Acute lymphoblastic leukaemia MRD+ blinatumomab

ID: 3483 v.1 **Endorsed**

⚠ The following have occurred in patients receiving blinatumomab:

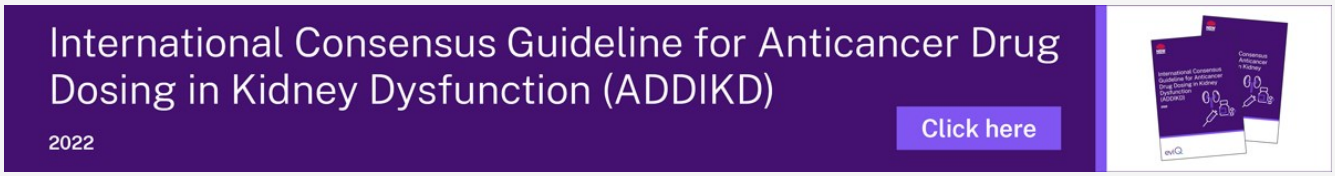
- Cytokine Release Syndrome, which may be life-threatening or fatal
- Neurological toxicities, which may be severe, life-threatening, or fatal
- Reactivation of JC viral infection

Interrupt or discontinue blinatumomab as recommended if any of these adverse events occur.

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 blinatumomab

Treatment schedule - Overview

Drug	Dose	Route	Day
Blinatumomab	28 micrograms *	CIV over 24 hours	1 to 28

* Patients weighing greater than or equal to 45 kg receive a fixed-dose. For patients weighing less than 45 kg, the dose is calculated using the patient's body surface area (BSA) at 15 micrograms/m2/day (not exceeding 28 micrograms/day)

Duration: 42 days . A single cycle of treatment is 28 days (4 weeks) of continuous infusion. Each cycle of treatment is separated by a 14 day (2 week) treatment-free interval.

Cycles: 1 to 4.

Notes:

- Hospitalisation is recommended at a minimum for the first 3 days of the first cycle and the first 2 days of the second cycle.
- Blinatumomab preparation and administration can be complex. It is important that the instructions for preparation and administration provided in the Product Information are strictly followed to minimise medication errors.
- Intrathecal chemotherapy prophylaxis is recommended before and during blinatumomab therapy to prevent central nervous system ALL relapse.

Drug status: **Blinatumomab:** (PBS authority)

Cost: ~ $77,360 per cycle

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		
Dexamethasone	20 mg (IV)	60 minutes before the start of treatment
Blinatumomab	28 micrograms (CIV over 24 hours)	in sodium chloride 0.9% over 24 hours as a continuous infusion

Day 2 to 28		
Blinatumomab	28 micrograms (CIV over 24 hours)	in sodium chloride 0.9% over 24 hours as a continuous infusion

Notes:

- Dexamethasone 20 mg should also be administered as a premedication when restarting an infusion after an interruption of 4 hours or more.
- Blinatumomab preparation and administration can be complex. It is important that the instructions for preparation and administration provided in the Product Information are strictly followed to minimise medication errors.
- Hospitalisation is recommended at a minimum for the first 3 days of the first cycle and the first 2 days of the second cycle.
- Intrathecal chemotherapy prophylaxis is recommended before and during blinatumomab therapy to prevent central nervous system ALL relapse.

Duration: 42 days . A single cycle of treatment is 28 days (4 weeks) of continuous infusion. Each cycle of treatment is separated by a 14 day (2 week) treatment-free interval.

Cycles: 1 to 4.

Indications and patient population

- Minimal residual disease (MRD) positive B-cell precursor acute lymphoblastic leukaemia (ALL) in patients in complete haematological remission

Clinical information

Venous access	Central venous access device (CVAD) is required to administer this treatment. Read more about central venous access device line selection
Premedication	The product information states that premedication is required for this treatment. Please refer to the treatment schedule for suggested premedication regimen. This may be substituted to reflect institutional policy.
Emetogenicity LOW	Dexamethasone has been included as both an antiemetic and premedication for hypersensitivity in this protocol. 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

Cytokine Release Syndrome/Infusion Reactions	Potentially life-threatening cytokine release syndrome (CRS) have been reported in patients receiving blinatumomab. Infusion reactions have also occurred and may be clinically indistinguishable from manifestations of CRS. Serious adverse events included pyrexia, asthenia, headache, hypotension, elevated liver enzymes, total bilirubin increased, and nausea. In some cases, disseminated intravascular coagulation, capillary leak syndrome, and haemophagocytic lymphohistiocytosis/macrophage activation syndrome have been reported in the setting of CRS. Patients should be closely monitored for signs or symptoms of these events. Management of CRS events may require either temporary interruption or discontinuation of blinatumomab.
Neurologic toxicity	Approximately 65% of patients experienced neurological toxicity. The most common neurological symptoms were headaches and tremor. Grade 3 or higher, including fatal neurological adverse events, included encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. The majority of events resolved and infrequently led to blinatumomab treatment discontinuation. Patients receiving blinatumomab should be closely monitored for signs and symptoms of neurological toxicity. If symptoms are severe blinatumomab should be temporarily interrupted or discontinued.
Leukoencephalopathy	There is a potential risk of leukoencephalopathy in patients receiving blinatumomab. Cranial magnetic resonance imaging (MRI) changes showing leukoencephalopathy have been observed, especially in patients with prior treatment with cranial irradiation and anti-leukaemic chemotherapy (including systemic high dose methotrexate or intrathecal cytarabine). The clinical significance of these imaging changes is unknown.
Progressive multifocal leukoencephalopathy	Use of monoclonal antibodies may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a rare but potentially fatal opportunistic viral infection of the brain. Patients must be monitored for any new or worsening neurological symptoms. Read more about progressive multifocal leukoencephalopathy and the Therapeutic Goods Administration Medicines Safety update on progressive multifocal leukoencephalopathy from the Australian Government, Department of Health.
Pancreatitis	Pancreatitis, life-threatening or fatal, have been reported in patients receiving blinatumomab. In some cases, high-dose steroid therapy may have contributed. Monitor patients who develop signs and symptoms of pancreatitis, and if severe blinatumomab may be temporary interruption or discontinued.
Tumour lysis risk	Assess patient for risk of developing tumour lysis syndrome. Read more about prevention and management of tumour lysis syndrome.
Pneumocystis jirovecii pneumonia (PJP) prophylaxis	PJP prophylaxis is recommended e.g. trimethoprim/sulfamethoxazole 160/800 mg PO one tablet twice daily, twice weekly (e.g. on Mondays and Thursdays) OR one tablet three times weekly (e.g. on Mondays, Wednesdays and Fridays). Read more about prophylaxis of pneumocystis jiroveci (carinii) in cancer patients
Antiviral prophylaxis	Read more about antiviral prophylaxis drugs and doses
Antifungal prophylaxis	Read more about antifungal prophylaxis drugs and doses.
Irradiated blood components	The use of irradiated of blood components is recommended for patients receiving this treatment. Read more about the indications for the use of irradiated blood components
Blood tests	FBC, EUC, LFTs, LDH, urate and lipase at baseline, then prior to each treatment or 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: If adverse effects cause an interruption to the treatment period of:

- Less than 7 days: continue the same cycle to a total of 28 days (inclusive of days before and after the interruption in that cycle)
- Greater than 7 days: start a new cycle

Dexamethasone 20 mg should also be administered as a premedication when restarting an infusion after an interruption of 4 hours or more.

Haematological toxicity

There is no information regarding dose adjustment based on haematological parameters. Neutropenia and febrile neutropenia, including life threatening cases have been reported. Monitor FBC during blinatumomab administration and interrupt blinatumomab if prolonged neutropenia occurs.

Renal impairment

There is no formal data in patients with renal impairment. However, based on pharmacokinetic analyses, dose adjustment in patients with mild to moderate renal impairment is not necessary.

Hepatic impairment

There is no formal data in patients with hepatic impairment. Since blinatumomab is a protein and not metabolised through the hepatic pathway, dose adjustment is not necessary.

Cytokine release syndrome (CRS)	
Grade 3	Interrupt treatment until toxicity resolved. Then recommence at: • **≥ 45 kg:** 9 micrograms/day. Escalate to 28 micrograms/day after 7 days if the toxicity does not recur. • **< 45 kg:** 5 micrograms/m^2/day. Escalate to 15 micrograms/m^2/day after 7 days if the toxicity does not recur.
Grade 4	Discontinue blinatumomab permanently

Neurological toxicity	
Seizure	Discontinue blinatumomab permanently if more than one seizure occurs
Grade 3	Interrupt treatment until toxicity has resolved to Grade 1 or less for at least 3 days. Then recommence at: • **≥ 45 kg:** 9 micrograms/day. Escalate to 28 micrograms/day after 7 days if the toxicity does not recur. For reinitiation, premedication with 24 mg dexamethasone with a 4 day taper. As secondary prophylaxis, consider appropriate anticonvulsant medication. If the toxicity occurred at 9 micrograms/day, or if the toxicity takes >7 days to resolve discontinue blinatumomab permanently. • **< 45 kg:** 5 micrograms/m^2/day. Escalate to 15 micrograms/m^2/day after 7 days if the toxicity does not recur. Consider appropriate anticonvulsant medication. If the toxicity occurred at 5 micrograms/m^2/day, or if the toxicity takes >7 days to resolve discontinue blinatumomab permanently.
Grade 4	Discontinue blinatumomab permanently

Non-Haematological toxicity	
Grade 3	Interrupt treatment until toxicity has resolved to Grade 1 or less. Then recommence at: • **≥ 45 kg:** 9 micrograms/day. Escalate to 28 micrograms/day after 7 days if the toxicity does not recur. • **< 45 kg:** 5 micrograms/m^2/day. Escalate to 15 micrograms/m^2/day after 7 days if the toxicity does not recur.
Grade 4	Discontinue blinatumomab permanently

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*

Blinatumomab		
No formal drug interaction studies have been conducted with blinatumomab.		
	Interaction	**Clinical management**
CYP450 substrates, especially those with a narrow therapeutic index	Transient blinatumomab-mediated cytokine elevation may suppress CYP450 enzyme activities and result in	Avoid combination or monitor for toxicity. Dosage of the substrate should be adjusted as needed.

Blinatumomab		
	increased toxicity or drug concentrations of the CYP450 substrate.	The risk of this interaction is increased during the first 9 days of the first cycle of blinatumomab and the first 2 days of the second cycle.

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.

Note: Blinatumomab preparation and administration can be complex. It is important that the instructions for preparation and administration provided in the Product Information are strictly followed to minimise medication errors.

Day 1

Handling of monoclonal antibodies and waste management

Safe administration

General patient assessment prior to each day of treatment.

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

Prime IV line(s).

Access CVAD.

- baseline weight
- baseline neurological assessment e.g. daily handwriting assessment that includes the date, time and location.

Pre treatment medication

Administer antiemetics if required

Dexamethasone

- administer 60 minutes **before** the start of blinatumomab treatment
- administer via IV infusion over 15 minutes
- flush with ~ 50mL sodium chloride 0.9%.

Treatment - Time out

Blinatumomab

Prior to administration

- ensure a PVC-free line is used and primed with blinatumomab only and attach a protein-sparing 0.2 micron in-line filter
- dedicate a CVAD lumen solely for blinatumomab and ensure that no other drug or fluid is given through this port
- ensure that the infusion is commenced at an appropriate time to facilitate outpatient infusion bag / cassette changes.

Administer blinatumomab

- via continuous IV infusion
- do not administer any remaining fluid once the prescribed infusion time has ceased as this may result in excess dosing
- observe for signs of an infusion reaction especially cytokine release syndrome and/or neurological problems e.g. seizures, headache, confusion, slurred speech, etc.

If an infusion reaction occurs notify medical officer immediately

- for severe reactions **stop** infusion and manage as per emergency

Note: do **NOT** flush the blinatumomab infusion line or the dedicated CVAD lumen, especially when changing infusion bags or cassettes. Flushing when changing bags or at completion of infusion can result in an excess dosage / drug bolus and complications to the patient.

Continue safe handling precautions (reproductive risk only) for 7 days after completion of drug(s).

Days 2 to 28

Handling of monoclonal antibodies 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.

- regular neurological assessment e.g. daily handwriting assessment that includes the date,time and location.

Pre treatment medication

Administer antiemetics if required

Treatment - Time out

Blinatumomab

Prior to administration

- ensure a PVC-free line is used and primed with blinatumomab only and attach a protein-sparing 0.2 micron in-line filter
- dedicate a CVAD lumen solely for blinatumomab and ensure that no other drug or fluid is given through this port
- ensure that the infusion is commenced at an appropriate time to facilitate outpatient infusion bag / cassette changes.

Administer blinatumomab

- via continuous IV infusion
- do not administer any remaining fluid once the prescribed infusion time has ceased as this may result in excess dosing
- observe for signs of an infusion reaction especially cytokine release syndrome and/or neurological problems e.g. seizures, headache, confusion, slurred speech, etc.

If an infusion reaction occurs notify medical officer immediately

- for severe reactions **stop** infusion and manage as per emergency

Note: do **NOT** flush the blinatumomab infusion line or the dedicated CVAD lumen, especially when changing infusion bags or cassettes. Flushing when changing bags or at completion of infusion can result in an excess dosage / drug bolus and complications to the patient.

Deaccess CVAD.

Continue safe handling precautions (reproductive risk only) for 7 days after completion of drug(s).

Discharge information

Antiemetics

- Antiemetics as prescribed.

Prophylaxis medications

- Prophylaxis medications (if prescribed) i.e. tumour lysis prophylaxis, 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)	
Flu-like symptoms	
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

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
Constipation	
Diarrhoea	Read more about treatment induced diarrhoea
Fatigue	Read more about fatigue
Fever	
Fluid retention and oedema	An excess amount of fluid around the cells, tissues or serous cavities of the body, leading to swelling.
Headache	
Hypokalaemia	Abnormally low levels of potassium in the blood.
Insomnia	

Late (onset weeks to months)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
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)
Progressive multifocal leukoencephalopathy (PML)	A rare opportunistic viral infection of the brain, usually leading to death or severe disability, can occur with monoclonal antibodies (e.g. rituximab, obinutuzumab, ofatumumab, brentuximab vedotin) and other targeted therapies (e.g. ibrutinib, ruxolitinib, idelalisib). Onset may occur up to months after the final dose. Read more about progressive multifocal leukoencephalopathy (PML)

Evidence

The main evidence supporting the use of blinatumomab in minimal residual disease (MRD) positive disease derives from a phase 2, open label, multicentre study.[1]

To be eligible, patients were required to be in complete haematological remission (CHR), defined as <5% blasts, neutrophil count >1.0 x 10^9/L, platelets >50000/uL and Hb >9 g/dL. They were required to have molecular failure with persistent or recurrent MRD >10^{-3} and to have received 3 blocks of high-dose chemotherapy. Patients could be in their first or subsequent CHR.[1]

The main intention of the study was to determine the rates of conversion from MRD positivity to negativity and to assess what effect conversion to MRD negativity had on overall outcomes.[1]

Given that this population of patients is expected to have substantially lower disease burden, there was no ramp-up dosing in cycle 1, as there was in studies using blinatumomab in situations of frank relapsed or refractory disease. Corticosteroid pre-treatment was given before each cycle to reduce the risk of neurological events or cytokine release syndrome.[1]

Patients were given up to 4 cycles of blinatumomab but could proceed to haematopoietic stem cell transplantation at any time after cycle 1. The primary endpoint was rate of MRD response after cycle 1. The key secondary endpoint was haematological relapse-free survival (RFS) at 18 months after commencing blinatumomab.[1]

Source	Study & Year Published	Supports Use	Is the dose and regimen consistent with the protocol?	Comments
Phase II trials	Gokbuget et al. 2018[1]	**Yes**	Yes	-
Guidelines	**Date published/revised**	**Supports Use**	**Is the dose and regimen consistent with the protocol?**	**Comments**
NCCN	Acute lymphoblastic leukaemia V1.2018	**Yes**	Yes	-
BCCA	N/A	**N/A**	N/A	-
CCO	March 2022	**Yes**	Yes	-

Efficacy

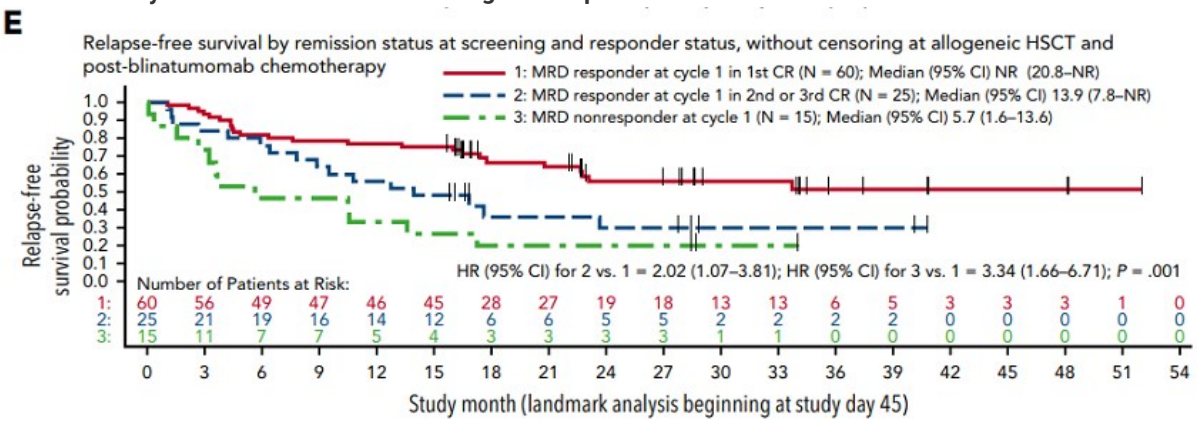
113 patients were evaluable (59% male, 41% female). 88/113 (78%) achieved MRD negativity after cycle 1, 2 more patients after cycle 2, and then no further patients in cycle 3 or 4. In comparing MRD responders to non-responders; RFS was 23.6 vs 5.7 months and OS was 38.9 vs 12.5 months.

Patients had better response rates if they were in their first CHR, compared with later CHRs, with a median RFS of 24.6 vs 11.0 months respectively.[1]

Allogeneic transplantation

74/110 (67%) proceeded to allogeneic transplant. Of these, 36/74 (49%) were in CR at 2 years. This is compared with the 36/110 (33%) who did not proceed to allogeneic transplant, 9/36 (25%) were in CR at 2 years.[1]

Relapse-free survival by remission status at screening and responder status[1]



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Toxicity

The most common adverse reactions among adult patients were pyrexia (89%), headache (38%), tremor (30%), chills (25.9%), fatigue (24.1%), nausea (23.3%), vomiting (22.4%), hypokalaemia (15.5%), and diarrhoea (19.8%). The most common grade 3 to 4 toxicities were neutropenia (17.2%) and pyrexia (7.8%).[1]

Patients with grade 4 neurologic adverse events were required to permanently discontinue blinatumomab. 12/110 (10%) had >grade 3 neurologic adverse events and required treatment interruption. 7 were able to resume at a lower dose, of whom 5 were able to continue at this dose. The other 2 stopped therapy in view of another neurological event. Tremor (5 pts), aphasia (3), seizure (3) and encephalopathy (3) were the commonest neurological events requiring treatment cessation.[1]

Summary of adverse events[1]

	All patients (N = 116)		
	Any grade	Grade 3	Grade 4
Any adverse event, n (%)	116 (100)	38 (33)	31 (27)
Non-neurologic adverse events, worst grade ≥3 occurring in ≥3% of patients			
Pyrexia	103 (89)	9 (8)	0 (0)
Headache	44 (38)	4 (3)	0 (0)
Neutropenia	18 (16)	2 (2)	16 (14)
Leukopenia	8 (7)	5 (4)	2 (2)
Anemia	7 (6)	4 (3)	1 (1)
ALT increased	7 (6)	2 (2)	4 (3)
Thrombocytopenia	6 (5)	2 (2)	3 (3)
AST increased	5 (4)	1 (1)	3 (3)
Any neurologic adverse event*	61 (53)	12 (10)	3 (3)
Neurologic events, worst grade ≥3			
Tremor	35 (30)	6 (5)	0 (0)
Aphasia	15 (13)	1 (1)	0 (0)
Dizziness	9 (8)	1 (1)	0 (0)
Confused state	6 (5)	1 (1)	0 (0)
Encephalopathy	6 (5)	3 (3)	2 (2)
Seizure	3 (3)	1 (1)	1 (1)
Disorientation	3 (3)	1 (1)	0 (0)
Depressed level of consciousness	1 (1)	1 (1)	0 (0)
Generalized tonic-clonic seizure	1 (1)	1 (1)	0 (0)

All adverse events regardless of causality that occurred during the treatment period plus 30 days. Thirty-six patients (31%) had treatment interruptions because of treatment-emergent adverse events, mainly as a result of neurologic events and flu-like symptoms. Those occurring in ≥2% of patients included pyrexia (8%) and aphasia, encephalopathy, overdose, tremor, ALT increased, AST increased, and chills (3% each).

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

*Among all patients. Multiple events may have occurred in some patients.

References

1 Gokbuget, N., H. Dombret, M. Bonifacio, et al. 2018. "Blinatumomab for minimal residual disease in adults with B-cell precursor acute lymphoblastic leukemia." Blood 131(14):1522-1531.

History

Version 1

Date	Summary of changes
21/09/2018	New protocol taken to Haematology Reference Committee meeting
01/11/2018	New protocol published on eviQ. V1.
9/12/2019	PBS status updated to authority.
23/10/2020	Protocol reviewed electronically by Haematology Reference Committee, no changes. Review in 2 years.
30/06/2022	Protocol reviewed electronically by Haematology Reference Committee. Minor updates include: • Interactions updated • CCO guideline added to evidence • Image titles and references added to efficacy and toxicity sections • Patient information title changed to MRD-positive blinatumomab • Minor grammatical changes

Date	Summary of changes
	Review in 1 year.
19/01/2023	Removed the note after cycles as it included "induction" and "consolidation" which is not relevant in this patient population.

First approved: 21 September 2018
Last reviewed: 30 June 2022
Review due: 30 June 2023

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/3483
28 Jun 2023

Patient information - Acute lymphoblastic leukaemia (ALL) - MRD-positive blinatumomab

Patient's name:

Your treatment

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

MRD-positive blinatumomab

This treatment cycle is repeated every 42 days (4 weeks of treatment followed by a 2 week rest). Your doctor will advise you of the number of treatments you will have.

Day	Treatment	How it is given	How long it takes
1 to 28	**Blinatumomab** *(blin-a-toom-oh-mab)*	By a drip into a vein	24 hours continuously each day

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 • leaking from your pump • 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

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 may need to have blood tests while you are receiving this treatment. Your doctor or nurse will tell you when to have these blood tests.

Pumps and central venous access devices (CVADs)

This treatment involves having chemotherapy through a pump. To have this, you will also need 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 pumps and CVADs. At home you will need to look at your pump 3 to 4 times a day to check it is working. Your nurse will teach you how to do this.

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)	

Flu-like symptoms	• You may get:
	  ◦ a fever
	  ◦ chills or sweats
	  ◦ muscle and joint pain
	  ◦ a cough
	  ◦ headaches.
	• Tell your doctor or nurse if you get any of the symptoms listed above.
	• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have a temperature of 38°C or higher.**

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.**

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.**
Constipation	• You may have bowel motions (stools, poo) that are less frequent, harder, smaller, painful or difficult to pass. • You may also get: ◦ bloating, cramping or pain ◦ a loss of appetite ◦ nausea or vomiting. • Drink plenty of fluids (unless you are fluid restricted). • Eat plenty of fibre-containing foods such as fruit, vegetables and bran. • Take laxatives as directed by your doctor. • Try some gentle exercise daily. • **Tell your doctor or nurse if you have not opened your bowels for more than 3 days.**
Diarrhoea	• You may get bowel motions (stools, poo) that are more frequent or more liquid. • You may also get bloating, cramping or pain. • Take your antidiarrhoeal medication as directed by your doctor. • Drink plenty of fluids (unless you are fluid restricted). • Eat and drink small amounts more often. • Avoid spicy foods, dairy products, high fibre foods, and coffee. • Ask your doctor or nurse for eviQ patient information - Diarrhoea during cancer treatment. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if your diarrhoea is not controlled, you have 4 or more loose bowel motions per day, and if you feel dizzy or light-headed.**
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.**
Fever	• You may feel warm. • Tell your doctor or nurse if you get this symptom.

Extra fluid in the body (fluid retention)	• You may gain weight over a short amount of time. • Your hands and feet may become swollen, appear red or feel hot and uncomfortable. • Wear loose clothing and shoes that are not too tight. • Try not to stand up or walk around too much at one time. • If your ankles or legs get swollen, try raising them. • Make sure that any cuts or areas of broken skin are treated as soon as possible. • **Tell your doctor or nurse as soon as possible if you get any of the symptoms listed above or gain 1 to 2 kg in a week.** • **Tell your doctor or nurse immediately or go to the nearest hospital Emergency Department if you become short of breath.**
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.**

Low blood potassium levels (hypokalaemia)	• This may be found from your routine blood tests and treated by your doctor.
	• If it is severe you may get:
	  ◦ muscle cramps or twitches
	  ◦ constipation
	  ◦ confusion
	  ◦ an irregular heartbeat.
	• **Tell your doctor or nurse as soon as possible if you get any of the signs or symptoms listed above.**

Difficulty sleeping (insomnia)	• You may have trouble falling or staying asleep. • Try some gentle exercise daily. • Avoid coffee, tea and other caffeinated drinks around bedtime. • Try something to relax before bed, like a bath or meditation. • If you can't sleep get up and do something quietly, such as reading, until you feel tired. • Tell your doctor or nurse if you have difficulty sleeping.

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.**
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.

Changes in the way your brain works [progressive multifocal leukoencephalopathy (PML)]	• This treatment can affect your central nervous system. This can be very serious.
	• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following symptoms:**
	  ◦ **trouble with your speech or vision**
	  ◦ **confusion or memory loss**
	  ◦ **changes in your personality**
	  ◦ **weakness in your arms and legs**
	  ◦ **poor balance or coordination**
	  ◦ **fits (seizures).**

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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