Blinatumomab (Blincyto) for B-precursor acute lymphoblastic leukaemia minimal residual disease – patients in remission

LAY SUMMARY

Acute lymphoblastic leukaemia (ALL) is a cancer of white blood cells that starts in the bone marrow and develops quickly, usually over days or weeks. It causes too many white blood cells to be produced and is the most common type of leukaemia to affect children, but it is rare in adults.

Minimal residual disease (MRD) is the name given to small numbers of cancer cells that remain in the patient after treatment when the patient is in remission (no symptoms or signs of disease). It is the major cause of relapse in leukaemia.

Blinatumomab is a new drug that is used prevent this small number of cancer cells from increasing once a patient is in remission. Blinatumomab is a type of drug called a monoclonal antibody, which can seek out and target cancer cells. Blinatumomab is given in a drip (directly into a vein) for four weeks at a time.

Blinatumomab is currently being studied to see how well it works and whether it is safe to use in people with ALL. If blinatumomab is licensed for use in the UK, it will offer a new treatment for people who have had ALL and are now in remission to prevent relapse.

NIHR HSRIC ID: 11723
TARGET GROUP

- B-precursor acute lymphoblastic leukaemia (ALL): adults; minimal residual disease (MRD) — patients in remission.

TECHNOLOGY

DESCRIPTION

Blinatumomab (Blincyto; MEDI - 538, MT-103, AMG103, bscCD19xCD3) is a bispecific T-cell engager (BiTE) with specificity for the pan-B cell antigen CD19 and the CD3/T cell receptor complex. BiTE technology combines two antibodies on a short single polypeptide chain. BiTE molecules bind to both the pathogenic target cell and T-cells, and can recruit and activate T-cells to destroy the target cell without the need for a co-stimulatory signal. In the phase II clinical trial, blinatumomab is administered by continuous intravenous (IV) infusion for 28-days at 15μg/m²/day followed by a 14-day treatment-free interval for up to four cycles1.

Blinatumomab received European Marketing Authorisation in November 2015 for the treatment of adults with Philadelphia chromosome negative (Ph-negative) relapsed or refractory B-precursor ALL.

Blinatumomab is currently in phase III clinical trials for paediatric subjects with high risk first relapse B-precursor ALL, and paediatric and adolescent subjects with relapsed and/or refractory B-precursor ALL. Blinatumomab is also in phase II clinical trials for relapsed or refractory diffuse large B-cell lymphoma, and relapsed/refractory Ph-positive B-precursor ALL in adult patients.

INNOVATION and/or ADVANTAGES

If licensed, blinatumomab will offer a novel treatment option for adult patients with minimal residual disease B-precursor ALL that may reduce the risk of relapse.

DEVELOPER

Amgen Ltd.

AVAILABILITY, LAUNCH OR MARKETING

In phase II clinical trials.

PATIENT GROUP

BACKGROUND

ALL is a malignancy of lymphocytes and lymphocyte-producing cells. In persons with ALL, there is excess production of immature lymphocyte-precursor cells, called blast cells, in the bone marrow. Eventually this overgrowth affects normal haemopoiesis, and there is a reduction in the numbers of red cells, white cells, and platelets in the blood2. The most common symptoms of ALL are3:
• Anaemia, which results in fatigue and breathlessness.
• Low platelet counts, which may result in bruising and bleeding from mucous membranes and the gut.
• Low white cell counts, high numbers of abnormal cells and high metabolic rate, resulting in persistent infections and fever or lymphadenopathy, which is often present even in the absence of clear indications of infection.

ALL can be classified into three groups based on immunophenotyping: B-precursor ALL (also known as precursor-B-cell ALL), mature B-cell ALL, and T-cell ALL. B-precursor ALL is characterised by the presence of cytoplasmic immunoglobulins and CD10, CD19, CD22, and CD79a expression.

Relapse is the main clinical problem for the survival of adult patients with ALL. The source of these relapses is the persistence of MRD, defined by the presence of 0.01% or more ALL cells. Higher levels of MRD are associated with a greater chance of relapse, and the risk of relapse is generally proportional to the level of MRD, particularly when measured during or at the end of remission-induction therapy.

NHS or GOVERNMENT PRIORITY AREA

This topic is relevant to:

CLINICAL NEED and BURDEN OF DISEASE

Acute leukaemia is an uncommon form of haematological malignancy. About 8,600 people are diagnosed with leukaemia each year in the UK; of these, less than 8% have ALL. B-precursor ALL constitutes approximately 70% of adult ALL cases. An estimated 40-50% of adult patients with ALL relapse following first line treatment, which is associated with a survival rate of less than 10%.

In England, there were 693 new cases (272 in adults) of ALL (ICD-10 C91.0) recorded in 2013. In 2014-15, there were 26,438 admissions for ALL in England, resulting in 41,046 bed days and 27,325 finished consultant episodes. In 2014, there were 216 deaths (191 in adults) due to ALL in England and Wales. In the case of childhood ALL, there is an overall survival rate of 80% at five years, but in adults, the survival rate falls to 35% at five years.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE Guidance

• NICE technology appraisal in development. Dasatinib for the treatment of acute lymphoblastic leukaemia (ID386). Expected date of issue to be confirmed.
• NICE technology appraisal in development. Leukaemia (acute lymphoblastic) – pegasparagase (ID863). Expected October 2016.

Other Guidance


CURRENT TREATMENT OPTIONS

Treatment for ALL aims to induce clinical remission, defined as less than 5% blasts on light microscopy with adequate haematopoietic recovery (induction phase), then consolidate that remission with further cycles of intensive therapy. Finally, to maintain the patient in remission “maintenance” treatment lasting 2-3 years is given as an outpatient^15 a. Additional CNS prophylaxis, which consists of intrathecal injections as well as high dose IV CNS-penetrating treatment, is also given throughout the entire period of treatment^16. In adults, stem cell transplantation is typically offered for those at high risk of relapse. A number of high risk features are well described and include clinical and cytogenetic risk factors, as well as the presence of MRD^15. Although selection of drugs, dose schedules and treatment duration may differ slightly between different subtypes of ALL, the basic treatment principles remain similar^4.

The prognosis for patients with systemic relapse of ALL is poor^17. Treatment of relapsed disease includes re-induction chemotherapy followed by an allogeneic stem cell transplant, where a suitably matched related or unrelated donor is found^18^a. Cord blood transplantation or haploidentical transplantation offer possibilities for allogeneic transplant in the small number of patients in whom a suitable matched related or unrelated donor cannot be found^18. The American Society for Blood and Marrow Transplantation (ASBMT) recommends stem cell transplantation over chemotherapy after achieving a second complete remission. Most patients are given a four drug induction chemotherapy with vincristine, prednisolone or dexamethasone, an anthracycline, and asparaginase^19.

There are currently no treatments specifically for MRD in patients with ALL following response to first line treatment.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>BLAST, NCT01207388, MT103-203; blinatumomab; phase II.</th>
</tr>
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<tbody>
<tr>
<td>Sponsor</td>
<td>Amgen Research GmbH.</td>
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<tr>
<td>Status</td>
<td>Ongoing.</td>
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<tr>
<td>Source of</td>
<td>Trial registry^1.</td>
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^a Expert personal communication
### Horizon Scanning Research & Intelligence Centre

<table>
<thead>
<tr>
<th>Information</th>
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<tbody>
<tr>
<td>Location</td>
<td>EU (incl UK) and Russia.</td>
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<tr>
<td>Design</td>
<td>Non-randomised, single arm.</td>
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<tr>
<td>Participants</td>
<td>n=116; aged ≥18 yrs; B-precursor ALL in complete haematological remission; MRD ≥10^-3 cells; Eastern Cooperative Oncology Group (ECOG) performance status ≤1; no previous treatment with blinatumomab; no prior allogeneic stem cell transplant; no presence of circulating blasts.</td>
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<tr>
<td>Schedule</td>
<td>Patients receive blinatumomab 15μg/m²/day continuous IV for 4 wks, followed by a 2 week treatment-free interval.</td>
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<td>Follow-up</td>
<td>Active treatment for up to 4 cycles (24 wks), follow-up 5 yrs.</td>
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<tr>
<td>Primary outcome/s</td>
<td>MRD response within the first treatment cycle.</td>
</tr>
<tr>
<td>Secondary outcome/s</td>
<td>Overall survival, time to haematological relapse; duration of complete MRD response; level of MRD; adverse events; quality of life determined using EORTC QLQ C30 and EQ-5D.</td>
</tr>
<tr>
<td>Key results</td>
<td>77.9% patients had a MRD response within the first treatment cycle.</td>
</tr>
<tr>
<td>Adverse effects (AEs)</td>
<td>69 serious AEs reported.</td>
</tr>
<tr>
<td>Expected reporting date</td>
<td>Study completion date reported as Jan 2019.</td>
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### ESTIMATED COST and IMPACT

#### COST

Blinatumomab is already marketed in the UK for the treatment of Ph-negative B-precursor ALL; a 35μg vial costs £2,017. One cycle of treatment (blinatumomab 15μg/m²/day continuous IV for 4 weeks, followed by a 2 week treatment-free interval) would cost £46,230. (Assuming an average body surface area of 1.91m² (Health Survey for England 2013))

### IMPACT - SPECULATIVE

<table>
<thead>
<tr>
<th>Impact on Patients and Carers</th>
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<tr>
<td>✓ Reduced mortality/increased length of survival</td>
<td>✓ Reduced symptoms or disability</td>
</tr>
<tr>
<td>□ Other</td>
<td>□ No impact identified</td>
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<tr>
<th>Impact on Health and Social Care Services</th>
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<tr>
<td>✓ Increased use of existing services: specialised equipment and possibly home care services will be needed to care for patients receiving this treatment</td>
<td>✓ Decreased use of existing services</td>
</tr>
<tr>
<td>□ Re-organisation of existing services</td>
<td>□ Need for new services</td>
</tr>
<tr>
<td>□ Other</td>
<td>□ None identified</td>
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</tbody>
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b Assuming an average body surface area of 1.91m² (Health Survey for England 2013)

c Expert personal communication
**Impact on Costs and Other Resource Use**

- **Increased drug treatment costs**
- **Reduced drug treatment costs**
- **Other increase in costs:** *specialised equipment and possibly home care services will be needed to care for patients receiving this treatment*.
- **Other reduction in costs**
- **Other**
- **None identified**

**Other Issues**

- **Clinical uncertainty or other research question identified**
- **None identified**

**REFERENCES**

17. Map of Medicine. Acute lymphoblastic leukaemia in adults - management