UKALL14v12 Consolidation Phase Cycle 3

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 Consolidation Phase 2	C91	00879a	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 3 only, which consists of two parts:

- Cycle 3 Part A (Days 1-28)
  - commences 3 weeks from day 1 cycle 2, when ANC >0.75 x 10^9/L and platelets >75 x 10^9/L **(Ref NCCP regimen 00878 UKALL 14v12 Consolidation Phase Cycle 2)**
- Cycle 3 Part B (Days 29-42)
  - commences 3 weeks and 29 days from day 1 cycle 2 or when ANC >0.75 x 10^9/L and platelets >75 x 10^9/L
- Once the cycle starts, therapy is not interrupted for myelosuppression alone. Any serious infection, such as varicella, pneumocystis pneumonia, neutropenia with fever, and presumed or proven infection, warrants chemotherapy interruption at any time during this phase.

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

Part A: Day 1-28

Day	Drug	Dose	Route and Method of Administration	Diluent & Rate
1-4, 8-11, 15-18, 22-25	dexAMETHasone[a]	10mg/m^2 (max 20mg)	PO	n/a
1,8[b]	riTUXimab (**CD20 positive patients** ONLY)	375mg/m^2	IV infusion[c] Observe post infusion[c]	500mL NaCl 0.9% at a maximum rate of 400mg/hour
1, 8, 15, 22	DAUNOrubicin[d]	25mg/m^2	IV bolus	Slow IV push via side arm of NaCl 0.9% infusion.
1, 8, 15, 22	vinCRIStine[e]	1.4mg/m^2 (max 2mg)	IV infusion	50mL NaCl 0.9% infused over 15 minutes
2 and 17	Methotrexate	12.5mg	Intrathecal[f,g]	n/a
1-28	Imatinib (**Philadelphia positive patients ONLY)**	600mg[h]	PO	n/a
4	PEG-asparaginase (**Philadelphia negative patients ONLY)** **Patients > 40 years old, use with caution**	1000 IU/m^2	IV infusion	100mL NaCl 0.9% infused over 2 hours

[a]dexAMETHasone should be capped at 20mg for larger patients

[b]Administration days can be amended at the discretion of the prescribing Consultant

[c]See Table 2: Guidance for riTUXimab administration

[d]Lifetime cumulative dose of DAUNOrubicin is 550mg/m^2**.** In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below[ii] and to the age of the patient**.**

[e]vinCRIStine is a neurotoxic chemotherapeutic agent.
Refer to **NCCP Guidance on the Safe Use of Neurotoxic drugs** (including Vinca Alkaloids) in the treatment of cancer Available on the NCCP website

[f]Refer to NCCP Guidance on the Safe Use of Intrathecal Chemotherapy in the Treatment of Cancer Available on the NCCP website
[g]Timing of intrathecal therapy can be moved +/- 3 days**.**

[h]Patient may require 400mg dose if 600mg not tolerated

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

Part B: Day 29-42

Day	Drug	Dose	Route of Administration	Diluent & Rate
29-42	Mercaptopurine	60mg/m^2	PO	n/a
29	cycloPHOSphamide	1000mg/m^2	IV infusion[a]	250mL NaCl 0.9 % over 30 minutes
30-33, 37-40	Cytarabine[b]	75mg/m^2	IV infusion	100mL NaCl 0.9% over 30 minutes
29-42	Imatinib[c] (**Philadelphia positive patients** ONLY)	600mg	PO	n/a
[a]125mL/m^2/hour 0.9% NaCl to start 30 minutes before cycloPHOSphamide and to continue for 3.5 hours afterwards (i.e. 4 hours in total). Do not add potassium. Mesna is not needed.				
[b] Timing of cytarabine blocks can be scheduled so that they take place during the week provided that full doses are given. May also be given by slow IV bolus (concentration of 20mg/mL)				
[c]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[iii] 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:

- Indications 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, DAUNOrubicin, vinCRIStine, dexAMETHasone, methotrexate, imatinib, PEG-asparaginase, mercaptopurine, cycloPHOSphamide, cytarabine 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 v 12 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 modification in renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
riTUXimab	No need for dose adjustment is expected Haemodialysis: no need for dose adjustment is needed		No need for dose adjustment is expected	
DAUNOrubicin	**CrCl (mL/min)**	**Dose**	**Bilirubin (micromol/L)**	**Dose**
	30-50	75% of the original dose	<50	100%
	<30	50% of the original dose	≥50 but <90	50%
			≥90 but <120	25%
	Haemodialysis	50% of the original dose	≥120	Omit dose
			Do not alter dose for abnormal transaminases	
vinCRIStine	No need for dose adjustment is expected Haemodialysis: no need for dose adjustment is expected		**Bilirubin (micromol/L)**	**Dose**
			>50	Withhold
			25-50	Administer 50% of dose
			Do not alter dose for abnormal transaminases.	
Imatinib	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		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.	
PEG-asparaginase	No dose adjustment is needed Haemodialysis: no need for dose adjustment is expected		Consider withholding if rising total bilirubin. Definitely withhold if total bilirubin > 50. For severely abnormal transaminases, discuss with treating clinician.	
cycloPHOSphamide	**CrCl (mL/min)**	**Dose**	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy.	
	≥30	No dose adjustment is needed		
	10-29	Consider 75% of the original dose		
	<10	Not recommended, if unavoidable consider 50% of the original dose		
	Haemodialysis	Not recommended, if unavoidable consider 50% of the original dose		
Cytarabine	No dose adjustments needed		**Bilirubin (micromol/L)**	**Dose**
			<50	100%
			≥50 but <90	50%
			≥90 but <120	25%
			≥120	Omit dose
			Do not alter dose for abnormal transaminases	

Mercaptopurine	CrCl (mL/min)	Dose	Bilirubin >50micromol/L • Omit mercaptopurine until it is less than 20micromol/L and then restart at half the previously dose. • Escalate from 50% to 75% to 100% dose at 10-day intervals provided that hyperbilirubinaemia does not recur. Consider dose modification for elevated aminotransferases.
	≥30	No need for dose adjustment is expected	
	<30	Increase dosing interval to 48 hours	
	Haemodialysis	Not recommended	

riTUXimab: Renal and hepatic – Giraud et al, 2023
DAUNOrubicin: Renal – Giraud et al,2023, Hepatic – UKALL14v12
vincristine: Renal – Giraud et al,2023, Hepatic – UKALL14v12
Imatinib: Renal and hepatic – Product SmPC
PEG-asparaginase: Renal – Giraud et al,2023, Hepatic – UKALL14v12 and as agreed with clinical reviewer/clinical advisory group
cycloPHOSphamide: Renal and hepatic – Giraud et al, 2023
Cytarabine: Renal – Giraud et al 2023, hepatic – UKALL14 v12
Mercaptopurine: Renal – Giraud et al 2023, hepatic – UKALL14 v12

Management of adverse events:

Table 4: Dose Modification for 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.
vinCRIStine	Neurotoxicity Grade 1 Grade 2 Grade 3-4			 100% dose Hold until recovery, then reduce dose by 50% Omit
Imatinib	**Bilirubin**		**Liver Transaminases**	
	> 3 x ULN	or	> 5 x ULN	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
	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 website

riTUXimab: Minimal **(Refer to local policy).**
DAUNOrubicin: Moderate **(Refer to local policy).**
vinCRIStine: Minimal (**Refer to local policy).**
cycloPHOSphamide: Moderate **(Refer to local policy).**
Cytarabine: Low **(Refer to local policy).**
Mercaptopurine: Minimal to 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 website
- NCCP Supportive Care Antiemetic Medicines for **Inclusion in NCIS** (Haemato-oncology) - available on the 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 pre-medications prior to riTUXimab infusion:

Drugs	Dose	Route
Paracetamol	1g	PO 60 minutes prior to rituximab infusion
Chlorphenamine	10mg	IV bolus 60 minutes prior to rituximab infusion
Ensure glucocorticoid component of the treatment regimen (dexAMETHasone 10mg/m^2) is given at least 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.

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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] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.
Risk factors for developing anthracycline-induced cardiotoxicity include:
• high cumulative dose, previous therapy with other anthracyclines or anthracenediones
• prior or concomitant radiotherapy to the mediastinal/pericardial area
• pre-existing heart disease
• concomitant use of other potentially cardiotoxic drugs
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient

[iii] 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.