

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Gemtuzumab ozogamicin for untreated acute
myeloid leukaemia**

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using gemtuzumab ozogamicin 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?

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 determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using gemtuzumab ozogamicin 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: 18 June 2018

Second appraisal committee meeting: 27 June 2018

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

1 Recommendations

- 1.1 Gemtuzumab ozogamicin, with daunorubicin and cytarabine, is recommended as an option for treating newly diagnosed de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia, in people 15 years and over, only if the disease has:
- favourable cytogenetics or
 - unknown cytogenetics because cytogenetic analysis was unsuccessful.
- 1.2 This recommendation is not intended to affect treatment with gemtuzumab ozogamicin that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For young people aged 15 to 17, this decision should be made jointly by the clinician and the young person and the young person's parents or carers.

Why the committee made these recommendations

AML is currently treated with daunorubicin plus cytarabine. Cytogenetic testing is used to look for specific gene mutations in certain leukaemias, that might predict how a person's disease responds to treatment and affect treatment options. People whose disease has favourable or intermediate cytogenetics have a better prognosis than those whose disease has unfavourable cytogenetics in terms of treatment response, risk of relapse and survival. However, cytogenetic test results are not always available at the start of the treatment.

Evidence from a randomised clinical trial shows that, for people whose disease has favourable or intermediate cytogenetics, gemtuzumab ozogamicin with daunorubicin and cytarabine is more clinically effective than daunorubicin and cytarabine alone.

People are more likely to live longer without the disease relapsing or symptoms returning.

Because no clinical or cost effectiveness evidence is presented for people whose disease has unfavourable cytogenetics, gemtuzumab ozogamicin cannot be recommended for this group.

The most plausible cost effectiveness estimates for gemtuzumab ozogamicin for a combined group of people with favourable, intermediate and unknown cytogenetics are below the range that NICE normally considers an acceptable use of NHS resources. However, for people whose disease has intermediate cytogenetics only, the cost-effectiveness estimate is higher than the range that NICE normally considers a cost-effective use of NHS resources, therefore gemtuzumab ozogamicin cannot be recommended for this group. For people whose disease has favourable or unknown cytogenetics, the cost effectiveness estimate is within the range that NICE considers a cost-effective use of NHS resources, therefore gemtuzumab ozogamicin can be recommended for this group.

2 Information about gemtuzumab ozogamicin

Marketing authorisation indication	Gemtuzumab ozogamicin (Mylotarg, Pfizer) is indicated for the treatment of previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL) for patients age 15 years and above, in combination with daunorubicin (DNR) and cytarabine (AraC). ¹
Dosage in the marketing authorisation	Based on the company's submission, gemtuzumab ozogamicin will be available as a 5-mg powder for concentrate for solution for infusion. Induction course: gemtuzumab ozogamicin 3 mg/m ² /dose (up to a maximum of 5 mg/dose) given on days 1, 4 and 7 of induction therapy course. Consolidation course 1 and 2: gemtuzumab ozogamicin 3 mg/m ² /dose (up to a maximum of 5 mg/dose) given on day 1 of each course of consolidation therapy.
Price	Anticipated price is confidential

3 Committee discussion

The appraisal committee (section 6) considered evidence submitted by Pfizer and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

New treatment option

People with acute myeloid leukaemia would welcome a new treatment option

- 3.1 Acute myeloid leukaemia (AML) is a rapidly progressing form of leukaemia. The committee heard that people with the disease have fatigue, weakness or breathlessness, memory loss, bruising, bleeding and frequent infections. The committee also heard that there is a poor prognosis for patients whose disease does not respond to treatment, or whose disease responds then relapses. The committee agreed that new treatments that could improve the chance of successfully inducing first remission would be welcomed.

Clinical management

Current treatment for acute myeloid leukaemia is daunorubicin plus cytarabine and this is the appropriate comparator

- 3.2 The committee heard that the aim of intensive chemotherapy is to induce complete remission, after which people would either have consolidation chemotherapy or a stem cell transplant. The committee heard that the majority of patients with AML in the UK are entered into NCRI AML trials. Currently these comprise AML 19 for younger patients and AML 18 for patients over the age of 60 years. It was also heard that both trials currently include gemtuzumab ozogamicin as an induction therapy for patients without a known adverse karyotype at diagnosis. Outside the setting of clinical trials, the majority of patients who are considered suitable for intensive chemotherapy currently receive 'standard' combination chemotherapy (daunorubicin plus cytarabine) without the

addition of gemtuzumab ozogamicin. Intensive treatment for acute myeloid leukaemia is essentially unchanged in 40 years and although survival has gradually improved this has been largely a result of improvements in supportive care and the judicious application of allogeneic stem cell transplantation. The committee concluded that established clinical management is daunorubicin plus cytarabine and this is the relevant comparator for this appraisal.

Cytogenetic testing is standard clinical practice in England

3.3 All people with newly diagnosed AML have cytogenetic testing as this provides the clinician with important information regarding prognosis and how the disease might respond to different treatments. People who have AML with favourable or intermediate cytogenetics have a better prognosis than those whose disease has unfavourable cytogenetics. The committee understood that larger centres have placed great emphasis in obtaining the cytogenetic results as quickly as possible, usually within days. However in smaller centres, it may take between 1-3 weeks to obtain cytogenetics. The clinical experts confirmed that cytogenetic testing takes between 7 to 10 days and it would be challenging to reduce this to less than 7 days. The committee acknowledged that cytogenetic testing is standard clinical practice and its importance in the clinical management of untreated AML.

Cytogenetic testing results are not always available at the start of the treatment

3.4 The committee heard that for some patients, there is an urgent need to start treatment before cytogenetic results have been received. The clinical experts explained that around 15-20% of patients have a very high or rapidly increasing white blood cell count, evidence of tumour lysis or disseminated intravascular coagulation or life-threatening bleeding or infection when they are diagnosed. The clinical experts also explained that for this group of patients, there is no evidence to suggest that starting treatment before cytogenetic results become available is harmful, and that

treatment would be stopped if the tests revealed that the patient has AML with unfavourable cytogenetics. The committee acknowledged the importance of being able to start treatment for these people before cytogenetic test results become available and agreed to account for this in its decision making (see section 3.15).

Population

The population specified in the company's decision problem is appropriate

3.5 Patients who have AML with favourable or intermediate cytogenetics have a better prognosis than those whose disease has unfavourable cytogenetics. The committee considered the population relevant to this appraisal and noted that the marketing authorisation does not define the population by cytogenetic status. But the company's base-case focused on patients 'not known to have unfavourable cytogenetics. This included people whose disease had favourable, intermediate and unknown cytogenetics. The clinical experts supported the company's rationale for excluding patients whose disease had unfavourable cytogenetics (see section 3.3). The committee concluded that the population specified in the company's decision problem is appropriate.

The intermediate 1 and 2 cytogenetic subgroup classification system is outdated

3.6 The ERG highlighted differences in the clinical benefit seen in patients whose disease had intermediate-1 (normal karyotype on cytogenetics) and intermediate-2 (t (9;11)(p22;q23); cytogenetic abnormalities not classified as favourable or adverse) cytogenetic and molecular risk profile (see section 3.12). These differences show that there is some heterogeneity in the group of patients whose disease has intermediate cytogenetics. However, clinical experts explained that the classification of intermediate-1 and intermediate-2 by only cytogenetics is outdated, and a new classification is being used in clinical practice. This updated classification takes account of more genetic abnormalities such as

abnormalities in FLT3, NPM1, CEBPA and other genes. The committee concluded that, although the clinical results are different between intermediate-1 and 2, it would prefer not to split the intermediate group using an outdated classification system.

Clinical evidence

The results from ALFA-0701 are generalisable to clinical practice

3.7 ALFA-0701 (n= 271) is an open-label, phase III, randomised controlled trial, done across 26 haematology centres in France. It included patients aged 50-70 years with previously untreated de novo (that is, excludes secondary leukaemia) AML. It compared gemtuzumab ozogamicin plus daunorubicin and cytarabine with daunorubicin and cytarabine alone. The data presented were from the 30 April 2013 data cut and the committee stated that a more recent data cut from the ALFA-0701 trial would be informative. The population in the marketing authorisation was extended to include people aged 15-17 years and restricted to de novo CD33-positive AML. Most patients diagnosed with AML are over 50 years of age. Therefore, the population included in the trial is likely to be reflective of most patients for whom gemtuzumab ozogamicin would be suitable in clinical practice. The trial did include a small number of patients whose disease was not CD33-positive. These patients would not have gemtuzumab ozogamicin according to the marketing authorisation. The committee agreed that it can only appraise gemtuzumab ozogamicin within its marketing authorisation and concluded that the ALFA-0701 trial is generalisable to the population who would have gemtuzumab ozogamicin plus daunorubicin and cytarabine in clinical practice.

The dosing schedule in ALFA-0701 differs from the dose in ongoing trials in the UK

3.8 The dosing schedule for gemtuzumab ozogamicin in the ALFA-0701 trial is in line with the marketing authorisation. However, 2 ongoing UK trials (AML 18 and AML 19) use different dosing regimens. Therefore, the

granting of the marketing authorisation may have implications for dosing in practice, because UK clinicians are currently using the dosing schedule from AML 18 and AML 19, rather than the licensed dosage. The committee agreed that they could only recommend gemtuzumab ozogamicin in line with the dosing schedule specified in the marketing authorisation.

The individual patient data meta-analysis is not generalisable to clinical practice

3.9 The main clinical evidence was supported by an individual patient data meta-analysis. However, the individual patient data meta-analysis included patients aged 15 years or older with newly diagnosed or secondary acute myeloid leukaemia or high-risk myelodysplastic syndrome. This is a broader population than the marketing authorisation. The committee concluded that the results may not be generalisable to people who would have gemtuzumab ozogamicin in clinical practice.

Clinical effectiveness results

Gemtuzumab ozogamicin increases event-free survival and relapse-free survival compared with chemotherapy alone in the overall ALFA-0701 population

3.10 The company reported outcomes by investigator assessment and by independent review committee. The analysis by independent review committee was considered to be academic-in-confidence by the company and therefore cannot be reported here. As analyses by investigator assessment are reported in the summary of product characteristics (SmPC), those results are reported here. The primary outcome measure in ALFA-0701 was event-free survival. An event was defined as induction failure, relapse or death. Treatment with gemtuzumab ozogamicin plus daunorubicin and cytarabine increased median event-free survival compared with daunorubicin and cytarabine alone. The analysis by investigator assessment shows increased median event free survival from

9.5 months to 17.3 months (hazard ratio [HR] 0.56; 95% confidence intervals [CI] 0.42 to 0.76, $p=0.0002$). Relapse-free survival and overall survival were secondary end points. Median relapse-free survival increased from 11.4 months to 28 months (HR; 0.53; 95% CI 0.36 to 0.76, $p=0.0006$) in patients who had gemtuzumab ozogamicin plus daunorubicin and cytarabine. Median overall survival increased from 21.8 months to 27.5 months (HR 0.81; 95% CI 0.60- to 1.09, $p=0.165$). However, the difference between treatment groups did not reach statistical significance. The committee concluded that gemtuzumab ozogamicin plus daunorubicin and cytarabine was clinically effective compared with chemotherapy alone.

Gemtuzumab ozogamicin increases event-free survival and relapse free-survival in the combined favourable and intermediate cytogenetic group but not in the unfavourable group compared with chemotherapy alone

3.11 The company presented results categorised by cytogenetic profile. The company reported outcomes by investigator assessment and by independent review committee. The analysis by independent review committee was considered to be academic-in-confidence by the company and therefore cannot be reported here. As analyses by investigator assessment are reported in the SmPC, those results are reported here. Treatment with gemtuzumab ozogamicin plus daunorubicin and cytarabine increased median event-free survival from 12.2 month to 22.5 months (HR 0.49; 95% CI 0.33 to 0.72, $p= 0.0003$) in those whose disease had favourable/intermediate cytogenetics. There was no statistically significant difference in median event-free survival in patients whose disease had unfavourable cytogenetics (from 4.5 months to 2.8 months [HR 1.111; 95% CI 0.63 to 1.95, $p= 0.72$]). For patients in the favourable or intermediate cytogenetic group, overall survival increased from 38.6 months to 26.0 months (HR 0.747, 95% CI 0.511 to 1.091, $p=0.1288$). For patients who disease had unfavourable cytogenetics, overall survival decreased from 3.14 months to 12.0 months (HR 1.553,

CI 0.878 to 2.748, $p=0.1267$). The committee concluded that gemtuzumab ozogamicin plus daunorubicin and cytarabine compared with chemotherapy alone was clinically effective when including patients whose disease had favourable and intermediate cytogenetics. Moreover, results from those subgroups were better than the overall population, but only when results from patients with unfavourable cytogenetics were not included.

There is heterogeneity in the clinical outcomes in the broader intermediate cytogenetic subgroup

3.12 The company provided additional analyses for the intermediate cytogenetic group by cytogenetic and molecular risk profile (that is by intermediate-1 and intermediate-2 subgroups). The company reported outcomes by independent review committee only. The analysis by independent review committee was considered to be academic-in-confidence by the company and therefore cannot be reported here. The committee acknowledged that results for the intermediate-2 group are based on small numbers of patients. The clinical experts explained that such classification of the intermediate group is not being used in clinical practice (see section 3.3). The committee concluded that they preferred not to split the intermediate group using an outdated classification system but the results highlighted heterogeneity in the clinical outcomes in the broader intermediate group. Therefore it agreed to account for this in its decision making (see section 3.26).

Gemtuzumab ozogamicin is generally well tolerated

3.13 There was an increase in veno-occlusive disease in the gemtuzumab ozogamicin plus daunorubicin and cytarabine group compared with daunorubicin and cytarabine alone. However, the numbers of people who had other adverse effects were similar between the 2 groups. The committee concluded that gemtuzumab ozogamicin was generally well tolerated.

The risk of developing veno-occlusive disease because of gemtuzumab ozogamicin therapy is low

3.14 The patient organisation stated that the risk of veno-occlusive disease appears to be relatively low when doses 3 mg/m² or less are used in combination with conventional therapy as part of initial therapy for AML. This is in line with the dosing in the marketing authorisation and in the ALFA-0701 trial. The clinical experts confirmed that it is a rare side effect but clinicians are experienced in managing it. The committee concluded that risk of developing veno-occlusive disease because of gemtuzumab ozogamicin therapy is low but that the costs associated with managing it should be included in the economic analysis.

Company's economic model

The model is complex but appropriate for decision making

3.15 The company presented a semi-Markov cohort state-transition model with 12 health states. The main effectiveness data came from the ALFA-0701 trial. It was used to estimate overall survival and relapse-free survival, using mixture cure models fit to Kaplan Meier data. The committee was aware that there was a lack of an explicit structural link between a number of key model parameters, including between relapse and haemopoietic stem cell transplant, the model structure was complex and challenging to critique. However, the committee concluded that model was appropriate for decision making.

People who have not relapsed after 5 years are considered to be cured

3.16 The company assumed that patients who were alive after 5 years from the start of the gemtuzumab ozogamicin treatment were considered to be functionally cured. The clinical experts confirmed that if patients have not had a haematopoietic stem cell transplantation and had not relapsed within 5 years, they would consider them cured. The clinical experts also estimated that relapses between 3 and 5 years happen in less than 5% of

acute myeloid leukaemia patients, and they are very rare. The committee concluded that using 5 years as a cure point was appropriate.

Survival curves for people considered to be cured are correctly modelled

3.17 The company explored various alternative approaches for extrapolating survival data. The company explored a range of mixture cure model survival functions and concluded that the lognormal and Weibull models showed the best statistical and visual fit. The difference in the cure fraction between treatment groups was broadly similar for both the mixture cure model lognormal and Weibull functions for both event-free survival and overall survival. The ERG noted that this is important because it is the difference between the groups which is the main driver of differences in the quality-adjusted life years (QALY) and the ICER estimates. The committee concluded that the company approach to curve fitting and the rationale for selecting lognormal in its base case to be appropriately justified.

Mortality risk higher than the general population is appropriate for patients who are considered to be cured

3.18 The company calculated an increased mortality risk for functionally cured patients compared with the general population. The company considered the increased mortality risk to be academic in confidence and therefore it cannot be reported here, The ERG noted that in some years the probability of death was still higher in the general population than in the functionally cured patients. The ERG adjusted the mortality calculations so that the mortality risk for functionally cured patients was always more than the general population. This increased the hazard ratio. The committee agreed that the hazard ratio applied by the ERG was more plausible.

Utility values in the model

Patients considered to be cured would have a lower quality of life than that of the general population

3.19 The company used utility values from literature sources, because information on health-related quality of life was not collected as part of ALFA-0701. In the economic model, the company assumed that functionally cured patients experience the same health-related quality of life as the general population. The ERG used a lower utility values for functionally cured patients. The committee considered it reasonable to assume that functionally cured patients would have lower quality of life than that of general population and that this was consistent with the assumption that functionally cured patients experience a higher mortality risk than the general population (see section 3.18). The committee concluded that the ERG's alternative utility values were most plausible.

Cost-effectiveness results

Gemtuzumab ozogamicin is cost-effective in the company's analysis

3.20 The company's deterministic base-case ICER for gemtuzumab ozogamicin compared with standard of care for patients whose disease did not have unfavourable cytogenetics (that is, they had favourable, intermediate and unknown cytogenetics) was £12,251 per QALY gained.

The ICER for gemtuzumab ozogamicin remains below £20,000 per QALY gained in the ERG's alternative base case

3.21 The ERG corrected some minor errors in the company's base-case which increased the ICER to £13,561 per QALY gained. In its preferred base-case, the ERG made 8 further adjustments to the company's base-case model:

- using initial treatment costs of induction and consolidation therapy based on investigators assessed data

- using individual rates of response based on unpooled ALFA-0701 trial data
- amending HSCT treatment costs to match those from NHS reference costs
- including hospital costs for the treatment of veno-occlusive disease
- excluding GVHD specific costs
- excluding veno-occlusive disease events from standard of care arm
- changing assumptions to ensure that patients who are functionally cured experience lower health-related quality of life than the general population
- adjusting the mortality rate, so it is equal to the general population mortality rate in instances when the observed mortality rate is reported to be lower than the general population.

These changes resulted in a deterministic ICER of £16,910 per QALY gained for gemtuzumab ozogamicin compared with standard of care for patients whose disease did not have unfavourable cytogenetics. The committee concluded that the changes made by the ERG were reasonable and that the new ICER was plausible.

Excluding people whose disease had unknown cytogenetics increases the ICERs

3.22 The company presented additional cost-effectiveness analyses for subgroups excluding patients whose disease had unknown cytogenetics. The company considered the ICER for the subgroup of patients whose disease had favourable and intermediate cytogenetics (excluding unknowns) to be commercial-in-confidence and therefore they cannot be reported here. The committee agreed to consider the impact of excluding patients whose disease had unknown cytogenetics on the cost-effectiveness estimates. The committee understood that the subgroup of

patients whose disease had unknown cytogenetics consisted of patients where the test was not undertaken or that the test result analysis was unsuccessful in determining cytogenetic status. The committee was aware that because of a lack of any additional information on the reasons for the unknown result, the ERG was unable to explore this issue further. However, the committee accepted that the exclusion of the subgroup of people whose disease had unknown cytogenetics increased the ICER and agreed to take this into account in its decision making.

The ERG's ICER for people whose disease had intermediate cytogenetics is above £30,000 per QALY gained

3.23 The committee was aware of the ERG's concerns regarding the heterogeneity in the clinical outcomes in the intermediate cytogenetics subgroup, a subgroup which was included in the company's base case. It therefore agreed to consider the ERG's exploratory analyses which explored the impact of the heterogeneity on the ICERs. The committee noted that the ERG's exploratory analyses (excluding the unknowns) resulted in ICERs of

- £24,581 per QALY gained for the subgroup of patients whose disease had a favourable or intermediate cytogenetic status,
- £31,709 per QALY gained for the subgroup of patients whose disease had intermediate cytogenetic status only,
- £17,614 per QALY gained for the subgroup of patients whose disease had favourable cytogenetic or intermediate-1 molecular status,
- and £16,343 per QALY gained for the subgroup of patients whose disease had intermediate-1 molecular status.

The committee accepted that there was heterogeneity in the clinical outcomes in the broader intermediate cytogenetic subgroup (see section 3.12). It agreed that it was reasonable to assume that the heterogeneity in clinical outcomes was leading to the increased higher ICER for the broader intermediate cytogenetic subgroup. The committee

accepted the ICER of £31,709 per QALY for the broader intermediate cytogenetic subgroup and agreed to take account of the heterogeneity in the subgroup in its decision making.

Gemtuzumab ozogamicin is recommended for people whose disease had favourable or unknown cytogenetics

3.24 The committee considered the most plausible ICER for the subgroup of patients whose disease had favourable cytogenetics. It was aware that neither the company nor the ERG had presented cost-effectiveness results for a subgroup of patients whose disease had favourable cytogenetics only. The committee noted that the ICER in the ERG's alternative base case was £16,910 per QALY gained for gemtuzumab ozogamicin compared with standard of care (see section 3.21) and this was for patients not known to have unfavourable cytogenetic profile (that is favourable, intermediate or unknown cytogenetics). The committee also noted that the ICER for the intermediate cytogenetic subgroup (excluding the unknowns) was £31,709 per QALY gained (see section 3.23) suggesting that ICERs presented for the company's base case and the ERG's alternative base case were being driven by the effectiveness of gemtuzumab ozogamicin in patients whose disease had favourable and unknown cytogenetics. The committee was aware that neither the company nor the ERG had presented cost-effectiveness results for a subgroup of patients whose disease had unknown cytogenetics only, but the removal of the subgroup with unknown cytogenetics would increase the ICER (see section 3.22). The committee agreed that the most plausible ICER for the subgroup of patients whose disease had favourable or unknown cytogenetic status would be within the range that NICE considers as an acceptable user of NHS resources.

Gemtuzumab ozogamicin is recommended for people whose disease had unknown cytogenetics if the test result analysis was unsuccessful

3.25 The committee recalled that the subgroup of patients whose disease had unknown cytogenetics could consist of 2 groups of patients: those where

the test was not undertaken and those where the test result analysis was unsuccessful in determining cytogenetic status (see section 3.22). The committee heard from the clinical experts that if the test results analysis was unsuccessful, it was not routine clinical practice to re-test. The committee agreed that its recommendation regarding patients whose disease had unknown cytogenetics should include those people where the test analysis results was unsuccessful. The committee recalled that some patients might require urgent treatment which would require immediate treatment to be initiated without cytogenetic results (see section 3.6). The committee also recalled that urgent therapy is required if the patient has a very high white blood cell count, a rapidly increasing white blood cell count, evidence of tumour lysis and/or disseminated intravascular coagulation or has life-threatening bleeding or infection (see section 3.6). The committee was aware that the treatment costs for patients whose disease had unknown cytogenetics, who require urgent treatment while waiting for the cytogenetic test results and who were later found to have unfavourable cytogenetics, were not included in the economic model and that if this was included, it would increase the ICER. The committee considered that in clinical practice, patients would receive gemtuzumab ozogamicin with the first course of chemotherapy while the cytogenetic results are awaited and treatment with gemtuzumab ozogamicin should only be continued in course 2 and beyond in patients whose disease had favourable cytogenetics. The committee agreed that it would like to see a cost effectiveness analysis undertaken by the company which took account of this stopping rule. It also would like to receive comments from consultees and commentators on whether such a stopping rule would be implementable in clinical practice. Until it considers this analysis and clarification, the committee agreed that it could not make recommendations for people with unknown cytogenetics where there is an urgent need to start treatment before the cytogenetic test results are available. However, it concluded that it would recommend gemtuzumab

ozogamicin for people with unknown cytogenetics status where the cytogenetic test result analysis has been unsuccessful.

Gemtuzumab ozogamicin is not recommended for people whose disease had intermediate cytogenetic status

3.26 The committee considered the most plausible ICERs for the subgroup of patients whose disease had intermediate cytogenetic status. It noted that the cost effectiveness estimate for the subgroup of patients whose disease had intermediate cytogenetic status only was £31,709 per QALY gained but that it was lower for the subgroup of patients whose disease had intermediate-1 molecular status (£16,343 per QALY gained) (see section 3.23). The committee recalled that it had heard from the clinical experts that such classification of the intermediate group is not being used in clinical practice and that it had concluded not to split the intermediate group using an outdated classification system (see section 3.12). The committee therefore concluded that the most relevant ICER for its decision making was the ICER for the broader intermediate group which was £31,709 per QALY gained. As this was above the range that NICE usually considers an acceptable use of NHS resources, the committee agreed that gemtuzumab ozogamicin could not be recommended for people whose disease had intermediate cytogenetics.

Gemtuzumab ozogamicin is not recommended for people whose disease had unfavourable cytogenetic status

3.27 The committee was aware that neither the company nor the ERG had presented clinical or cost effectiveness evidence for the subgroup of patients whose disease had unfavourable cytogenetic status. The committee recalled that the clinical experts supported the company's rationale for excluding patients whose disease had unfavourable cytogenetics (see sections 3.3 and 3.6). The committee agreed not to recommend gemtuzumab ozogamicin for patients whose disease had unfavourable cytogenetics.

Innovation

There are no additional benefits that are not captured in the QALY calculations

- 3.28 The company considered gemtuzumab ozogamicin to be an innovative treatment because when used with daunorubicin and cytarabine it extends the duration of remission. It works in novel way to directly target CD33-positive acute myeloid leukaemia blasts and induce death of leukaemia cells. The committee concluded that gemtuzumab ozogamicin would be beneficial for patients, but it had not been presented with evidence of any additional benefits that were not captured in the measurement of QALYs.

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

- 3.29 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [Cancer Drugs Fund technology appraisal process and methods](#). This states that a treatment can be considered as a 'life-extending treatment at the end of life' if it is indicated for patients with a short life expectancy, normally less than 24 months, and it offers an extension to life, normally of a mean value of at least an additional 3 months compared with current NHS treatment. The committee noted that the results of ALFA-0701 showed that gemtuzumab ozogamicin could increase life expectancy compared with standard care by more than 3 months. However, the short life expectancy criteria were not met (company model standard of care life years gained: 6.02).

4 Implementation

- 4.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions,

local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

- 4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.
- 4.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has acute myeloid leukaemia and the doctor responsible for their care thinks that gemtuzumab ozogamicin is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Proposed date for review of guidance

- 5.1 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.

Professor Stephen O’Brien
Chair, appraisal committee
May 2018

6 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.

Julia Sus

Technical Lead

Nicola Hay and Alex Filby

Technical Advisers

Stephanie Callaghan

Project Manager

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