UKALL14v12 Maintenance Therapy

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 Cycle 4	C91	00881a	Imatinib - CDS Other drugs - N/A

* This applies to post 2012 indications

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.

Treatment is administered as described in the treatment table below. The treatment cycle is 84 days, and treatment should continue for 2 years (i.e. 8 cycles).

Note:

- Treatment should commence once ANC >0.75 x 10^9/L and platelets >75 x 10^9/L following Cycle 4 consolidation **(Ref NCCP regimen 00878 UKALL 14v12 Consolidation Phase Cycle 2 and 4).**
- Dosing of mercaptopurine and methotrexate should be adjusted to maintain the neutrophil count between 0.75 and 1.5 x 10^9/L and platelet count between 75 and 150 x 10^9/L.
    - Mercaptopurine and methotrexate are usually prescribed every 4 weeks to support dose variations (see dose modifications section). If a dose increase is indicated, the dose for the next 4-week block should be prescribed in line with this to minimise dose alterations in cycle.

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

Day	Drug	Dose	Route of Administration	Diluent & Rate	Cycle (84 days)
1	vinCRIStine[a]	1.4mg/m^2 (max 2mg)	IV infusion	50mL NaCl 0.9% over 15 minutes	1-8
1-5	prednisoLONE	60mg/m^2	PO	n/a	1-8
1-84	Mercaptopurine	75 mg/m^2	PO		1-8
1,8,15,22, 29, 36,43, 50, 57, 64, 71 and 78	Methotrexate[b]	20 mg/m^2	PO		1-8
1	Methotrexate	12.5mg	Intrathecal[c,d]	n/a	1-8
1-84	Imatinib (**Philadelphia positive patients** ONLY)	600mg[e]	PO	n/a	1-8

[a]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

[b]Not to be administered on same day as co-trimoxazole

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

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

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

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 vinCRIStine, prednisoLONE, mercaptopurine, 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

Regular tests:

- Refer to UKALL14 v 12 trial protocol for full details
- FBC, renal and liver profile as required
- 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.
- Adjust dosing of maintenance therapy to maintain ANC 0.75-1.5 $x10^9$/L and platelets 75-150 $x10^9$/L as per table 2 below
- Doses may need to be increased or decreased from starting dose to maintain the correct level of haematological suppression.
- Maintenance should not be interrupted unnecessarily, with the exception of intrathecal methotrexate.
- If doses are omitted for cytopenias or infectious complications, they do not need to be made up with additional doses later.
- If cytopenias occur and maintenance is halted, consider stopping co-trimoxazole if blood counts do not recover within 2-3 weeks. Doses of mercaptopurine and oral methotrexate should not be compromised in order to permit continuation of co-trimoxazole. Alternative prophylaxis against PJP should be given.
- Further detailed information on managing dose modifications can be found in the UKALL14 v12 trial protocol.

Haematological:

Table 2: Dose modifications of mercaptopurine and methotrexate for haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose modification
>1.5	And	>150	Increase mercaptopurine dose by 25% If counts remain at these levels after 4 weeks, increase oral methotrexate by 25%. There are no maximum doses of mercaptopurine and oral methotrexate
<0.75	Or	<75	Reduce mercaptopurine and oral methotrexate by 50%
<0.5	Or	<50	Stop maintenance and restart at 100% when ANC >0.75 and Plt >75

Renal and Hepatic Impairment:

Table 3: Dose modification 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 rowspan="4">vinCRIStine</td><td colspan="2" rowspan="4">No need for dose adjustment is expected

Haemodialysis: no need for dose adjustment is expected</td><td>Bilirubin (micromol/L)</td><td>Dose</td></tr>
<tr><td>>50</td><td>Withhold</td></tr>
<tr><td>25-50</td><td>Administer 50% of dose</td></tr>
<tr><td colspan="2">Do not alter dose for abnormal transaminases.</td></tr>
<tr><td>Methotrexate (PO)</td><td colspan="2">Grade 3-4:

Omit methotrexate until grade 0 toxicity (ie completely resolved). Resume at 100% of the previously attained dose and continue at 10-day intervals.</td><td colspan="2">If bilirubin is >50 micromol/L omit methotrexate until it is less than 20 micromol/L, and then restart at half of the previously attained dose. Escalate from 50% to 75% to 100% dose at 10-day intervals provided hyperbilirubinaemia does not recur.

Consider dose modification for elevated aminotransferases.</td></tr>
<tr><td rowspan="4">Mercaptopurine</td><td>CrCl (mL/min)</td><td>Dose</td><td colspan="2" rowspan="4">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.</td></tr>
<tr><td>≥30</td><td>No need for dose adjustment is expected</td></tr>
<tr><td><30</td><td>Increase dosing interval to 48 hours</td></tr>
<tr><td>Haemodialysis</td><td>Not recommended</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">vinCRIStine: Renal – Giraud et al,2023, Hepatic – UKALL14v12
Methotrexate (PO) – Renal and hepatic - UKALL14v12
Mercaptopurine: Renal – Giraud et al 2023, hepatic – UKALL14 v12
Imatinib: Renal and hepatic – Product SmPC</td></tr>
</table>

Management of adverse events:

Table 4: Dose Modification for Adverse Events

Drug	Adverse reactions			Recommended dose modification
vinCRIStine	Neurotoxicity Grade 1 Grade 2 Grade 3-4			 100% dose Hold until recovery, then reduce dose by 50% Omit
Methotrexate (PO)	**Mucositis** Grade 2 (>3 days duration) Grade 3-4			 Decrease methotrexate dose by 30%. Withhold methotrexate until resolved; resume at 50% of the previously attained dose and subsequently escalate to 75% to 100% dose at 10-day intervals provided grade 3-4 toxicity does not recur. Consider culturing lesions for herpes simplex if mucositis persists or recurs.
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

vinCRIStine: Minimal (**Refer to local policy).**
Methotrexate: Minimal to 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:

- No specific recommendations

OTHER SUPPORTIVE CARE:

- Anti-viral prophylaxis **(Refer to local policy)**
- Anti-fungal prophylaxis **(Refer to local policy)** Antifungal prophylaxis is not generally required when a patient is on maintenance therapy unless that patient is deemed to be high risk for fungal disease (this is protocol)
- PJP prophylaxis **(Refer to local policy)**
    - Consider interactions between methotrexate and co-trimoxazole. If co-trimoxazole cannot be avoided, avoid administration on the same day.
- Proton pump inhibitor (PPI) **(Refer to local policy)**
- Norethisterone (menstruating women only) **(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

REFERENCES:

1. UKALL14. A randomized trial for adults with newly diagnosed acute lymphoblastic leukaemia. Eudract No: 2009-012717-22. Version 12.0, 26.06.2018
2. NHS Thames Valley. ML.50 ALL Maintenance. Version 1.2. Last updated Oct 2019. Accessed 14.01.2025. Available at: https://nssg.oxford-haematology.org.uk/myeloid/protocols/ML-50-all-maintenance.pdf
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V6 2025. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

4. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://pubmed.ncbi.nlm.nih.gov/37269847/
5. Vinca alkaloids + Azoles. Stockley's Drug Interactions 12th Edition. Accessed 20/08/2025. https://www.medicinescomplete.com/#/interactions/stockley?terms=methotrexate,a,azoles
6. Imatinib (Glivec®) Summary of Product Characteristics. Last updated: 04/08/2025. Accessed September 2025. Available at: https://www.ema.europa.eu/en/documents/product-information/imatinib-teva-epar-product-information_en.pdf
7. vinCRIStine Summary of Product Characteristics. Last updated 01/09/2025. Accessed September 2025. Available at: https://assets.hpra.ie/products/Human/22135/Licence_PA0822-232-001_26032025095432.pdf
8. Methotrexate Summary of Product Characteristics. Last updated: 10/06/2025. Accessed September 2025. Available at: https://assets.hpra.ie/products/Human/22087/Licence_PA0822-206-002_10042025112938.pdf
9. Mercaptopurine Summary of Product Characteristics. Last updated 04/07/2025. Accessed September 2025. Available at: https://assets.hpra.ie/products/Human/36253/Licence_PPA1463-128-001_12042022162740.pdf

Version	Date	Amendment	Approved By
1	01/10/2025		Dr Robert Henderson, Dr Janusz Krawczyk

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.