NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Blinatumomab for treating acute lymphoblastic leukaemia in remission with minimal residual disease activity

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using blinatumomab in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: February 2019

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using blinatumomab in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 25 March 2019

Second appraisal committee meeting: 03 April 2019

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 The committee was minded not to recommend blinatumomab as an option for treating acute lymphoblastic leukaemia in adults with Philadelphia-chromosome-negative CD19-positive B-precursor whose disease is in first or second complete remission with minimal residual disease (MRD) of at least 0.1%.

1.2 The committee recommends that NICE requests further clarification and analyses from the company, which should be made available for the second appraisal committee meeting. This should include:

- a revised cost-effectiveness analysis reflecting the current treatment pathway and comparing blinatumomab with standard care. The revised economic model should:
  - include costs, health-related quality-of-life estimates and outcomes associated with the current treatment pathway for people with relapsed or refractory acute lymphoblastic leukaemia
  - include the proportion of people with and without MRD after blinatumomab treatment and how many have haematopoietic stem cell transplantation (HSCT)
  - incorporate an explicit causal link between the probability of HSCT and relapse-free survival and overall survival in both groups
  - explicitly model a cure for people whose disease is expected to be cured and include scenario analyses considering different cure fractions and cure points
  - factor in the different positions in the treatment pathway at which HSCT might be given
- the latest available evidence on survival outcomes after HSCT
- the latest trial data cut.

Why the committee made these recommendations

Current treatment for acute lymphoblastic leukaemia that is in complete remission with MRD of at least 0.1% is salvage chemotherapy followed by HSCT if possible. Some people with MRD have an HSCT straightaway, but this is less likely to cure the disease than it is in people who do not have MRD.

Evidence from 2 studies suggests that blinatumomab may help people have longer without their disease relapsing. Also, their disease responds well to treatment. But there are no data directly comparing blinatumomab with salvage chemotherapy, with or without HSCT. This means that the exact size of the benefit of blinatumomab compared with salvage treatment is unknown.

The cost-effectiveness estimates for blinatumomab are uncertain. The economic model structure is not acceptable for decision making and does not reflect the current treatment pathway. More evidence is needed to address these uncertainties.

Blinatumomab does not meet NICE's criteria to be considered a life-extending treatment at the end of life. Because of the uncertainties, it is not possible to make recommendations.

2 Information about blinatumomab

Marketing authorisation indication	Blinatumomab (Blincyto, Amgen) is indicated as 'monotherapy for the treatment of adults with Philadelphia-chromosome-negative CD19 positive B-precursor acute lymphoblastic leukaemia in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%'.
Dosage in the marketing authorisation	Blinatumomab is administered by continuous intravenous infusion delivered at a constant rate using an infusion pump. A single cycle of blinatumomab treatment comprises continuous intravenous infusion at a dose of 28 micrograms/day for 28 days, followed by a 14-day treatment-free interval.
Price	The list price of blinatumomab is £2,017 per 38.5 microgram vial. The average cost of blinatumomab per cycle at the list price is £56,476 (company submission). The company has a commercial arrangement (simple discount patient access scheme). This makes blinatumomab available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Amgen and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Potential new treatment option

3.1 People with acute lymphoblastic leukaemia in remission with Philadelphia-chromosome-negative CD19-positive B-precursor disease, and with minimal residual disease (MRD) would welcome a new treatment option. MRD in this document refers to detectable MRD of at least 0.1%. Acute lymphoblastic leukaemia is a rare, rapidly progressing form of cancer of the white blood cells. Outcomes for adults with acute lymphoblastic leukaemia are poor. Common symptoms include fatigue, breathlessness, infections, bleeding, bruising, fever and sweating. About 44% of adults

have acute lymphoblastic leukaemia that is expected to relapse. Both patient and clinical experts explained that people with MRD experience symptoms, even if their disease is in remission, because they are often having treatment that has a lot of side effects. Although the degree of symptoms varies across patients, overall, they are not well and cannot work. The clinical experts noted that current treatment options (chemotherapy) are difficult for patients to tolerate and they could benefit from novel treatment options. Currently, no approved treatments exist specifically for MRD B-precursor acute lymphoblastic leukaemia that is in haematological complete remission. The committee concluded that people with MRD B-precursor acute lymphoblastic leukaemia would welcome a new treatment option that would improve symptoms and the chance of survival.

Clinical management

The clinical importance of MRD is clearly established

3.2 The committee considered the treatment pathway for B-precursor acute lymphoblastic leukaemia. Once patients have had induction, consolidation and maintenance therapy and their disease is in complete remission, they will be monitored for the presence of MRD. The clinical experts explained that MRD status is a major predictive factor for patients whose disease is in haematological complete remission. MRD is a marker of chemotherapy resistance and is therefore a predictor of response to subsequent chemotherapy. They noted that there is no current therapy specifically to reduce MRD. The committee acknowledged that MRD is an important factor in predicting future treatment outcomes. It concluded that a treatment for MRD would be a valuable addition to the treatment pathway.

The main aim of treatment is cure, and haematopoietic stem cell transplantation (HSCT) is important in achieving cure

3.3 The clinical experts stated that the main treatment goal for people with acute lymphoblastic leukaemia is to achieve cure through sustained

absence of MRD and maintained haematological complete remission. They explained that, in most people whose disease is cured, it is cured after HSCT. However, the use of HSCT may vary based on a patient's fitness, donor availability and their personal preferences. The committee understood that the aim of treatment for B-precursor acute lymphoblastic leukaemia is a cure. People with MRD may proceed to HSCT, but it is more likely to be successful in the absence of MRD. The committee concluded that HSCT has an important role in achieving a cure in people with acute lymphoblastic leukaemia.

People with untreated MRD are likely to need subsequent treatment for relapse

3.4 The committee noted that people with MRD are at high risk of relapse. The clinical experts explained that, if the disease relapses, the treatment options are salvage chemotherapy, inotuzumab ozogamicin or blinatumomab, although salvage chemotherapy is now rarely used at this stage. They also said that it is unlikely that people would have blinatumomab for a relapse if they had previously had it for MRD. The committee concluded that people with untreated MRD are likely to need subsequent treatment for relapse, and blinatumomab is a relevant option at this stage.

Salvage chemotherapy is not the only comparator for blinatumomab

3.5 The committee noted that the company submission suggested that blinatumomab may be an alternative to salvage chemotherapy in people with MRD whose disease has not relapsed. The clinical experts explained that, in this situation, people can either have salvage chemotherapy or go directly to HSCT if they are well enough and a donor is available. Because MRD is indicative of resistance to chemotherapy, it is likely that the option of proceeding directly to HSCT will be taken when it is available. The committee concluded that the position of blinatumomab in the treatment pathway is more complex than is implied by a comparison with salvage chemotherapy because some patients may have HSCT.

The definition and measurement of MRD is standardised

3.6 The clinical experts noted that MRD testing is standardised across treatment centres in England. One of the clinical experts stated that MRD presence is established across a quantifiable scale: at least 0.001% is the lowest end of detection possible with current technology. However, they noted that technology is rapidly progressing and there will be more sensitive technologies which will detect even smaller numbers of leukaemic cells in the future. The trial population presented by the company included MRD detected at a level of at least 0.1%. The committee was aware that the marketing authorisation applies to people with MRD of at least 0.1%; this is what is meant by MRD in this document. It agreed that MRD testing is standard practice and was aware it could only make recommendations within the marketing authorisation.

Clinical evidence

Blinatumomab is clinically effective but immature data and the lack of direct comparative trial data means the size of this benefit is unclear

3.7 The clinical evidence for blinatumomab came from 2 single-arm studies (BLAST and MT103-202). The committee understood that both studies included patients with acute lymphoblastic leukaemia in complete haematological remission with MRD. The company presented results from 116 patients from BLAST and 20 patients from MT103-202 (see table 1). All patients had at least 1 blinatumomab infusion. At the August 2015 data cut, the median follow-up in BLAST was 18 months. The survival data were immature. The committee noted a plateau in the Kaplan–Meier curves for overall and relapse-free survival. However, it was aware there were very few patients still at risk in this part of the curves, and no events were recorded after 41 months and 35 months for overall and relapse-free survival respectively. The MT103-202 study had a follow-up of about 4 years, but included only 20 patients and did not record overall survival. The committee was concerned that the single-arm design of the studies meant that the results were potentially biased. It noted that there was no

evidence on the effectiveness of blinatumomab directly compared with salvage chemotherapy. The committee concluded that blinatumomab is clinically effective, but immature survival data and the lack of direct comparative data means the size of this benefit is unclear.

Table 1 Clinical effectiveness results for blinatumomab

Outcome	BLAST (n=116, August 2015 data cut)*	MT103-202 (n=20)
Complete MRD response rate in 1 cycle	n=88 (77.9%)	n=16 (80.0%)
Median overall survival	36.5 months (19.2 months, not estimable)	N/A
Overall survival at 18 months	65% (95% CI 55 to 73)	N/A
Median progression-free survival	18.9 months (12.3 to 35.2)	not estimable (at 1,550 days of follow-up)
Progression-free survival	53.0% (95% CI 44 to 62)	52.6% (N/A) at 5.9 years
Abbreviations: CI, confidence interval; MRD, minimal residual disease; N/A, not applicable; n, number		

*Results presented for primary company analyses, which are not censored at HCST

Blinatumomab can only be recommended within its marketing authorisation

3.8 Blinatumomab's marketing authorisation includes adult patients with acute lymphoblastic leukaemia in first or second complete remission and which is Philadelphia-chromosome-negative with MRD of at least 0.1%. The study population in BLAST was wider than the population outlined in the marketing authorisation. Although most patients had disease that was in first or second complete remission, it also included patients whose disease was in third complete remission. Also, it included patients with Philadelphia-chromosome-positive and Philadelphia-chromosome-negative disease. In the MT103-202 study, all patients had disease that was in complete remission, but it also included both Philadelphia-chromosome-positive and negative disease. The committee concluded that it could only make recommendations within the population outlined in the marketing authorisation.

The indirect comparison is appropriate but is not generalisable to the wider marketing authorisation population

3.9 The committee was aware that there were no data directly comparing blinatumomab with salvage chemotherapy. The company therefore did an indirect comparison of blinatumomab and salvage chemotherapy. The comparator data came from Study 20120148, a retrospective study with data on patients with Philadelphia-chromosome-negative B-precursor acute lymphoblastic leukaemia in complete haematological remission and MRD. The study collected data on overall and relapse-free survival but not on adverse effects. It was used as a matched control for BLAST. Because of differences between the populations in BLAST and the historical comparator, the company used a subset of the original study populations. The committee was aware that the population in the indirect comparison was narrower than the marketing authorisation and excluded the following groups:

- patients who could not have HSCT or tolerate chemotherapy
- patients whose disease is in second complete remission.

The clinical experts suggested that survival outcomes for the excluded groups of people were poor and that they could potentially benefit from treatment with blinatumomab. This was because some patients who had blinatumomab have had good outcomes even without subsequently having HSCT. The committee concluded that the indirect comparison was appropriate, given the absence of randomised controlled trial data, but that the results are not generalisable to the full population outlined in the marketing authorisation.

The indirect comparison method is appropriate but subject to uncertainty

3.10 The company used a propensity score model to compare the primary analysis set from BLAST and the direct comparator Study 20120148. This method produced weights that were applied to the control study (Study 20120148). The aim was to estimate the response to

chemotherapy that would be expected in a population with the same characteristics as the population in the BLAST primary analysis set. The ERG noted that the chosen method of applying weights to balance the datasets was appropriate given the lack of randomised controlled trials. The company used 2 different methods to produce weights: (i) average treatment effect and (ii) average treatment effect on the treated. For both methods, the company used stabilised and non-stabilised weights. It used stabilised weights to produce the average treatment effect on the treated estimates in the clinical effectiveness analysis. However, non-stabilised weights were used to produce the treatment effect on the treated estimates that were used in the cost-effectiveness analysis. The results are confidential and cannot be reported here. The ERG noted that there were inconsistencies in efficacy data presented by the company presented and the data used to inform the economic model. The committee noted that it would have been helpful to see the range of weights used in the model, as an indicator of the model reliability and the appropriateness of using stabilised weights. It concluded that the method used to compare the 2 studies was appropriate but subject to uncertainty.

Cost-effectiveness model

The company's model is not acceptable for decision making

3.11 The company's model was a partitioned survival model based on relapse-free survival and overall survival, with 3 health states: (1) relapse free; (2) post relapse and (3) dead. The main partitioned survival structure had 2 linked sub-models which were intended to estimate additional costs and utility decrements associated with HSCT received before or after disease has relapsed. The pre-relapse sub-model was not causally related to relapse-free or overall survival, whereas the post-relapse sub-model was partially related to relapse-free survival. The ERG noted that the causal effect of transplant on outcome was not adequately modelled. The clinical experts also explained that MRD status highly correlates with HSCT outcomes: HSCT is less likely to be successful in people with MRD.

However, the committee acknowledged that the model did not show how many patients with or without MRD have HSCT. The clinical expert further noted that there is unpublished but more mature and up-to-date data on survival outcomes after HSCT that could be included. The clinical experts highlighted that this model is not reflective of current practice or the treatment pathway (see section 3.2). They clarified that the treatment pathway has recently changed and now includes inotuzumab ozogamicin or blinatumomab for treating relapses (see section 3.4). The committee noted that while the model implicitly incorporated HSCT within the relapse-free survival and the overall survival curves, it did not show how many patients had HSCT. Without this direct link, it was not clear what proportion of patients had HSCT, and what their outcomes after HSCT were. Given the importance of HSCT to the likelihood of cure (see section 3.3), the committee was aware that this made it difficult to assess the reliability and clinical plausibility of the model. It concluded that it would have liked to have seen a cost-effectiveness model including:

- a revised cost-effectiveness analysis reflecting the current treatment pathway and comparing blinatumomab with standard care. The revised economic model should:
  - include costs, health-related quality-of-life estimates and outcomes associated with the current treatment pathway for people with relapsed or refractory acute lymphoblastic leukaemia
  - include the proportion of people with and without MRD after blinatumomab treatment and how many have HSCT
  - incorporate an explicit causal link between the probability of HSCT and relapse-free survival and overall survival in both groups
  - explicitly model a cure for people whose disease is expected to be cured and include scenario analyses considering different cure fractions and cure points
  - factor in the different positions in the treatment pathway at which HSCT might be given.

- the latest available evidence on survival outcomes after HSCT
- the latest trial data cut.

Cost-effectiveness results cannot be generalised to the full population in the marketing authorisation

3.12 The company modelled the cost effectiveness of blinatumomab using data from the indirect comparison. The committee recalled that this was a narrower population than the marketing authorisation (see section 3.9). Therefore, it concluded that the population in the cost-effectiveness model cannot be generalised to the full population in the marketing authorisation.

The cure point assumption should be evaluated because the original assumption is not clinically plausible

3.13 The company's preferred model did not have a fixed cure point. Instead, the model predicted the timepoint at which patients were assumed to be cured and had mortality rates similar to those of the general population with some additional excess mortality risk after a cure. This approach resulted in different cure points between the relapse-free survival and the overall survival extrapolations. The ERG's preferred model was based on the company's original model but had a fixed cure point at 5 years in both the blinatumomab and the chemotherapy groups. The 5-year cure point was chosen based on the ERG's clinical experts' opinion. The ERG noted that applying the 5-year cure point to a partitioned model, such as the one submitted by the company, may introduce more bias in favour of patients who are alive but whose disease has relapsed. This bias was likely to have favoured the chemotherapy group, but the ERG noted that its impact would be small. The committee concluded that having a large gap between the resulting cure points (company model) is not clinically plausible. It was aware that the assumptions around the cure fraction or cure point were a key driver in the cost-effectiveness analysis. Therefore, the committee would have liked to have seen a clinically plausible, explicitly modelled cure for the patients whose disease is expected to be cured.

Survival extrapolations

Parametric curves for overall and relapse-free survival should be re-evaluated because the company model is not acceptable for decision making

3.14 The committee considered the parametric survival curves used by the company. In its base case, the company modelled overall survival using a log normal mixture cure model in both the blinatumomab and the standard care groups (which allows for different cure fractions to be predicted by the model). The company used a Gompertz distribution in both groups to model the relapse-free survival. The company fitted over 30 different curves but chose the ones with the best fit to the data. The ERG noted that in their exploratory analyses they consulted clinical experts on the appropriate survival curves. The committee noted that the model needs to be updated which may lead to using different survival curves.

Health-related quality of life

The company's post-relapse utility value is too high

3.15 The company used a post-relapse utility value equal to 0.69 in the model, which was lower than the 1 seen in the BLAST study (0.819). However, the ERG's clinical experts noted that both values are too high for relapsed patients and were not clinically plausible. The ERG ran exploratory analyses with lower utility values (0.50 and 0.25) which had a small effect on the incremental cost-effectiveness ratio (ICER). The committee further noted that blinatumomab may limit exposure to chemotherapy for some patients, but it is not clear whether this was factored in the model. It concluded that the post-relapse quality-of-life estimates included in the company model were too high but were not a key driver of the results.

Cost-effectiveness results

The cost effectiveness of blinatumomab compared with chemotherapy is uncertain

3.16 The company's base case showed that the ICER for blinatumomab compared with standard care was £28,655 (probabilistic) and £27,779 (deterministic) per quality-adjusted life year (QALY) gained. All analyses included the patient access scheme for blinatumomab. The committee noted that only the deterministic results could be manipulated for exploratory analyses by the ERG. The ERG's preferred base-case analysis produced an ICER of £27,717 per QALY gained. It implemented some changes to reflect its preferred base-case analysis. Specifically it used:

- a fixed cure point applied to all surviving patients at year 5 (see section 3.13)
- correction of minor implementation and programming errors identified during model verification.

The committee noted that neither the company's nor the ERG's base-case analyses included the committee's preferred model structure and concluded that it would like to see an updated analysis (see sections 3.11 and 3.13).

Innovation

Blinatumomab is innovative but there are no benefits not captured by the QALY

3.17 The committee considered blinatumomab to be innovative because it represents a step change in the treatment of CD19-positive B-precursor acute lymphoblastic leukaemia with MRD. The company did not present any evidence to suggest that there were additional benefits that were not captured in the QALY calculations. The committee concluded that there were no benefits that would not be captured in the QALY calculations.

End of life

Blinatumomab does not meet the criteria to be considered a life-extending treatment at the end of life

3.18 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The company proposed that blinatumomab met the criteria for life-extending treatments for people with a short life expectancy (normally less than 24 months). The committee considered the median and mean survival and the proportion of patients alive at 2 years for the standard care arm from the company and the ERG's model. The clinical experts suggested that for patients with MRD, survival at 2 years would be around 20%. The mean and median survival outcomes are confidential and cannot be reported here. The committee discussed whether blinatumomab met the criterion for extension to life, which is normally at least an additional 3 months. It concluded that it was plausible that blinatumomab offered more than 3-months' additional survival but they could not be certain because of flaws in the modelling. Based on the evidence presented to it, the committee agreed that blinatumomab could not be considered a life-extending treatment at the end of life.

Cancer Drugs Fund considerations

Blinatumomab does not meet the criteria to be included in the Cancer Drugs Fund

3.19 Having concluded that blinatumomab could not be recommended for routine use, the committee then considered whether it could be recommended for treating acute lymphoblastic leukaemia within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). It noted that the company had not made a case for blinatumomab to be included in the Cancer Drugs Fund. The committee noted that the uncertainties in the

analyses presented could not be answered though data collection and that there was no plausible ICER, so it could not be recommended in the Cancer Drugs Fund.

Conclusion

The committee is minded not to recommend blinatumomab

3.20 Because of a number of uncertainties, the committee was unable to recommend blinatumomab for routine commissioning. It requested further analyses from the company (see section 3.11)

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, Appraisal Committee
February 2019

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Lyudmila Marinova
Technical Lead

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