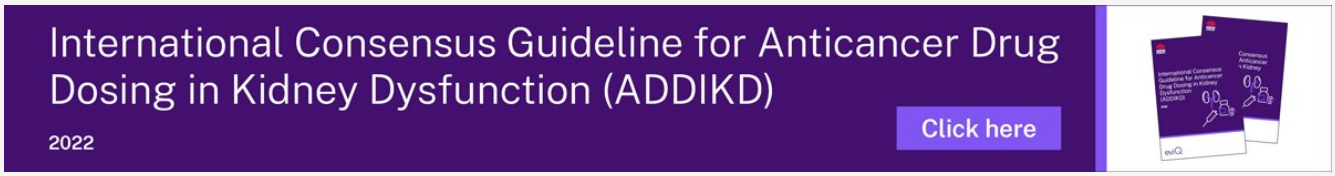
Acute lymphoblastic leukaemia ALL06 Protocol M

ID: 3828 v.2 **Endorsed**

Patients with leukaemia should be considered for inclusion into clinical trials. Link to ALLG website and ANZCTR website.

This protocol is based on limited evidence; refer to the evidence section of this protocol for more information.

The anticancer drug(s) in this protocol may have been included in the ADDIKD guideline. Dose recommendations in kidney dysfunction have yet to be updated to align with the ADDIKD guideline. Recommendations will be updated once the individual protocol has been evaluated by the reference committee. For further information refer to the ADDIKD guideline. To assist with calculations, use the eviQ Estimated Glomerular Filtration Rate (eGFR) calculator.



Related pages:

- Acute lymphoblastic leukaemia ALL06 overview
- Acute lymphoblastic leukaemia ALL06 - Treatment schema
- Acute lymphoblastic leukaemia ALL06 - Protocol flow diagram

Treatment schedule - Overview

Drug	Dose	Route	Day
mercaptOPURine	25 mg/m^2 ONCE a day	PO	1 to 56
Methotrexate	500 mg/m^2	IV infusion	8, 22, 36, 50
Methotrexate	4,500 mg/m^2	IV infusion	8, 22, 36, 50
Methotrexate	12 mg	Intrathecal *	8, 22, 36, 50
Calcium folinate (Leucovorin)	15 mg/m^2 every 6 hours **	IV bolus	9, 23, 37, 51

* If it is not possible to administer the dose 2 hours after the start of the methotrexate infusion, the IT methotrexate should be administered before the end of the methotrexate infusion.

** Commence 36 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.

The commencement of calcium folinate (leucovorin) rescue has been modified from a more complex algorithm to start at 36 hours after the start of the methotrexate infusion in all patients to reduce the risk of error or treatment delay. Similarly the number of calcium folinate doses has been modified, in line with other eviQ protocols, to continue until methotrexate level is less than 0.1 micromol/L.

Criteria for starting Protocol M:

- good general condition with no active infection
- WCC ≥ 1.5 x 10^9/L, neutrophils ≥ 0.5 x 10^9/L, platelets ≥ 50 x 10^9/L
- creatinine/creatinine clearance within normal limits
- AST/ALT < 5x ULN, bilirubin < 3x ULN

A bone marrow aspirate is required for MRD testing on day 1 of Protocol M (i.e. day 79 from the start of Protocol I

induction) ('Timepoint 2'). If the MRD Timepoint 2 result identifies the patient as high-risk, cease mercaptopurine and proceed to HR block 1 as soon as possible (once the criteria for proceeding to HR block 1 are met). If the MRD results are delayed, proceed with the first high dose methotrexate block of protocol M. Once the MRD results are available and if patient is identified as high-risk, convert to HR block 1 as soon as recovery permits.

Duration: 56 days

Cycles: 1
For standard-risk and medium-risk patients, Protocol M commences on day 79 after the start of protocol I induction (2 weeks after the last dose of cyclophosphamide in protocol I consolidation). High-risk and very high-risk patients should proceed to the High Risk (HR) blocks.

Notes:
- This treatment should only be carried out in a major centre as intensive monitoring and support is required
- Consider thiopurine methyltransferase (TPMT) testing prior to administration of mercaptopurine.

Drug status: All drugs in this protocol are on the PBS general schedule

Mercaptopurine is available as **50 mg** tablets

Treatment schedule - Detail

The supportive therapies (e.g. antiemetics, premedications, etc.), infusion times, diluents, volumes and routes of administration, if included, are listed as defaults. They may vary between institutions and can be substituted to reflect individual institutional policy.

*Antiemetics if included in the treatment schedule are based upon recommendations from national and international guidelines. These are **defaults only** and may be substituted to reflect individual institutional policy. Select here for recommended doses of alternative antiemetics.*

Day 1 to 7		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.

Day 8		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.
Methotrexate	500 mg/m^2 (IV infusion)	in 250 mL sodium chloride 0.9% over 30 minutes
Methotrexate	4,500 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 23.5 hours
Methotrexate	12 mg (Intrathecal)	administer 2 hours after the start of the methotrexate infusion. Adhere to local institution intrathecal policy.*

Day 9		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.
Calcium folinate (Leucovorin)	15 mg/m^2 (IV bolus)	Commence 36 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L

Day 10 to 21		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.

Day 22		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.
Methotrexate	500 mg/m^2 (IV infusion)	in 250 mL sodium chloride 0.9% over 30 minutes

Day 22		
Methotrexate	4,500 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 23.5 hours
Methotrexate	12 mg (Intrathecal)	administer 2 hours after the start of the methotrexate infusion. Adhere to local institution intrathecal policy.*
Day 23		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.
Calcium folinate (Leucovorin)	15 mg/m^2 (IV bolus)	Commence 36 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L
Day 24 to 35		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.
Day 36		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.
Methotrexate	500 mg/m^2 (IV infusion)	in 250 mL sodium chloride 0.9% over 30 minutes
Methotrexate	4,500 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 23.5 hours
Methotrexate	12 mg (Intrathecal)	administer 2 hours after the start of the methotrexate infusion. Adhere to local institution intrathecal policy.*
Day 37		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.
Calcium folinate (Leucovorin)	15 mg/m^2 (IV bolus)	Commence 36 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L
Day 38 to 49		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.
Day 50		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.
Methotrexate	500 mg/m^2 (IV infusion)	in 250 mL sodium chloride 0.9% over 30 minutes
Methotrexate	4,500 mg/m^2 (IV infusion)	in 1000 mL sodium chloride 0.9% over 23.5 hours
Methotrexate	12 mg (Intrathecal)	administer 2 hours after the start of the methotrexate infusion. Adhere to local institution intrathecal policy.*
Day 51		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one hour before or two hours after food.
Calcium folinate (Leucovorin)	15 mg/m^2 (IV bolus)	Commence 36 hours after the start of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L
Day 52 to 56		
mercaptOPURine	25 mg/m^2 (PO)	ONCE a day. Take on an empty stomach at least one

Day 52 to 56		
		hour before or two hours after food.

* If it is not possible to administer the dose 2 hours after the start of the methotrexate infusion, the IT methotrexate should be administered before the end of the methotrexate infusion.

Criteria for starting Protocol M:

- good general condition with no active infection
- WCC ≥ 1.5 x 10^9/L, neutrophils ≥ 0.5 x 10^9/L, platelets ≥ 50 x 10^9/L
- creatinine/creatinine clearance within normal limits
- AST/ALT < 5x ULN, bilirubin < 3x ULN

A bone marrow aspirate is required for MRD testing on day 1 of Protocol M (i.e. day 79 from the start of Protocol I induction) ('Timepoint 2'). If MRD Timepoint 2 result identifies patient as high risk, cease mercaptopurine and proceed to HR block 1 as soon as possible (once criteria for proceeding to HR block 1 are met). If MRD results are delayed, proceed with the first high dose methotrexate block of protocol M and once available if MRD suggests patient is high risk, convert to HR block 1 as soon as recovery permits.

Duration: 56 days

Cycles: 1
For standard-risk and medium-risk patients, Protocol M commences on day 79 after the start of protocol I induction (2 weeks after the last dose of cyclophosphamide in protocol I consolidation). High-risk and very high-risk patients should proceed to the High Risk (HR) blocks.

Indications and patient population

Indications:

- For the treatment of adolescent and young adult (AYA) patients with acute lymphoblastic leukaemia (precursor B-ALL, T-ALL but not mature B-ALL/Burkitt lymphoma).
- This regimen is for the treatment of adolescents aged 15 years and above, and young adults aged up to 40 years.
- For information on which protocol is used for each risk group, refer to the definition of risk groups.

Contraindications[1]

Pegaspargase should not be used in patients who have:

- previous anaphylaxis or severe hypersensitivity to asparaginase formulations
- severe hepatic impairment
- existing or a history of pancreatitis
- previous haemorrhagic or severe thrombotic events.

Cautions/exclusions[2]

- Pegaspargase should be used with caution in patients over 40 years of age and those with a body mass index (BMI) greater than 30 due to an increased risk of side effects.

See ID 918 Management of asparaginase therapy for more information.

Clinical information

Caution with oral anti-cancer drugs	Select links for information on the safe prescribing, dispensing and administration of orally administered anti-cancer drugs. Read more about the COSA guidelines and oral anti-cancer therapy
Venous access	Central venous access device (CVAD) is required to administer this treatment. Read more about central venous access device line selection

Antiemetics for multi-day protocols	Antiemetic therapy should be administered throughout the duration of the chemotherapy protocol and to cover delayed nausea. The acute and delayed emetic risk of multi-day chemotherapy protocols will overlap depending on the individual drugs and their sequence of administration. More or less antiemetic cover may be required. Ensure that patients also have sufficient antiemetics for breakthrough emesis: Metoclopramide 10 mg three times a day when necessary (maximum of 30 mg/24 hours, up to 5 days) OR Prochlorperazine 10 mg PO every 6 hours when necessary. Read more about preventing anti-cancer therapy induced nausea and vomiting
Thiopurine-S-methyltransferase (TPMT) enzyme deficiency	Patients with an inherited deficiency of the TPMT enzyme are at an increased risk of, and prone to developing, rapid bone marrow depression which may lead to severe, life-threatening myelosuppression when undergoing treatment with thiopurines (azathioprine, mercaptopurine, tioguanine). This may be exacerbated by coadministration with drugs that inhibit TPMT, such as olsalazine, mesalazine or sulfasalazine. Consider assessing thiopurine-S-methyltransferase (TPMT) activity prior to administration of thiopurines.
Pre-hydration	Pre-hydration with sodium bicarbonate 8.4% infusion. Urinary pH must be greater than 7 prior to commencing methotrexate infusion. Consider prescribing sodium bicarbonate oral capsules for administration prior to methotrexate infusion. Sodium bicarbonate 8.4% should continue until the methotrexate level is equal to or less than 0.1 micromol/L. Read more about high dose methotrexate-induced toxicity.
High dose methotrexate	Monitoring of methotrexate levels is essential as delayed methotrexate excretion is potentially an emergency situation. Methotrexate levels to be monitored every 24 hours until level is less than 0.1 micromol/L. Methotrexate is renally eliminated. Kidney function must be evaluated prior to treatment. Methotrexate exits slowly from third space compartments (e.g. pleural effusions or ascites), resulting in a prolonged terminal plasma half-life and unexpected toxicity. In patients with significant third space accumulations, it is advisable to evacuate the fluid before treatment and to monitor plasma methotrexate levels. Glucarpidase is recommended in patients with high dose methotrexate (HDMTX)-induced acute kidney injury and delayed methotrexate clearance. It can rapidly lower methotrexate levels and early administration within 48 to 60 hours from the start of the HDMTX infusion is critical, as life-threatening toxicities may not be preventable beyond this time point.[3] Read more about high dose methotrexate-induced toxicity.
Methotrexate interactions	Avoid administering the following drugs in combination with high dose methotrexate: ciprofloxacin, NSAIDs, probenecid, proton pump inhibitors (PPIs) (e.g. esomeprazole, omeprazole, pantoprazole), sulphonamides (e.g. sulfamethoxazole (in Bactrim®, Septrin®)), penicillins (e.g. piperacillin (in Tazocin®)) and trimethoprim. Severe mucositis may occur if administered together.
Pneumocystis jirovecii pneumonia (PJP) prophylaxis	PJP prophylaxis is recommended. Myelosuppression may be exacerbated if trimethoprim/sulfamethoxazole is used in combination with methotrexate. Read about prophylaxis of pneumocystis jirovecii (carinii) in cancer patients
Antiviral prophylaxis	Antiviral prophylaxis is recommended. Read more about antiviral prophylaxis drugs and doses
Antifungal prophylaxis	Antifungal prophylaxis is recommended. e.g. posaconazole 300 mg PO twice daily for one day then 300 mg PO daily. Read more about antifungal prophylaxis drugs and doses.

Blood product support	The use of FFP and cryoprecipitate may be required to maintain fibrinogen levels to a normal range. Read more about Management of asparaginase therapy
Blood tests	FBC, EUC, LFTs, LDH, bilirubin, albumin, uric acid, lipase, amylase at baseline and twice a week or more frequent as clinically indicated.
Hepatitis B screening and prophylaxis	Routine screening for HBsAg and anti-HBc is recommended prior to initiation of treatment. Prophylaxis should be determined according to individual institutional policy. Read more about hepatitis B screening and prophylaxis in cancer patients requiring cytotoxic and/or immunosuppressive therapy
Vaccinations	Live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. Refer to the recommended schedule of vaccination for immunocompromised patients, as outlined in the Australian Immunisation Handbook. Read more about COVID-19 vaccines and cancer.
Fertility, pregnancy and lactation	Cancer treatment can have harmful effects on fertility and this should be discussed with all patients of reproductive potential prior to commencing treatment. There is a risk of foetal harm in pregnant women. A pregnancy test should be considered prior to initiating treatment in females of reproductive potential if sexually active. It is important that all patients of reproductive potential use effective contraception whilst on therapy and after treatment finishes. Effective contraception methods and adequate contraception timeframe should be discussed with all patients of reproductive potential. Possibility of infant risk should be discussed with breastfeeding patients. Read more about the effect of cancer treatment on fertility

Dose modifications

Evidence for dose modifications is limited, and the recommendations made on eviQ are intended as a guide only. They are generally conservative with an emphasis on safety. Any dose modification should be based on clinical judgement, and the individual patient's situation including but not limited to treatment intent (curative vs palliative), the anti-cancer regimen (single versus combination therapy versus chemotherapy versus immunotherapy), biology of the cancer (site, size, mutations, metastases), other treatment related side effects, additional co-morbidities, performance status and patient preferences.Suggested dose modifications are based on clinical trial findings, product information, published guidelines and reference committee consensus . The dose reduction applies to each individual dose and not to the total number of days or duration of treatment cycle unless stated otherwise. Non-haematological gradings are based on Common Terminology Criteria for Adverse Events (CTCAE) unless otherwise specified. Renal and hepatic dose modifications have been standardised where possible. For more information see dosing considerations & disclaimer .

The dose recommendations in kidney dysfunction (i.e.renal impairment) displayed may not reflect those in the ADDIKD guideline and have been included for historical reference only. Recommendations will be updated once the individual protocol has been evaluated by the reference committee, with this version of the protocol then being archived. Clinicians are expected to refer to the ADDIKD guideline prior to prescribing in kidney dysfunction.
International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD).

Note:

- All dose reductions are calculated as a percentage of the starting dose.
- Dose modifications are based on the ALL06 trial.

Renal impairment	
Creatinine clearance (mL/min)	
Creatinine clearance must be greater than 100 mL/min prior to administration of high dose methotrexate	
60 to 100	Consideration may be given to a reduced dose of high dose methotrexate

Renal impairment	
< 60	Withhold high-dose methotrexate

Hepatic impairment	
ALT/AST	
> 5 x ULN	Withhold high-dose methotrexate till ALT/AST ≤ 5 x ULN
Bilirubin > 3 x ULN or ALT/AST > 10 x ULN and rising	Consider dose reducing mercaptopurine

Mucositis	
Grade 3/4	Withhold high-dose methotrexate until resolved. Consideration may be given to reducing the next dose to 2 g/m^2. If no recurrence of grade 3/4 mucositis, then subsequent doses should be at full dose.

Interactions

Drug interactions in eviQ protocols are under review and being updated to align with current literature. Further site-wide updates and changes will occur in due course. ***References & Disclaimer***

The drug interactions shown below are not an exhaustive list. For a more comprehensive list and for detailed information on specific drug interactions and clinical management, please refer to the specific drug product information and the following key resources:

- *MIMS - interactions tab (includes link to a CYP-450 table) (login required)*
- *Australian Medicines Handbook (AMH) – interactions tab (login required)*
- *Micromedex Drug Interactions (login required)*
- *Cancer Drug Interactions*
- *Cytochrome P450 Drug Interactions*

Mercaptopurine		
	Interaction	**Clinical management**
Allopurinol	Increased toxicity of mercaptopurine due to reduced clearance as a result of inhibition of xanthine oxidase	If the combination is used the dose of mercaptopurine must be reduced by 75 % (i.e. only one quarter of the usual mercaptopurine dose is used)
Methotrexate, aminosalicylate derivatives (e.g. balsalazide, olsalazine, mesalazine, sulfasalazine)	Increased toxicity of mercaptopurine possible due to reduced clearance	Avoid combination or monitor closely for mercaptopurine toxicity
Ribavirin	Increased toxicity and reduced efficacy of mercaptopurine possible due to metabolic enzyme inhibition by ribavirin	Avoid combination or monitor closely for toxicity of and decreased clinical response to mercaptopurine

Methotrexate		
	Interaction	**Clinical management**
Ciprofloxacin **NSAIDS** **Probenecid** **Proton pump inhibitors (e.g. esomeprazole, omeprazole, pantoprazole)**	Increased toxicity of methotrexate possible due to reduced clearance	Avoid combination or monitor for methotrexate toxicity Important note: with high-dose methotrexate therapy, many of these drug combinations are *contraindicated*
Sulphonamides and penicillins (e.g. sulfamethoxazole (in Bactrim®, Septrin®), piperacillin (in Tazocin®) etc.)	Increased toxicity of methotrexate possible due to displacement from serum protein binding	Avoid combination or monitor for methotrexate toxicity
Trimethoprim	Increased toxicity of methotrexate possible due to additive antifolate activity	Avoid combination or monitor for methotrexate toxicity
Mercaptopurine	Increased toxicity of mercaptopurine possible due to reduced clearance	Avoid combination or monitor for mercaptopurine toxicity
Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)	Additive nephrotoxicity	Avoid combination or monitor kidney function closely
Hepatotoxic drugs (e.g. azathioprine, leflunomide, retinoids, sulfasalazine)	Additive hepatotoxicity	Avoid combination or monitor liver function closely
Folic acid (e.g. as in multivitamins) **Asparaginase (administered immediately prior or concurrently)**	Reduced efficacy of methotrexate possible due antagonism of its action	Avoid combination or monitor for decreased clinical response to methotrexate Note: asparaginase administered shortly after methotrexate can enhance its efficacy and reduce its toxicity

General		
	Interaction	**Clinical management**
Warfarin	Anti-cancer drugs may alter the anticoagulant effect of warfarin.	Monitor INR regularly and adjust warfarin dosage as appropriate; consider alternative anticoagulant.
Direct oral anticoagulants (DOACs) e.g. apixaban, rivaroxaban, dabigatran	Interaction with both CYP3A4 and P-gp inhibitors /inducers. DOAC and anti-cancer drug levels may both be altered, possibly leading to loss of efficacy or toxicity (i.e. increased bleeding).	Apixaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. If treating VTE, avoid use with strong CYP3A4 and P-gp inducers. Rivaroxaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. Dabigatran: avoid combination with strong P-gp inducers and inhibitors. If concurrent use is unavoidable, monitor closely for efficacy/toxicity of both drugs.
Digoxin	Anti-cancer drugs can damage the lining of the intestine; affecting the absorption of digoxin.	Monitor digoxin serum levels; adjust digoxin dosage as appropriate.
Antiepileptics	Both altered antiepileptic and anti-cancer drug levels may occur, possibly leading to loss of efficacy or toxicity.	Where concurrent use of an enzyme-inducing antiepileptic cannot be avoided, monitor antiepileptic serum levels for toxicity, as well as seizure frequency for efficacy; adjust dosage as appropriate. Also monitor closely for efficacy of the anti-cancer therapy.
Antiplatelet agents and NSAIDs	Increased risk of bleeding due to treatment related thrombocytopenia.	Avoid or minimise combination. If combination deemed essential, (e.g. low dose aspirin for ischaemic heart disease) monitor for signs of bleeding.
Serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs e.g. paroxetine) and serotonin noradrenaline reuptake inhibitors (SNRIs e.g. venlafaxine)	Increased risk of serotonin syndrome with concurrent use of 5-HT3 receptor antagonists (e.g. palonosetron, ondansetron, granisetron, tropisetron, dolasetron, etc.)	Avoid combination. If combination is clinically warranted, monitor for signs and symptoms of serotonin syndrome (e.g. confusion, agitation, tachycardia, hyperreflexia). For more information link to TGA Medicines Safety Update
Vaccines	Diminished response to vaccines and increased risk of infection with live vaccines.	Live vaccines (e.g. BCG, MMR, zoster and varicella) are contraindicated in patients on immunosuppressive therapy. Use with caution in patients on non-immunosuppressive therapy. For more information; refer to the recommended schedule of vaccination for cancer patients, as outlined in the Australian Immunisation Handbook

Administration

eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual

product information monographs via the TGA website for further information.

Day 1

This is an oral treatment

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Mercaptopurine

- administer orally ONCE a day on **days 1 to 56**
- to be swallowed whole with a glass of water; do not break, crush or chew
- preferably to be taken on an empty stomach, one hour before or at least 2 hours after food
- avoid concomitant consumption of milk or dairy products

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Continue safe handling precautions until 7 days after completion of drug(s)

Day 8

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Prime IV line(s).

Access CVAD.

Note: A large volume of intravenous fluid may be given with this protocol. If weight increases by more than 1 kg from baseline or fluid balance becomes positive by one litre or any other signs of fluid overload are present, review by medical officer (diuretics may be required).

- daily weight
- monitor pH on all urine output
- strict fluid balance input and output

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Mercaptopurine

- administer orally ONCE a day on **days 1 to 56**
- to be swallowed whole with a glass of water; do not break, crush or chew
- preferably to be taken on an empty stomach, one hour before or at least 2 hours after food
- avoid concomitant consumption of milk or dairy products

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Methotrexate infusion

Prehydration:

- administer 100 mL sodium bicarbonate 8.4% in 1000 mL glucose 5% **OR** sodium chloride 0.9% over 4 hours
- continuous hydration with sodium bicarbonate 8.4% as prescribed
- when urine pH is greater than 7 commence methotrexate

If the urine pH drops below 7 during the methotrexate infusion:

- administer stat dose of 100 mL sodium bicarbonate 8.4% over 15 minutes
- continue to test all urine for pH, if the pH continues to drop below 7 seek medical review as further doses of sodium bicarbonate may be required

First dose of methotrexate:

- administer via IV infusion over 30 minutes
- the starting time of the methotrexate infusion **must** be documented as the calcium folinate (leucovorin) rescue is to commence exactly 36 hours after the commencement of the methotrexate and continue until the methotrexate level is less than 0.1 micromol/L

Second dose of methotrexate (to commence immediately after the first dose):

- administer via IV infusion over 23 and a half hours
- flush with ~50 mL of sodium chloride 0.9%
- **Stop the methotrexate infusion after 23 and a half hours even if the infusion is not completed**

Post methotrexate:

- continue hydration over 8 hours with sodium bicarbonate 8.4% until methotrexate level is less than 0.1 micromol/L
- a minimum of 3 litres of fluid should be administered daily
- continue to monitor all urine pH and fluid input and output
- monitor methotrexate concentration every 24 hours until the level is less than 0.1 micromol/L

Intrathecal methotrexate

⚠ **Intrathecal methotrexate is to be administered today. Intrathecal should be administered 2 hours after the start of the methotrexate infusion.**

Read more about the procedure for intrathecal methotrexate administration.

Post intrathecal care:

Local policies and guidelines regarding bed rest post dural puncture should be adhered to. At a minimum:

- the patient should have at least 1 set of observations including:
  - vital signs and GCS
  - any abnormal neurological signs such as nausea, vomiting, chills, fever, confusion, headache or other changes in neurological status
- educate the patient to recognise and immediately report any adverse reactions including blurred vision, dizziness, pain and or headache
- observe the lumbar puncture site for any leakage or bleeding post procedure
- document the procedure including outcomes in the patients notes

Calcium Folinate (Leucovorin)

Commence 36 hours after commencement of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.

- administer via IV bolus via the side port of the IV line over 1 to 2 minutes
- flush with ~ 50 mL of sodium chloride 0.9%

Continue safe handling precautions until 7 days after completion of drug(s)

Day 9

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require delay of treatment and review by medical officer before commencing treatment.

Prime IV line(s).

- daily weight
- monitor pH on all urine output
- strict fluid balance input and output

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Mercaptopurine

- administer orally ONCE a day on **days 1 to 56**
- to be swallowed whole with a glass of water; do not break, crush or chew
- preferably to be taken on an empty stomach, one hour before or at least 2 hours after food
- avoid concomitant consumption of milk or dairy products

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Calcium Folinate (Leucovorin)

Commence 36 hours after commencement of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.

- administer via IV bolus via the side port of the IV line over 1 to 2 minutes
- flush with ~ 50 mL of sodium chloride 0.9%

Deaccess CVAD.

Continue safe handling precautions until 7 days after completion of drug(s)

Day 22

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Prime IV line(s).

Access CVAD.

Note: A large volume of intravenous fluid may be given with this protocol. If weight increases by more than 1 kg from baseline or fluid balance becomes positive by one litre or any other signs of fluid overload are present, review by medical officer (diuretics may be required).

- daily weight
- monitor pH on all urine output
- strict fluid balance input and output

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Mercaptopurine

- administer orally ONCE a day on **days 1 to 56**
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Methotrexate infusion

Prehydration:

- administer 100 mL sodium bicarbonate 8.4% in 1000 mL glucose 5% **OR** sodium chloride 0.9% over 4 hours
- continuous hydration with sodium bicarbonate 8.4% as prescribed
- when urine pH is greater than 7 commence methotrexate

If the urine pH drops below 7 during the methotrexate infusion:

- administer stat dose of 100 mL sodium bicarbonate 8.4% over 15 minutes
- continue to test all urine for pH, if the pH continues to drop below 7 seek medical review as further doses of sodium bicarbonate may be required

First dose of methotrexate:

- administer via IV infusion over 30 minutes
- the starting time of the methotrexate infusion **must** be documented as the calcium folinate (leucovorin) rescue is to commence exactly 36 hours after the commencement of the methotrexate and continue until the methotrexate level is less than 0.1 micromol/L

Second dose of methotrexate (to commence immediately after the first dose):

- administer via IV infusion over 23 and a half hours
- flush with ~50 mL of sodium chloride 0.9%
- **Stop the methotrexate infusion after 23 and a half hours even if the infusion is not completed**

Post methotrexate:

- continue hydration over 8 hours with sodium bicarbonate 8.4% until methotrexate level is less than 0.1 micromol/L
- a minimum of 3 litres of fluid should be administered daily
- continue to monitor all urine pH and fluid input and output
- monitor methotrexate concentration every 24 hours until the level is less than 0.1 micromol/L

Calcium Folinate (Leucovorin)

Commence 36 hours after commencement of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.

- administer via IV bolus via the side port of the IV line over 1 to 2 minutes
- flush with ~ 50 mL of sodium chloride 0.9%

Intrathecal methotrexate

⚠ Intrathecal methotrexate is to be administered today. The intrathecal procedure is to be done separately to the IV administration of all other cytotoxic drugs

Read more about the procedure for intrathecal methotrexate administration.

Post intrathecal care:

Local policies and guidelines regarding bed rest post dural puncture should be adhered to. At a minimum:

- the patient should have at least 1 set of observations including:
  - vital signs and GCS

- any abnormal neurological signs such as nausea, vomiting, chills, fever, confusion, headache or other changes in neurological status

- educate the patient to recognise and immediately report any adverse reactions including blurred vision, dizziness, pain and or headache
- observe the lumbar puncture site for any leakage or bleeding post procedure
- document the procedure including outcomes in the patients notes

Continue safe handling precautions until 7 days after completion of drug(s)

Day 23

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require delay of treatment and review by medical officer before commencing treatment.

Prime IV line(s).

- daily weight
- monitor pH on all urine output
- strict fluid balance input and output

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Mercaptopurine

- administer orally ONCE a day on **days 1 to 56**
- to be swallowed whole with a glass of water; do not break, crush or chew
- preferably to be taken on an empty stomach, one hour before or at least 2 hours after food
- avoid concomitant consumption of milk or dairy products

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Calcium Folinate (Leucovorin)

Commence 36 hours after commencement of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.

- administer via IV bolus via the side port of the IV line over 1 to 2 minutes
- flush with ~ 50 mL of sodium chloride 0.9%

Deaccess CVAD.

Continue safe handling precautions until 7 days after completion of drug(s)

Day 36

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Prime IV line(s).

Access CVAD.

Note: A large volume of intravenous fluid may be given with this protocol. If weight increases by more than 1 kg from baseline or

fluid balance becomes positive by one litre or any other signs of fluid overload are present, review by medical officer (diuretics may be required).

- daily weight
- monitor pH on all urine output
- strict fluid balance input and output

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Mercaptopurine

- administer orally ONCE a day on **days 1 to 56**
- to be swallowed whole with a glass of water; do not break, crush or chew
- preferably to be taken on an empty stomach, one hour before or at least 2 hours after food
- avoid concomitant consumption of milk or dairy products

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Methotrexate infusion

Prehydration:

- administer 100 mL sodium bicarbonate 8.4% in 1000 mL glucose 5% **OR** sodium chloride 0.9% over 4 hours
- continuous hydration with sodium bicarbonate 8.4% as prescribed
- when urine pH is greater than 7 commence methotrexate

If the urine pH drops below 7 during the methotrexate infusion:

- administer stat dose of 100 mL sodium bicarbonate 8.4% over 15 minutes
- continue to test all urine for pH, if the pH continues to drop below 7 seek medical review as further doses of sodium bicarbonate may be required

First dose of methotrexate:

- administer via IV infusion over 30 minutes
- the starting time of the methotrexate infusion **must** be documented as the calcium folinate (leucovorin) rescue is to commence exactly 36 hours after the commencement of the methotrexate and continue until the methotrexate level is less than 0.1 micromol/L

Second dose of methotrexate (to commence immediately after the first dose):

- administer via IV infusion over 23 and a half hours
- flush with ~50 mL of sodium chloride 0.9%
- **Stop the methotrexate infusion after 23 and a half hours even if the infusion is not completed**

Post methotrexate:

- continue hydration over 8 hours with sodium bicarbonate 8.4% until methotrexate level is less than 0.1 micromol/L
- a minimum of 3 litres of fluid should be administered daily
- continue to monitor all urine pH and fluid input and output
- monitor methotrexate concentration every 24 hours until the level is less than 0.1 micromol/L

Calcium Folinate (Leucovorin)

Commence 36 hours after commencement of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.

- administer via IV bolus via the side port of the IV line over 1 to 2 minutes
- flush with ~ 50 mL of sodium chloride 0.9%

Intrathecal methotrexate

⚠ Intrathecal methotrexate is to be administered today. The intrathecal procedure is to be done separately to the IV administration of all other cytotoxic drugs

Read more about the procedure for intrathecal methotrexate administration.

Post intrathecal care:

Local policies and guidelines regarding bed rest post dural puncture should be adhered to. At a minimum:

- the patient should have at least 1 set of observations including:
  - vital signs and GCS
  - any abnormal neurological signs such as nausea, vomiting, chills, fever, confusion, headache or other changes in neurological status
- educate the patient to recognise and immediately report any adverse reactions including blurred vision, dizziness, pain and or headache
- observe the lumbar puncture site for any leakage or bleeding post procedure
- document the procedure including outcomes in the patients notes

Continue safe handling precautions until 7 days after completion of drug(s)

Day 37

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require delay of treatment and review by medical officer before commencing treatment.

Prime IV line(s).

- daily weight
- monitor pH on all urine output
- strict fluid balance input and output

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Mercaptopurine

- administer orally ONCE a day on **days 1 to 56**
- to be swallowed whole with a glass of water; do not break, crush or chew
- preferably to be taken on an empty stomach, one hour before or at least 2 hours after food
- avoid concomitant consumption of milk or dairy products

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Calcium Folinate (Leucovorin)

Commence 36 hours after commencement of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.

- administer via IV bolus via the side port of the IV line over 1 to 2 minutes
- flush with ~ 50 mL of sodium chloride 0.9%

Deaccess CVAD.

Continue safe handling precautions until 7 days after completion of drug(s)

Day 50

Safe handling and waste management

Safe administration

General patient assessment prior to each treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before recommencing treatment.

Prime IV line(s).

Access CVAD.

Note: A large volume of intravenous fluid may be given with this protocol. If weight increases by more than 1 kg from baseline or fluid balance becomes positive by one litre or any other signs of fluid overload are present, review by medical officer (diuretics may be required).

- daily weight
- monitor pH on all urine output
- strict fluid balance input and output

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Mercaptopurine

- administer orally ONCE a day on **days 1 to 56**
- to be swallowed whole with a glass of water; do not break, crush or chew
- preferably to be taken on an empty stomach, one hour before or at least 2 hours after food
- avoid concomitant consumption of milk or dairy products

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Methotrexate infusion

Prehydration:

- administer 100 mL sodium bicarbonate 8.4% in 1000 mL glucose 5% **OR** sodium chloride 0.9% over 4 hours
- continuous hydration with sodium bicarbonate 8.4% as prescribed
- when urine pH is greater than 7 commence methotrexate

If the urine pH drops below 7 during the methotrexate infusion:

- administer stat dose of 100 mL sodium bicarbonate 8.4% over 15 minutes
- continue to test all urine for pH, if the pH continues to drop below 7 seek medical review as further doses of sodium bicarbonate may be required

First dose of methotrexate:

- administer via IV infusion over 30 minutes
- the starting time of the methotrexate infusion **must** be documented as the calcium folinate (leucovorin) rescue is to commence exactly 36 hours after the commencement of the methotrexate and continue until the methotrexate level is less than 0.1 micromol/L

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- administer via IV infusion over 23 and a half hours
- flush with ~50 mL of sodium chloride 0.9%
- **Stop the methotrexate infusion after 23 and a half hours even if the infusion is not completed**

Post methotrexate:

- continue hydration over 8 hours with sodium bicarbonate 8.4% until methotrexate level is less than 0.1 micromol/L
- a minimum of 3 litres of fluid should be administered daily
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Post intrathecal care:

Local policies and guidelines regarding bed rest post dural puncture should be adhered to. At a minimum:

- the patient should have at least 1 set of observations including:
  - vital signs and GCS
  - any abnormal neurological signs such as nausea, vomiting, chills, fever, confusion, headache or other changes in neurological status
- educate the patient to recognise and immediately report any adverse reactions including blurred vision, dizziness, pain and or headache
- observe the lumbar puncture site for any leakage or bleeding post procedure
- document the procedure including outcomes in the patients notes

Continue safe handling precautions until 7 days after completion of drug(s)

Day 51

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require delay of treatment and review by medical officer before commencing treatment.

Prime IV line(s).

Access CVAD.

- daily weight
- monitor pH on all urine output
- strict fluid balance input and output

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Mercaptopurine

- administer orally ONCE a day on **days 1 to 56**
- to be swallowed whole with a glass of water; do not break, crush or chew
- preferably to be taken on an empty stomach, one hour before or at least 2 hours after food
- avoid concomitant consumption of milk or dairy products

Note: missed doses should not be replaced; if a dose is forgotten or vomited, normal dosing should be resumed at the next scheduled dose.

Calcium Folinate (Leucovorin)

Commence 36 hours after commencement of methotrexate infusion and repeat every 6 hours until methotrexate level is less than 0.1 micromol/L.

- administer via IV bolus via the side port of the IV line over 1 to 2 minutes
- flush with ~ 50 mL of sodium chloride 0.9%

Deaccess CVAD.

Continue safe handling precautions until 7 days after completion of drug(s)

Discharge information

Mercaptopurine tablets

- Mercaptopurine tablets with written instructions on how to take.

Antiemetics

- Antiemetics as prescribed.

Prophylaxis medications

- Prophylaxis medications (if prescribed) e.g. PJP prophylaxis, antifungals, antivirals.

Patient information

- Ensure patient receives patient information sheet.

Side effects

The side effects listed below are not a complete list of all possible side effects for this treatment. Side effects are categorised into the approximate onset of presentation and should only be used as a guide.

Immediate (onset hours to days)	
Headache	
Hypersensitivity reaction	Anaphylaxis and infusion related reactions can occur with this treatment. Read more about hypersensitivity reaction
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
Taste and smell alteration	Read more about taste and smell changes

Early (onset days to weeks)	
Neutropenia	Abnormally low levels of neutrophils in the blood. This increases the risk of infection. Any fever or suspicion of infection should be investigated immediately and managed aggressively. Read more about immediate management of neutropenic fever
Thrombocytopenia	A reduction in the normal levels of functional platelets, increasing the risk of abnormal bleeding. Read more about thrombocytopenia
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Fatigue	Read more about fatigue
Hepatotoxicity	Anti-cancer drugs administered either alone or in combination with other drugs and/or radiation may cause direct or indirect hepatotoxicity. Hepatic dysfunction can alter the metabolism of some drugs resulting in systemic toxicity.
Nephrotoxicity	Renal dysfunction resulting from damage to the glomeruli, tubules or renal vasculature.
Oral mucositis	Erythematous and ulcerative lesions of the gastrointestinal tract (GIT). It commonly develops following chemotherapy, radiation therapy to the head, neck or oesophagus, and high dose chemotherapy followed by a blood and marrow transplant (BMT). Read more about oral mucositis
Photosensitivity	Increased sensitivity to ultraviolet (UV) light resulting in an exaggerated sunburn-like reaction accompanied by stinging sensations and urticaria.
Skin rash	Anti-cancer drugs can cause a number of changes in the skin with maculo-papular rash the most common type of drug-induced skin reaction. Read more about skin rash

Late (onset weeks to months)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
Alopecia - partial	Hair thinning and/or patchy hair loss. Patients can also experience mild to moderate discomfort of the hair follicles, and rarely pain as the hair is falling out. Read more about alopecia and scalp cooling
Cognitive changes (chemo fog)	Changes in cognition characterised by memory loss, forgetfulness and feeling vague. This is also referred to as 'chemo brain' or 'chemo fog'. Read more about cognitive changes (chemo fog)
Pulmonary toxicity	Pulmonary toxicity may include damage to the lungs, airways, pleura and pulmonary circulation. Read more about pulmonary toxicity associated with anti-cancer drugs

Evidence

A search of the literature found limited evidence to support the use of intensive paediatric-inspired regimens in the treatment of acute lymphoblastic leukaemia (ALL) in older adolescents and young adults. The expert reference committee supported publication of the protocol on the basis of the information summarised below. The committee was most strongly influenced by data from the ALL06 phase II trial.[4]

Intensive paediatric regimens have been extensively used for the treatment of ALL in children and young adolescents. A French retrospective study[5] of 177 adolescent patients (15-20 years) compared outcomes of patients treated with either a paediatric regimen (FRALLE-93) or an adult regimen (LALA-94). Patients who received the paediatric regimen were more likely to reach complete remission (CR; 94% vs 83%, p=0.04) and had improved 5-year event-free survival (EFS; 67% vs 41%, p < 0.0001).

When compared to children and adolescents, adults with ALL tend to have poorer outcomes. This may be in part due to differences in the biology of ALL in adults, the increased prevalence of poor risk cytogenetic changes such as presence of the Philadelphia

chromosome (9;22 translocation) and reduced prevalence of good risk cytogenetic changes such as hyperdiploidy.[6]

The use of paediatric protocols in adults with ALL is promising. A retrospective study by the PETHEMA group[7] compared the outcomes of adolescents (age 15-18) and young adults (age 19-30) treated with a paediatric regimen (ALL-96). There was no significant difference in overall survival (OS; 77% vs 63%, p=0.44) or 6-year EFS (60% vs 63%, p=0.97) between the two groups.

The GRAALL 2003 study[8] treated 225 Philadelphia negative ALL patients aged 15–60 with a paediatric-inspired regimen. The CR rate was 93.5%, with an EFS rate of 55% and OS rate of 60%. Results were compared with the LALA-94 study of 712 patients treated with an adult regimen: the CR rate, EFS and OS rate were more favourable in patients treated with the GRAALL 2003 protocol.

The current ALL06 protocol is a BFM 2000-derived protocol developed for the ALL06 study of adults with ALL. The efficacy data from ALL06 is presented below.[4]

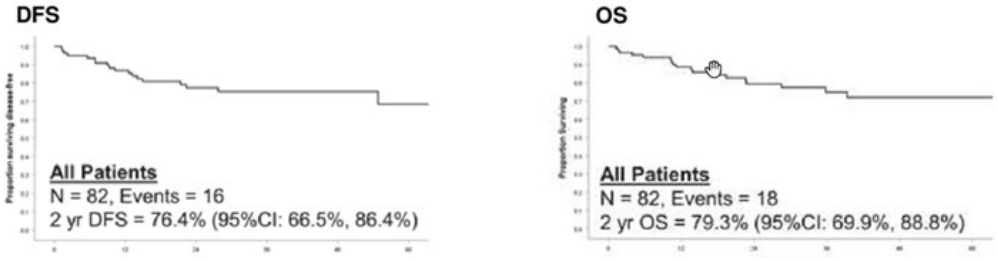
Source	Study & Year Published	Supports Use	Is the dose and regimen consistent with the protocol?	Comments
Phase II trials	ALL06 (2021)[4]	**Yes**	Yes	
	PETHEMA (2008)[7]	**Yes**	No	
	GRAALL (2009)[8]	**Yes**	No	

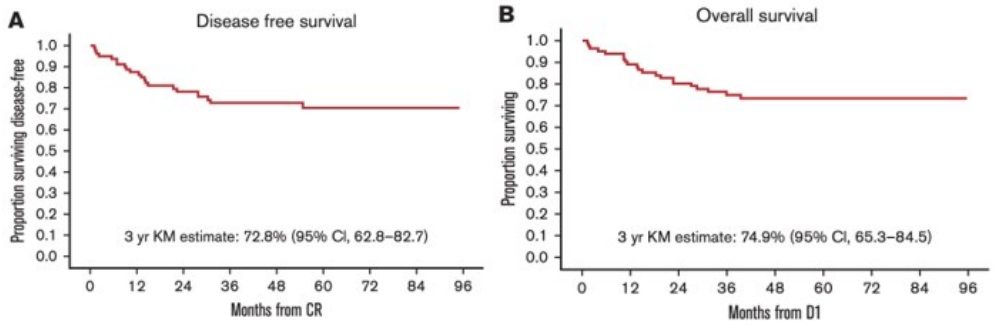
Efficacy

The ALL06 regimen, a BFM 2000-derived protocol, was used by Greenwood et al.[4, 9] in a phase II trial of 82 patients between 15-40 years with newly diagnosed Philadelphia-negative ALL. The primary outcome was the proportion of patients that commenced protocol M or High Risk (HR) Block 1 by day 94. The results were as follows:

Outcome[4]	ALL06
Total patients	82
Proportion receiving protocol M by day 94	34 (41.5%, p=0.77)
Median time to commencement of protocol M	97 days (IQR 87.5 - 103)
Induction mortality	3.6%
Complete response (CR)	79 (96.3%)
3-year overall survival (OS)	74.9% (95% CI: 65.3 - 84.5%)
3-year disease-free survival (DFS)	72.8% (95% CI: 62.8 - 82.7%)

Figure 1: Disease-free survival (DFS) and overall survival (OS) in the ALL06 Study[4, 9]



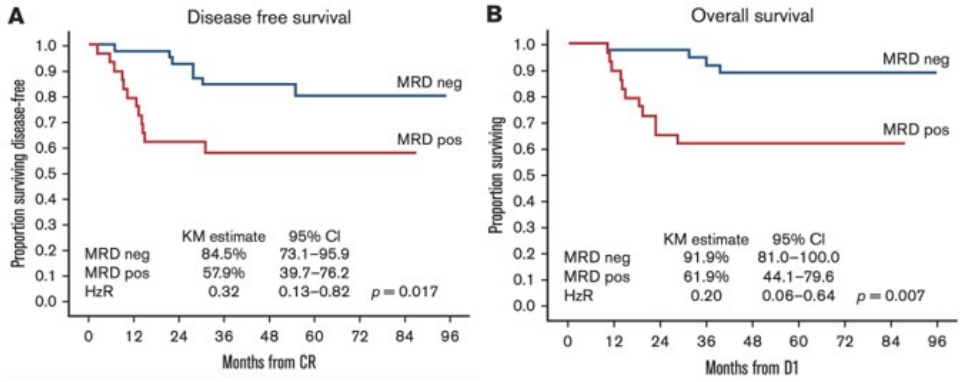


Role of Minimal Residual Disease Testing

Minimal residual disease (MRD) testing has commonly been used in a research setting in order to stratify risk, and is increasingly used in clinical practice for this purpose.

In the ALL06 study[4, 9], those who achieved a negative MRD at day 79 had improved 3-year DFS (HR 0.35, p=0.034) and OS (HR 0.19, p=0.006) when compared to those whose day 79 MRD was positive.

Figure 2: Role of MRD testing[4]



Toxicity

In the ALL06 study,[4] the most frequent grade 3 and grade 4 toxicities in the 34 patients who achieved protocol M / HR by day 94 were neutropenia (100%), anaemia (94%) and thrombocytopenia (91%).

The most common non-haematological toxicities were hepatic of which the most common were mild elevation of transaminases, cholestatic enzymes and bilirubin. 6% of patients experienced grade 4 non-haematological toxicities.

Neutropenic fevers and related infections were the most commonly seen infectious toxicities.

References

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3 Ramsey, L. B., F. M. Balis, M. M. O'Brien, et al. 2018. "Consensus Guideline for Use of Glucarpidase in Patients with High-Dose Methotrexate Induced Acute Kidney Injury and Delayed Methotrexate Clearance." Oncologist 23(1):52-61.

4 Greenwood, M., T. Trahair, R. Sutton, et al. 2021. "An MRD-stratified pediatric protocol is as deliverable in adolescents and young adults as in children with ALL." Blood Adv 5(24): 5574-5583.

5 Boissel, N., M. F. Auclerc, V. Lheritier, et al. 2003. "Should adolescents with acute lymphoblastic leukemia be treated as old children or young adults? Comparison of the French FRALLE-93 and LALA-94 trials." J.Clin Oncol. 21(5):774-780.

6 Moorman, Anthony V., Lucy Chilton, Jennifer Wilkinson, et al. 2010. "A population-based cytogenetic study of adults with acute lymphoblastic leukemia." Blood 115(2):206-214.

7 Ribera, J., A. Oriol, M. Sanz. et al. 2008. "Comparison of the results of the treatment of adolescents and young adults with standard-risk acute lymphoblastic leukemia with the Programa Espanol de Tratamiento en Hematologia Pediatric-based Protocol ALL-96". Journal of Clinical Oncology 10;26(11): 1843-9

8 Huguet, F., T. Leguay, E. Raffoux, et al. 2009. "Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study." Journal of Clinical Oncology 27(6):911-918.

9 Greenwood, M. T. Trahair, M. Osborn. et al. 2019. "Intensive Paediatric Therapy is as Deliverable in Adolescents and Young Adults as Children with ALL - Preliminary Results of the Australasian Leukaemia and Lymphoma Group (ALLG) ALL06 Study. EHA Poster presentation.

History

Version 2

Date	Summary of changes
29/11/2022	Protocol reviewed electronically by Haematology Reference Committee. Updates include: • Added further information on the administration of intrathecal methotrexate under the treatment schedule. • Evidence update - study data published for ALL06. • Removed 'interim' from protocol title. Other changes include: • Methotrexate target level updated.
15/05/2023	Approved and published as version number v.2. For review in 2 years.

Version 1

Date	Summary of changes
23/10/2020	New protocol taken to Haematology Committee meeting.
29/03/2021	Approved and published on eviQ. Version 1. Review in 1 year.
12/11/2021	Protocol flow diagram updated.
08/02/2022	PJP prophylaxis clinical information block updated.

First approved: 29 March 2021
Last reviewed: 15 May 2023
Review due: 30 June 2025

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/p/3828
28 Jun 2023

Patient information - Acute lymphoblastic leukaemia (ALL) - ALL06 Protocol M

Patient's name:

Your treatment

The treatment schedule below explains how the drugs for this treatment are given.

ALL06 Protocol M			
This treatment cycle is given once only.			
Day	**Treatment**	**How it is given**	**How long it takes**
1 to 56	**Mercaptopurine** (*mer-KAP-toe-PURE-een*)	Take orally ONCE a day on days 1 to 56 on an empty stomach, at least one hour before or two hours after food. Swallow whole with a glass of water, do not break, crush or chew. Avoid taking with dairy products as they may decrease its absorption. If you forget to take a tablet or vomit a tablet, take your normal dose the next time it is due. Do not take an extra dose.	
8, 22, 36 and 50	**Methotrexate (IV)** (*meth-o-TREX-ate*)	By a drip into a vein	For 24 hours
	Methotrexate (intrathecal)	By injection into your spine	About 4 hours
9, 23, 37 and 51	**Calcium folinate (Leucovorin)** (loo-koe-VOR-in)	By a drip into a vein every 6 hours after methotrexate infusion	About 5 minutes

When to get help

Anticancer drugs (drugs used to treat cancer) can sometimes cause serious problems. It is important to get medical help immediately if you become unwell.

IMMEDIATELY go to your nearest hospital Emergency Department, or contact your doctor or nurse if you have any of the following at any time:	**Emergency contact details** Ask your doctor or nurse from your treating team who to contact if you have a problem
• a temperature of 38°C or higher • chills, sweats, shivers or shakes • shortness of breath • uncontrolled vomiting or diarrhoea • pain, tingling or discomfort in your chest or arms • you become unwell.	Daytime: Night/weekend: Other instructions:

During your treatment immediately tell the doctor or nurse looking after you if you get any of the following problems:

- leaking from the area where the drugs are being given
- pain, stinging, swelling or redness in the area where the drugs are being given or at any injection sites
- a skin rash, itching, feeling short of breath, wheezing, fever, shivers, or feeling dizzy or unwell in any way (allergic reaction).

Other information about your treatment

Information for patients on allopurinol

Tell your doctor, nurse or pharmacist if you are taking allopurinol tablets (including Progout®, Zyloprim® and Allosig®). This treatment contains mercaptopurine, and allopurinol can increase the levels of this drug in the body. This can cause low white blood cells and increase your risk of infection. If you need to take both medicines, your doctor will reduce your dose of mercaptopurine and monitor your blood counts more regularly.

Changes to your dose or treatment delays

Sometimes a treatment may be started at a lower dose or the dose needs to be changed during treatment. There may also be times when your treatment is delayed. This can happen if your doctor thinks you are likely to have severe side effects, if you get severe side effects, if your blood counts are affected and causing delays in treatment, or if you are finding it hard to cope with the treatment. This is called a dose reduction, dose change or treatment delay. Your doctor will explain if you need any changes or delays to your treatment and the reason why.

Blood tests and monitoring

You will need to have a blood test before you start treatment and regularly throughout your treatment. Your doctor or nurse will tell you when to have these blood tests.

Central venous access devices (CVADs)

This treatment involves having chemotherapy through a central venous access device (CVAD). Your doctor or nurse will explain this to you. For more information see the eviQ patient information sheets on CVADs.

Other medications given during this treatment

- **Anti-sickness (anti-nausea) medication:** you may be given some anti-sickness medication. Make sure you take this medication as your doctor or nurse tells you, even if you don't feel sick. This can help to prevent the sickness starting.
- **Prophylaxis medication:** you may need to take some medications to prevent infection and to help prevent or reduce some of the side effects of the chemotherapy. Your doctor or nurse will tell you how and when to take these medications.

Side effects

Cancer treatments can cause damage to normal cells in your body, which can cause side effects. Everyone gets different side effects, and some people will have more problems than others.

The table below shows some of the side effects you may get with this treatment. You are unlikely to get all of those listed and you may also get some side effects that have not been listed.

Tell your doctor or nurse about any side effects that worry you. Follow the instructions below and those given to you by your doctor or nurse.

Immediate (onset hours to days)	
Headache	• You can take paracetamol if you have a headache. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get a very bad headache that is not helped by pain medication.**
Allergic reaction	• Allergic reactions are uncommon but can be life threatening. • **If you feel unwell during the infusion or shortly after it, or:** ◦ **get a fever, shivers or shakes** ◦ **feel dizzy, faint, confused or anxious** ◦ **start wheezing or have difficulty breathing** ◦ **have a rash, itch or redness of the face** **<u>While you are in hospital:</u> Tell your doctor or nurse immediately.** **<u>After you leave:</u> Contact your doctor or nurse immediately, or go to the nearest hospital Emergency Department.**
Nausea and vomiting	• You may feel sick (nausea) or be sick (vomit). • Take your anti-sickness medication as directed even if you don't feel sick. • Drink plenty of fluids (unless you are fluid restricted). • Eat small meals more frequently. • Try food that does not require much preparation. • Try bland foods like dry biscuits or toast. • Gentle exercise may help with nausea. • Ask your doctor or nurse for eviQ patient information - Nausea and vomiting during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have uncontrolled vomiting or feel dizzy or light-headed.**
Taste and smell changes	• You may find that food loses its taste or tastes different. • These changes are likely to go away with time. • Do your mouth care regularly. • Chew on sugar-free gum or eat sugar-free mints. • Add flavour to your food with sauces and herbs. • Ask your doctor or nurse for eviQ patient information - Taste and smell changes during cancer treatment.

Early (onset days to weeks)	
Infection risk (neutropenia)	• This treatment lowers the amount of white blood cells in your body. The type of white blood cells that help to fight infection are called neutrophils. Having low level of neutrophils is called neutropenia. If you have neutropenia, you are at greater risk of getting an infection. It also means that your body can't fight infections as well as usual. This is a serious side effect, and can be life threatening. • Wash your hands often. • Keep a thermometer at home and take your temperature regularly, and if you feel unwell. • Do your mouth care regularly. • Inspect your central line site (if you have one) daily for any redness, pus or swelling. • Limit contact with people who are sick. • Learn how to recognise the signs of infection. • Ask your doctor or nurse for eviQ patient information - Infection during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:** ◦ **a temperature of 38°C or higher** ◦ **chills, shivers, sweats or shakes** ◦ **a sore throat or cough** ◦ **uncontrolled diarrhoea** ◦ **shortness of breath** ◦ **a fast heartbeat** ◦ **become unwell even without a temperature.**

Low platelets (thrombocytopenia)	• This treatment lowers the amount of platelets in your blood. Platelets help your blood to clot. When they are low, you are at an increased risk of bleeding and bruising. • Try not to bruise or cut yourself. • Avoid contact sport or vigorous exercise. • Clear your nose by blowing gently. • Avoid constipation. • Brush your teeth with a soft toothbrush. • Don't take aspirin, ibuprofen or other similar anti-inflammatory medications unless your doctor tells you to. • Tell your doctor or nurse if you have any bruising or bleeding. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if you have any uncontrolled bleeding.**
Appetite loss (anorexia)	• You may not feel like eating. • Try to avoid drinking fluids at meal times. • Try to eat small meals or snacks regularly throughout the day. • Try to eat food that is high in protein and calories. • If you are worried about how much food you can eat, or if you are losing weight, ask to speak to a dietitian.
Tiredness and lack of energy (fatigue)	• You may feel very tired, have no energy, sleep a lot, and not be able to do normal activities or things you enjoy. • Do not drive or operate machinery if you are feeling tired. • Nap for short periods (only 1 hour at a time) • Prioritise your tasks to ensure the best use of your energy. • Eat a well balanced diet and drink plenty of fluids (unless you are fluid restricted). • Try some gentle exercise daily. • Allow your friends and family to help. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Liver problems	• You may get: ◦ yellowing of your skin or eyes ◦ itchy skin ◦ pain or tenderness in your stomach ◦ nausea and vomiting ◦ loss of appetite • You will have regular blood tests to check how well your liver is working. • **Tell your doctor or nurse as soon as possible if you notice that your urine is a dark colour, the whites of your eyes look yellow, or if you have stomach pain.**
Kidney damage	• This treatment can cause changes to how your kidneys work. • You will have blood tests to make sure your kidneys are working properly. • You may need to drink more fluids while you are having treatment. Your doctor or nurse will tell you if you need to do this. • **Tell your doctor or nurse as soon as possible if you notice that your urine changes colour or you don't need to empty your bladder as often.**

Mouth pain and soreness (mucositis)	• You may have:
	  ◦ bleeding gums
	  ◦ mouth ulcers
	  ◦ a white coating on your tongue
	  ◦ pain in the mouth or throat
	  ◦ difficulty eating or swallowing.
	• Avoid spicy, acidic or crunchy foods and very hot or cold food and drinks.
	• Try bland and soft foods.
	• Brush your teeth gently with a soft toothbrush after each meal and at bedtime. If you normally floss continue to do so.
	• Rinse your mouth after you eat and brush your teeth, using either:
	  ◦ 1/4 teaspoon of salt in 1 cup of warm water, or
	  ◦ 1/4 teaspoon of bicarbonate of soda in 1 cup of warm water
	• Ask your doctor or nurse for eviQ patient information - Mouth problems during cancer treatment.
	• **Tell your doctor or nurse if you get any of the symptoms listed above.**

Skin that is more sensitive to the sun (photosensitivity)	• After being out in the sun you may develop a rash like a bad sunburn. • Your skin may become red, swollen and blistered. • Avoid direct sunlight. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and a sunscreen of SPF 50 or higher. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Skin rash	• You may get a red, bumpy rash and dry, itchy skin. • Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream. • Do not scratch your skin. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher. • **Talk to your doctor or nurse about other ways to manage your skin rash.**

Late (onset weeks to months)	
Low red blood cells (anaemia)	• You may feel dizzy, light-headed, tired and appear more pale than usual. • Tell your doctor or nurse if you have any of these signs or symptoms. You might need a blood transfusion. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have any chest pain, trouble breathing, or feel like your heart is racing.**
Hair thinning	• Your hair may become dry and may break easily. • You may lose some of your hair. • Use a gentle shampoo and a soft hairbrush. • Take care with hair products like hairspray, hair dye, bleaches and perms. • Protect your scalp from the cold with a hat or scarf. • Protect your scalp from the sun with a hat and sunscreen of SPF 50 or higher. • Ask your doctor or nurse about the Look Good Feel Better program (www.lgfb.org.au)
Chemo brain (chemotherapy-related cognitive impairment)	• You may notice that you are unable to concentrate, feel unusually disorganised or tired (lethargic) and have trouble with your memory. • These symptoms usually improve once treatment is completed. • Ask your doctor or nurse for eviQ patient information – Memory changes and chemotherapy (chemo brain). • Tell your doctor or nurse if you get any of the symptoms listed above.
Lung problems	• Lung problems are rare, but can be serious. They may occur throughout treatment or after the completion of treatment. • You may get: ◦ shortness of breath ◦ fever ◦ dry cough ◦ wheezing ◦ fast heartbeat ◦ chest pain. • Your doctor will monitor how well your lungs are working during your treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have chest pain or become short of breath.**

General advice for people having cancer treatment

Chemotherapy safety

- Learn how to keep you and your family safe while you are having anticancer drugs.
- See our patient information sheet - Chemotherapy safety at home.

Blood clot risk

- Cancer and anticancer drugs can increase the risk of a blood clot (thrombosis).
- Tell your doctor if you have a family history of blood clots.
- A blood clot can cause pain, redness, swelling in your arms or legs, shortness of breath or chest pain.
- If you have any of these symptoms go to your nearest hospital Emergency Department.

Medications and vaccinations

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal supplements.
- Don't stop or start any medications during treatment without talking to your doctor and pharmacist first.
- Paracetamol is safe to take if you have a headache or other mild aches and pains. It is recommended that you avoid taking aspirin, ibuprofen and other anti-inflammatory type medications for pain while you are having treatment. However, if these medications have been prescribed by your doctor, do not stop taking them without speaking with your doctor.
- Vaccinations such as flu and tetanus vaccines are safe to receive while having treatment. Do not have any live vaccines during your treatment or for 6 months after it finishes. If you are unsure, check with your doctor before you have any vaccinations.
- People you live with should be fully vaccinated, including having live vaccines according to the current vaccination schedule. Extra

care needs to be taken with hand washing and careful disposal of soiled nappies for infants who have recently received the rotavirus vaccine.

Other medical and dental treatment

- If you go to hospital or any other medical appointment (including dental appointments), always tell the person treating you that you are receiving anticancer drugs.
- Before you have any dental treatment, talk to your doctor.

Diet and food safety

- While you are receiving this treatment it is important that you try to maintain a healthy diet.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.
- There are some foods that may cause infection in high risk individuals and should be avoided. For more information on foods to avoid and food hygiene please ask for a copy of the Listeria and food brochure.

Fertility

- Some cancer treatments can reduce your fertility. This can make it difficult or impossible to get pregnant or father a child.
- Talk to your doctor or nurse before you start any treatment. Depending on your situation there may be fertility sparing options available to you and/or your partner, discuss these with your doctor or nurse.

Pregnancy and breastfeeding

- Some cancer treatments can be dangerous to unborn babies. Talk to your doctor or nurse if you think there is any chance that you could be pregnant.
- Do not try to get pregnant or father a child during this treatment. Contraception should be used during treatment and after stopping treatment. Ask your doctor or nurse about what type of contraception you should use.
- If you are planning pregnancy/fatherhood after completing this treatment, talk to your doctor. Some doctors advise waiting between 6 months and 2 years after treatment.
- Do not breastfeed if you are on this treatment, as anti-cancer medications can also pass into breast milk.

Sex life and sexuality

- The desire to have sex may decrease as a result of this treatment or its side effects.
- Your emotions and the way you feel about yourself may also be affected by this treatment.
- It may help to discuss your concerns with your partner and doctor or nurse.

Quitting smoking

- It is never too late to quit smoking. Quitting smoking is one of the best things you can do to help your treatment work better.
- There are many effective tools to improve your chances of quitting.
- Talk to your treating team for more information and referral to a smoking cessation support service.

Staying active

- Research shows that exercise, no matter how small, has many benefits for people during and after cancer treatment.
- Talk to your doctor before starting an exercise program. Your doctor can advise whether you need a modified exercise program.

For more information about cancer treatment, side effects and side effect management see our Patient and carers section.

Where to get more information

Telephone support

- Call Cancer Council on 13 11 20 for cancer information and support
- Call the Leukaemia Foundation on 1800 620 420 (Mon to Fri 9am – 5pm)
- Call the Lymphoma Nurse Support Line on 1800 953 081 (Mon to Fri 9am - 5pm)

Haematology, transplant and cellular therapy information

- Arrow bone marrow transplant foundation – arrow.org.au
- Australasian Menopause Society – menopause.org.au
- Chris O'Brien Lifehouse - Total Body Irradiation - mylifehouse.org.au/departments/radiation-oncology/total-body-irradiation/

- Healthy Male Andrology Australia – healthymale.org.au/
- International Myeloma Foundation – myeloma.org
- Leukaemia Foundation – leukaemia.org.au
- Lymphoma Australia – lymphoma.org.au
- Myeloma Australia – myeloma.org.au
- NSW Agency for Clinical Innovation, Blood & Marrow Transplant Network – aci.health.nsw.gov.au/resources/blood-and-marrow-transplant
- NSW Agency for Clinical Innovation - aci.health.nsw.gov.au/projects/immune-effector-cell-service
- NCCN Guidelines for Patients Immunotherapy Side Effects: CAR T-Cell Therapy - nccn.org/patientresources/patient-resources/guidelines-for-patients
- Talk Blood Cancer – cmlsupport.org.uk/organisation-type/social-media-groups

General cancer information and support

- Australian Rare Cancer (ARC) Portal – arcportal.org.au/
- Beyondblue – beyondblue.org.au
- Cancer Australia – canceraustralia.gov.au
- Cancer Council Australia – cancer.org.au
- Cancer Voices Australia – cancervoicesaustralia.org
- CanTeen – canteen.org.au
- Carers Australia – carersaustralia.com.au
- eviQ Cancer Treatments Online – eviQ.org.au
- Food Standards Australia New Zealand: Listeria & Food Safety – foodstandards.gov.au/publications/pages/listeriabrochuretext.aspx
- LGBTQI+ People and Cancer - cancercouncil.com.au/cancer-information/lgbtqi
- Look Good Feel Better – lgfb.org.au
- Patient Information - patients.cancer.nsw.gov.au
- Radiation Oncology Targeting Cancer - targetingcancer.com.au
- Redkite – redkite.org.au
- Return Unwanted Medicines – returnmed.com.au
- Staying active during cancer treatment – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/staying-active

Quit smoking information and support

Quitting smoking is helpful even after you have been diagnosed with cancer. The following resources provide useful information and support to help you quit smoking. Talk to your treating team about any other questions you may have.

- Call Quitline on 13 QUIT (13 78 48)
- iCanQuit – iCanQuit.com.au
- Patient Information - patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking
- Quitnow – quitnow.gov.au

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The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/pi/3828
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