine: Low **(Refer to local policy).**
Etoposide: Low **(Refer to local policy).**
Imatinib: Moderate to high* **(Refer to local policy).**

*Based on clinical experience, the emetogenic potential of imatinib may be regarded as moderate as opposed to moderate to high.

For information:
Within NCIS regimens, antiemetics have been standardised by the Medical Oncologists and Haemato-oncologists and information is available in the following documents:

- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Medical Oncology) available on the NCCP website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) available on the NCCP website

PREMEDICATIONS:

- Premedicate patients as per table 5 below prior to administration of PEG-asparaginase to decrease the risk and severity of both infusion and hypersensitivity reactions

Table 5: Suggested pre-medications prior to PEG-asparaginase infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60 minutes prior to infusion
Chlorphenamine*	10mg	IV bolus at least 30 minutes prior to infusion
* This can be given +/- hydrocortisone 100mg IV)		

- Premedication consisting of an anti-pyretic and an anti-histamine should always be administered before each dose of riTUXimab as per table 6 below. Consider the inclusion of a glucocorticoid in patients not receiving glucocorticoid containing chemotherapy.

Table 6: Suggested premedications prior to riTUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60minutes prior to riTUXimab infusion
Chlorphenamine	10mg	IV bolus 60 minutes prior to riTUXimab infusion
Hydrocortisone	100mg	IV bolus 60 minutes prior to riTUXimab infusion

OTHER SUPPORTIVE CARE:

- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)**
- PJP prophylaxis **(Refer to local policy)**
- Norethisterone (menstruating women only) **(Refer to local policy)**
- Proton pump inhibitor (PPI) **(Refer to local policy)**

ADVERSE EFFECTS

- Please refer to the relevant Summary of Product Characteristics (SmPC) for details.

REGIMEN SPECIFIC COMPLICATIONS

- **Hepatitis B Reactivation:** Patients should be tested for both HBsAg and HBcoreAb as per local policy. If either test is positive, such patients should be treated with anti-viral therapy **(Refer to local infectious disease policy).** These patients should be considered for assessment by hepatology.

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information

COMPANY SUPPORT RESOURCES/Useful Links:

Please note that this is for information only and does not constitute endorsement by the NCCP

riTUXimab:

Please refer to the HPRA website (www.hpra.ie) for the individual product for list of relevant support resources.

REFERENCES:

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3. Rituximab administration schedule agreed at NCCP ALL SACT Clinical Advisory Group meeting 5/3/2025.
4. NHS Thames Valley. ML.45 ALL Consolidation – Cycle 1. Version 1.2 Last updated Oct 2019. Accessed 14.01.2025. Available at: https://nssg.oxford-haematology.org.uk/myeloid/protocols/ML-45-all-consolidation-cycle-1.pdf
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Version	Date	Amendment	Approved By
1	01/10/2025		Dr Robert Henderson, Dr Janusz Krawczyk

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] This is an unlicensed indication for the use of riTUXimab in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label"

indication has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.

[ii] The rapid infusion is an unlicensed means of administration of riTUXimab for the indications described above, in Ireland. Patients should be informed of this and consented to treatment in line with the hospital's policy on the use of unlicensed medication and unlicensed or "off label" indications. Prescribers should be fully aware of their responsibility in communicating any relevant information to the patient and also ensuring that the unlicensed or "off label" means of administration has been acknowledged by the hospital's Drugs and Therapeutics Committee, or equivalent, in line with hospital policy.