Health Technology Briefing
January 2024

Blinatumomab with chemotherapy for frontline consolidation treatment of Philadelphia chromosome negative, measurable residual disease negative, B-lineage acute lymphoblastic leukaemia

Company/Developer	Amgen Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 9917	NICE ID: Not Available	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Acute lymphoblastic leukaemia (ALL) is a rare and aggressive blood cancer, characterised by proliferation of immature and abnormal white blood cells responsible for the immune system (lymphocytes), in the bone marrow and blood. These immature/abnormal lymphocytes dominate bone marrow, resulting in a decrease of red blood cells, normal white blood cells and platelets. ALL can be Philadelphia chromosome positive or negative (Ph+/-), both of which are aggressive. Current treatment options for Ph- is consolidation therapy, which involves several cycles of intensive chemotherapy, however this is associated with risks of disease resistance and subsequent relapse. As such, there is an unmet need for the development of alternative consolidation strategies.

Blinatumomab is an antibody (a protein) that works by bringing healthy T cells (immune cells that help kill cancer cells) and leukaemia cells close together so the T cells can more effectively kill the leukaemia cells. Blinatumomab is administered by continuous intravenous infusion. If the licence was extended to include frontline consolidation for Ph-, measurable residual disease negative (MRD-), B-lineage ALL population, it would offer a specific treatment option in an area of unmet need for adults where current therapies are insufficient to address high rates of relapse.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

Blinatumomab with chemotherapy for frontline consolidation treatment for Philadelphia chromosome negative (Ph-), Measurable Residual Disease negative (MRD-), B-lineage acute lymphoblastic leukaemia (ALL) in adults.[a]

Technology

Description

Blinatumomab (Blincyto) is a bispecific T-cell engager (BiTE®) molecule that binds specifically to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T-cells.[1] It activates endogenous T-cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B-cells. The anti-tumour activity of blinatumomab immunotherapy is not dependent on T-cells bearing a specific TCR or on peptide antigens presented by cancer cells but is polyclonal in nature and independent of human leukocyte antigen molecules on target cells. Blinatumomab mediates the formation of a cytolytic synapse between the T-cell and the tumour cell, releasing proteolytic enzymes to kill both proliferating and resting target cells. Blinatumomab is associated with transient upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T-cells, and results in elimination of CD19+ cells.[1]

Blinatumomab with chemotherapy is in a phase III clinical trial (NCT02003222) for the treatment of newly diagnosed Ph-, MRD-, B-lineage ALL in adults.[2,a] Blinatumomab is administered by intravenous (IV) infusion continuously on days 1-28. Treatment repeats every 6 weeks for 2 cycles.[2]

Key Innovation

Blinatumomab is a first-in-class bispecific T-cell engager, with a novel mechanism of action.[3] In a phase II study (NCT01209286) of adults, aged 18 to 77 years old, with relapsed/refractory B-precursor ALL, 25 patients (69%) achieved complete remission (CR) or CR with partial haematologic recovery, with 88% of responders treated with blinatumomab experiencing a complete minimal residual disease (MRD) response.[4]

In a phase III study (BLAST, NCT01207388) of adults with MRD+ B-precursor acute ALL 88 (78%) evaluable patients achieved a complete MRD response. In the subgroup of patients with Ph- ALL, in haematological remission, the estimated relapse-free survival (RFS) at 18 months was 54%. Median overall survival was 36.5 months. Complete MRD responders had statistically significant longer RFS and Overall Survival (OS) compared with MRD non-responders.[5]

Current treatment options for newly diagnosed ALL frequently lead to remission, but relapses often occur in patients which leads to poor survival rates.[6] Blinatumomab addresses an area of unmet need by being the only bispecific T-cell engager licensed in the US and Europe for ALL.[7,8] If licenced, blinatumomab will offer a consolidation therapy option for adults with Ph-, MRD-, B-lineage ALL where current therapies are insufficient to address high rates of relapse.

Regulatory & Development Status

Blinatumomab is licensed in the EU/UK as a monotherapy for the following indications:[9]

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- For the treatment of adults with CD19+ relapsed or refractory B-precursor ALL. Patients with Ph+ B-precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options
- For the treatment of adults with Ph-, CD19+, B-precursor ALL in first or second complete remission with MRD ≥0.1%
- For the treatment of paediatric patients aged ≥1 years old with Ph-, CD19+, B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies, or in relapse after receiving prior allogeneic haemopoietic stem cell transplantation
- For the treatment of paediatric patients aged ≥1 years old with high-risk relapsed Ph-, CD19+, B-precursor ALL as part of consolidation therapy

In the UK, blinatumomab has an Orphan Drug designation (PLGB 13832/0018/OD1) for the following indications:[10]

- Monotherapy for the treatment of adults with Ph-, CD19+ relapsed or refractory B-precursor acute lymphoblastic leukaemia (ALL)
- Monotherapy for the treatment of adults with Ph-, CD19+, B-precursor ALL in first or second complete remission with MRD greater than or equal to 0.1%
- Monotherapy for the treatment of paediatric patients aged 1 year or older with Ph-, CD19+, B-precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation

In the EU, blinatumomab has received Orphan Drug designation (EU/3/09/650) for the treatment of ALL in 2009.[11]

Blinatumomab is also in phase II and III clinical development for the following indications:[12]

- B-cell non-Hodgkin lymphoma
- Diffuse large B-cell lymphoma
- Mixed phenotypic acute leukaemia
- Richter syndrome

Patient Group

Disease Area and Clinical Need

ALL is a rare type of blood cancer (leukaemia) that starts from white blood cells called lymphocytes in the bone marrow. ALL develops rapidly over days or weeks, with cancerous cells building up in the bone marrow and spreading into the blood.[13] ALL has several types and subgroups based on the structure and characteristics of the leukaemia cells, with the three main types, T-cell, B-cell depending on the lymphocytes it affects, and Ph+ ALL. Ph+ ALL is when a particular change in the chromosome of leukaemia results in a gene called ABL1 on chromosome 9 breaking off and sticking to a gene called BCR on chromosome 22. This produces a new gene called BCR-ABL1, which causes the cell to make too much of a protein called tyrosine kinase.[13] Absence of the Philadelphia chromosome is Ph-. Measurable residual disease (previously known as minimal residual disease) is used to describe the small number of cancer cells in the body after cancer treatment, a positive (MRD+) result means the disease is still detected after treatment, whereas a negative (MRD-) result means there was no disease detected after treatment.[14,15] Common symptoms of ALL include feeling weak or tired, flu-like symptoms, fever, weight loss breathlessness and pain in your bones or joints.[16] Current therapy for Ph-, MRD-, B-lineage ALL is several cycles of chemotherapy.[17] Older adults with Ph-, B-cell ALL have the highest rate of treatment failure and treatment complications with current therapy.[18]

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ALL accounts for <1% of new cancer cases in the UK.[19] There are no UK-wide survival statistics for ALL, but they are available for one area of England (Yorkshire) between 2004-16. For people aged between 15 and 39 years old almost 65% will survive ALL for 5 years or more after diagnosis, whereas those aged 40 years or older have a 20% chance of surviving for 5 years or more.[20] In England, 2022-23, there were 16,719 finished consultant episodes (FCE) for adults aged 30-69 years old with a primary diagnosis of lymphoid leukaemia (ICD-10 C91), resulting in approximately 13,765 day cases and 18,744 FCE bed days.[21] The specific population likely to be eligible to receive blinatumomab could not be estimated from available published sources.

Recommended Treatment Options

There are no National Institute for Health and Care Excellence (NICE) recommended treatment options specific to the adult population of Ph-, MRD-, B-lineage ALL.

The current treatment standard of care for ALL is the UKALL14 regimen:[17]

- **Pre-phase (5-7 days):** Dexamethasone 6mg/m^2/day orally
- **Phase 1 induction (4 weeks):** Pegylated asparaginase (PEG-ASP) and standard phase 1 induction chemotherapy
- **Phase 2 induction (4 weeks):** Standard phase 2 induction chemotherapy
- **If sibling donor present:**
  - Patients over 40 years old receive intensification with high-dose methotrexate and PEG-ASP, conditioning regimen with fludarabine, melphalan and alemtuzumab, followed by allogeneic stem cell transplantation (allo-SCT)
  - Patients 40 years old and under receive myeloablative conditioning regimen (e.g. etoposide) and total body irradiation (TBI), followed by allo-SCT
- **If no sibling donor present and patient is at standard risk** continue methotrexate intensification, consolidation and maintenance
- **If no sibling donor present and patient is at high risk:**
  - Patients over 40 years old receive intensification with high-dose methotrexate and PEG-ASP, condition regimen with fludarabine, melphalan and alemtuzumab, followed by allo-SCT from matched unrelated donor (MUD)
  - Patients 40 years old and under receive myeloablative conditioning regimen (e.g. etoposide) and TBI, followed by allo-SCT from MUD

Clinical Trial Information

Trial	NCT02003222; **ECOG-ACRIN E1910;** A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed BCR-ABL-Negative B Lineage Acute Lymphoblastic Leukemia in Adults **Phase III –** Active, not recruiting **Location(s):** USA, Canada, Israel and Puerto Rico **Actual study completion date:** June 2023
Trial Design	Randomised; parallel assignment; open-label

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Population	N=488 (actual); patients with newly diagnosed breakpoint cluster region (BCR)-c-abl oncogene 1, non-receptor tyrosine kinase (ABL)-negative B lineage acute lymphoblastic leukaemia; aged 30 to 70 years old
Intervention(s)	Blinatumomab continuous IV infusion on days 1-28. Treatment repeats every 6 weeks for 2 cycles in the absence of disease progression or unacceptable toxicity.
Comparator(s)	Standard of care (consolidation chemotherapy).
Outcome(s)	**Primary outcome:** Overall survival (OS) [Time frame: Time between randomisation and death from any cause, assessed up to 10 years] See trial record for full list of other outcomes.
Results (efficacy)	224 MRD- patients were randomised, 112 patients to each arm. 22 patients in each arm proceeded to allogeneic bone marrow transplant. The morphologic complete remission rate after induction chemo was 81%. Among the MRD- patients, at the third interim efficacy analysis, 56 patients had died, 17 in the blinatumomab arm and 39 in the control chemotherapy arm. The upper boundary for efficacy analysis was crossed in favour of blinatumomab with a significant improvement in OS in favour of the blinatumomab arm (median OS: not reached vs. 71.4 months; Hazard ratio 0.42, 95% CI: 0.24 - 0.75; two-sided p=0.003). Median follow-up was 43 months. The addition of blinatumomab to consolidation chemotherapy resulted in a significantly better OS in patients with newly diagnosed B-lineage ALL who were MRD- after intensification chemo.[22]
Results (safety)	No significant safety concerns were noted.[22]

Estimated Cost

The list price of blinatumomab is £2,017 per 38.5 microgram vial.[23]

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Blinatumomab for treating acute lymphoblastic leukaemia in remission with minimal residual disease activity (TA589). July 2019
- NICE technology appraisal. Pegaspargase for treating acute lymphoblastic leukaemia (TA408). September 2016
- NICE clinical guideline. Haematological cancers: improving outcomes (NG47). May 2016
- NICE quality standard. Haematological cancers (QS150). June 2017

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a
- NHS England. 2017. Clinical commissioning policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 16068/P

Other Guidance

- NHS Northern Cancer Alliance. Haematology Cancer Clinical Guidelines V17. November 2019.[24]

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- University College London, National Cancer Research Institute and Cancer Research UK. UKALL14 Protocol v5.0. July 2012.[17]

Additional Information

Amgen Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

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