NICE National Institute for Health and Care Excellence

NICE guidance

Inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia

Technology appraisal guidance

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The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Recommendations

1.1 Inotuzumab ozogamicin is recommended, within its marketing authorisation, as an option for treating relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia in adults. People with relapsed or refractory Philadelphia-chromosome-positive disease should have had at least 1 tyrosine kinase inhibitor.

Inotuzumab ozogamicin is recommended only if the company provides it according to the commercial arrangement.

Why the committee made these recommendations

Treatment for relapsed or refractory B-cell acute lymphoblastic leukaemia is usually fludarabine, cytarabine and granulocyte colony-stimulating factor based chemotherapy (FLAG) with idarubicin. People with Philadelphia-chromosome-positive disease can have FLAG-based therapy with tyrosine kinase inhibitors or tyrosine kinase inhibitors alone. Clinical trial evidence does not show an overall survival benefit for people having inotuzumab ozogamicin compared with those having FLAG, high-dose cytarabine or cytarabine with mitoxantrone-based chemotherapy. However, more people having inotuzumab ozogamicin are able to go on to have a stem cell transplant when compared with people having the other treatments. Inotuzumab ozogamicin also meets NICE's criteria to be a life-extending treatment at the end of life.

The most plausible cost-effectiveness estimates for inotuzumab ozogamicin compared with standard care are in the range NICE considers an acceptable use of NHS resources. Therefore it can be recommended for treating relapsed or refractory B-cell acute lymphoblastic leukaemia.

2 Information about inotuzumab ozogamicin

Marketing authorisation	Inotuzumab ozogamicin (Besponsa, Pfizer) is indicated as monotherapy for the treatment of adults with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia (ALL). Adult patients with Philadelphia-chromosome-positive relapsed or refractory B-cell precursor ALL should have failed treatment with at least 1 tyrosine kinase inhibitor.
Dosage in the marketing authorisation	Intravenously at a starting dose of 1.8 mg/m^2 per cycle (0.8 mg/m^2 on day 1 and 0.5 mg/m^2 on days 8 and 15), in 3- to 4-week cycles. Cycle 1 lasts for 3 weeks, and each subsequent cycle lasts for 4 weeks. See the summary of product characteristics for further details.
Price	£8,048 per 1 mg vial of powder concentrate for solution for infusion (excluding VAT; BNF 2018). The company has a commercial arrangement. This makes inotuzumab ozogamicin 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 Pfizer and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Clinical management

People with B-cell acute lymphoblastic leukaemia would welcome a new treatment option

3.1 The clinical and patient experts noted that people with relapsed or refractory B-cell acute lymphoblastic leukaemia have limited treatment options. The committee understood that current treatment can cause unpleasant side effects. The clinical expert explained that inotuzumab ozogamicin is innovative, reduces the need for hospitalisation, and has potential to have a substantial effect on health-related benefits. The committee understood that although inotuzumab ozogamicin can cause a serious side effect (veno-occlusive liver disease), it is generally well tolerated. The committee concluded that inotuzumab ozogamicin could be an important treatment option for people with relapsed or refractory B-cell acute lymphoblastic leukaemia.

FLAG-based therapy is the most appropriate comparator

3.2 The committee considered the most appropriate comparators for inotuzumab ozogamicin and its likely position in the treatment pathway. The patient and clinical experts stated that people with relapsed or refractory acute B-cell lymphoblastic leukaemia have combination chemotherapy. For most people this would be fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG) with idarubicin (FLAG-IDA), which involves prolonged hospitalisation for treatment and is associated with debilitating side effects. Also, patients with Philadelphia-chromosome-positive disease can have FLAG-based therapy with tyrosine kinase inhibitors (TKIs) or TKIs alone. Clofarabine is sometimes used instead of FLAG-based therapy, but the committee noted that its marketing authorisation is only for people aged 21 years or younger. The committee noted there was an ongoing appraisal of blinatumomab, but that this was not included in the scope because it is not established clinical practice in the NHS. It was also aware that in the main clinical trial (INO-VATE 1022), neither TKIs nor clofarabine were used and that most patients in the standard care arm had

FLAG-based therapy without idarubicin. The clinical expert stated that in clinical practice in England, inotuzumab ozogamicin would be used for patients at first relapse before considering other salvage therapies, which are poorly tolerated. The committee concluded that FLAG-based therapy was the most appropriate comparator for this appraisal.

Clinical evidence

The clinical-effectiveness evidence is relevant to NHS practice

3.3 INO-VATE 1022 (n=326) is an open-label, phase III, randomised controlled trial comparing inotuzumab ozogamicin with 3 different standard care chemotherapy regimens (FLAG, high-dose cytarabine, and cytarabine with mitoxantrone). The trial population broadly represents patients in the NHS. INO-VATE 1022 included patients with relapsed or refractory acute lymphoblastic leukaemia having trial treatments as the first or second salvage therapy. Patients with Philadelphia-chromosome-positive disease had to have had at least 1 TKI. The trial only recruited adults fit for intensive treatments; a subgroup of inotuzumab ozogamicin's marketing authorisation population. Patients who would have best supportive care and patients expected to have 3 or more salvage therapies were not included in the trial. The committee was aware that high-dose cytarabine and cytarabine with mitoxantrone are currently not used in clinical practice in England and that most patients in the trial had FLAG-based therapy. The committee concluded that the trial populations broadly correspond to those that would be seen in NHS clinical practice, even though the marketing authorisation is wider.

Clinical effectiveness

Inotuzumab ozogamicin does not increase overall survival but increases the rate of stem cell transplant

3.4 The median overall survival in INO-VATE 1022 was 7.7 months for inotuzumab ozogamicin compared with 6.7 months for standard care in the intention-to-treat population. This difference was not statistically significant. The company's post-hoc restricted mean survival time analysis (cut short at 37.7 months) suggested a median overall survival of 13.9 and 9.9 months for inotuzumab ozogamicin and standard care respectively (p=0.0023). The ERG stated that the results of the restricted mean survival time analysis depended on when it was

cut short and that the company results appeared to inflate overall survival. However, more patients had complete remission or complete remission with incomplete haematological recovery with inotuzumab ozogamicin than with standard care: 88 (80.7%) compared with 32 (29.4%) respectively ($p<0.0001$; based on the analysis of results for the first 218 patients enrolled in the trial). Similarly, more patients were able to have haematopoietic stem cell transplant (HSCT) directly after inotuzumab ozogamicin compared with standard care; 45 (41%) and 12 (11%) respectively ($p<0.001$; analysis of results for the first 218 patients). These results were confirmed by the intention-to-treat analyses (the results were submitted as academic in confidence and cannot be reported here). The company stated that in general, by increasing the rate of HSCT, inotuzumab ozogamicin could increase mean survival. The clinical expert and the ERG agreed that this is plausible. The committee noted that although inotuzumab ozogamicin's survival benefits are uncertain, it increased the response rate and the rate of HSCT. The committee therefore concluded that inotuzumab ozogamicin is clinically effective compared with FLAG-based chemotherapy.

Adverse events

Inotuzumab ozogamicin has an acceptable safety profile

3.5 Inotuzumab ozogamicin is associated with potentially life-threatening veno-occlusive liver disease. The clinical expert noted that this mainly happens in people who have had conditioning alkylating treatments that are not used in the UK. Continued experience with inotuzumab ozogamicin could minimise the risk of veno-occlusive disease. The committee acknowledged the risks associated with inotuzumab ozogamicin treatment and concluded that it has an acceptable safety profile.

The company's original economic model

The model structure is appropriate for decision-making

3.6 The company model consisted of 3 partitioned survival sub models, with sub states for progression-free disease, progressed disease and death:

- no complete remission or complete remission with incomplete haematological recovery and no HSCT

- complete remission or complete remission with incomplete haematological recovery and no HSCT
- HSCT and post-HSCT (patients could enter this state regardless of remission status).

The company's sensitivity analyses showed that the incremental cost-effectiveness ratio (ICER) was most sensitive to the cost of HSCT, the proportion of patients having blinatumomab and inotuzumab ozogamicin as subsequent induction treatments, and the utility of progressive disease. All clinical parameters in the model were derived from the safety population of INO-VATE 1022. The company explained that because some patients in the standard care arm were randomised but did not have treatment (and all patients randomised to inotuzumab ozogamicin had treatment), it considered the safety population to be more appropriate for modelling. This is because it excluded patients who did not have treatment; these patients would be classified as not having complete remission or complete remission with incomplete haematological recovery in the intention-to-treat population. The company considered that this approach was conservative. The ERG disagreed with the company, noting that there were other factors to be considered. The ERG stated that it was not clear whether using the safety population instead of the intention-to-treat population for the modelling would result in bias towards patients who had inotuzumab ozogamicin or standard care. The committee agreed that because it had not seen the intention-to-treat population's results it was not able to decide about the most appropriate population for modelling, but it concluded that the model structure was appropriate for decision-making.

Overall survival extrapolation in the original economic model

The company's extrapolation in the HSCT and post-HSCT state is not appropriate for decision-making

3.7 In each sub-model population, the company applied parametric curves for overall and progression-free survival, using the same type of curve in each case. The ERG stated that the company used a non-standard way of fitting parametric curves to the HSCT and non-HSCT data, which resulted in wide separation of the 2 survival curves. The ERG also explained that splitting the INO-VATE 1022 population and fitting multiple parametric curves is a very complex approach. The company's approach resulted in populations that are small and no longer support randomised comparisons. Specifically, a very small number of patients remained in the HSCT and post-HSCT state after 2 years. The committee noted that after having HSCT, people could be considered to act as a single group. The

committee understood that about 95% of the quality-adjusted life year (QALY) gain was in the HSCT and post-HSCT state after the trial follow-up period (after data extrapolation). The clinical expert noted that veno-occlusive liver disease happens after HSCT and causes some early mortality. The clinical expert further noted that the prognosis after HSCT depends on the pre-HSCT conditioning treatments and that fitter and younger patients would have a better prognosis. The committee was not persuaded that the use of treatment-specific overall survival curves in the HSCT and post-HSCT state was justified. The committee did not agree with the company's overall survival extrapolation in the HSCT and post-HSCT state and therefore concluded that it was not appropriate for decision-making.

ERG's exploratory analyses

Pooled overall survival analysis with minimal residual disease status as a covariate in the HSCT and post-HSCT state is appropriate for decision-making

3.8 The ERG presented 2 alternative analyses for survival extrapolation in the HSCT and post-HSCT state. The first scenario was a non-parametric approach to survival analysis using the observed INO-VATE 1022 data with Kaplan–Meier data pooled across treatment groups. The second scenario was a fully parametric model (including treatment, age group, duration of first remission at randomisation, Philadelphia-chromosome category, previous HSCT and region as covariates) with pooled overall survival in the HSCT and post-HSCT state, using minimal residual disease status as a separate covariate. This resulted in overall survival for patients having inotuzumab ozogamicin and standard care based on the proportions in each treatment group with negative minimal residual disease status. The clinical expert stated that minimal residual disease status is a known predictive biomarker and can be measured with great precision, but has not been shown to be a prognostic indicator for overall survival. However, the clinical expert noted that no minimal residual disease is associated with better outcomes after HSCT. The committee previously agreed that the company's overall survival extrapolation in the HSCT and post-HSCT state was not suitable for decision-making (see section 3.7). It further agreed that the ERG's exploratory analyses have limitations, but considered the second scenario (pooled overall survival with minimal residual disease status as a covariate in the HSCT and post-HSCT states) to be clinically plausible and the most suitable analysis of those presented. The committee concluded that the

parametric model with pooled overall survival with minimal residual disease status as a covariate fitted to the HSCT and post-HSCT state is appropriate for decision-making.

Long-term survival in the original economic model

A 4-fold increase in mortality 3 years after stem cell transplant is the preferred assumption

3.9 In the HSCT and post-HSCT state, the company model assumed that patients are cured after HSCT if they are still alive after 3 years. It assumed general population mortality estimates from 3 years after HSCT. The company's sensitivity analyses suggested that the ICERs were not sensitive to a different cure point. Similarly, the ERG's sensitivity analyses applied to its parametric preferred analysis were relatively insensitive to the variation in cure point. However, the ERG disagreed with the company's assumption and stated that post-HSCT patients would continue to have increased mortality compared with the general population. The clinical expert's view was the same as the ERG's. The ERG stated that although mortality improves 5 years after HSCT, it remains 4 to 9 times higher for at least 25 years after that (Martin et al. 2010). The committee was aware that the Martin et al. mortality estimates were based on a cohort of 2,574 patients in the US between 1970 and 2002 who survived without their original disease recurring for at least 5 years after HSCT. The committee noted that it is difficult to determine the best time point in the model to assume a change in derivation of mortality post-HSCT. It agreed that the company's time point of 3 years is plausible for decision-making but that other time points may be also suitable. The committee also agreed with the ERG and the clinical expert that mortality remains increased after HSCT. The committee noted that assuming a 4-fold increase in mortality for patients from 3 years after HSCT is at the lower end of the Martin et al. 2010 range and concluded that this is its' preferred assumption.

Health-related quality of life in the original economic model

Age-adjusted utilities and INO-VATE 1022 utilities pooled across treatment groups are preferred

3.10 The company's model used:

- INO-VATE 1022-based utilities for the no complete remission or complete remission with incomplete haematological recovery and no HSCT state and the complete remission or complete remission with incomplete haematological recovery and no HSCT state
- utilities based on Kurosawa et al. 2016 (time dependent) for the HSCT and post-HSCT state and
- a utility for progressed disease from Aristides et al. 2015.

The ERG stated that the utilities used in the model were not age adjusted (and could exceed the utility in the general population) and that the utility value for progressed disease had a large effect on the estimated QALY gains. INO-VATE 1022 was an open-label trial and to minimise bias, the ERG suggested averaging utilities across the treatment groups for each (pre-progression) state. The clinical expert and committee agreed with the ERG that utility values decline with age and that utilities should be age adjusted. The committee noted that the pooled utilities across the trial did not differentiate between adverse events from inotuzumab ozogamicin or standard care. It acknowledged that using pooled utilities had only a marginal effect on the company's base-case ICER. The committee agreed that because of the possibility of bias for subjective end points, although conservative, the analysis with pooled utilities is more suitable for decision-making. The committee concluded that age-adjusted utilities and pooled INO-VATE 1022 utilities are its preferred assumptions.

Cost of comparators in the original economic model

Basing the cost of the comparators on the actual therapy taken in INO-VATE 1022 is preferred

3.11 INO-VATE 1022 compared inotuzumab ozogamicin with the investigator's choice of standard care (FLAG, high-dose cytarabine or cytarabine with mitoxantrone). The company's model included the cost of FLAG and added the cost of idarubicin, and imatinib for patients with Philadelphia-chromosome-positive disease, assuming no changes to the clinical effectiveness of the treatments. The ERG stated that including the costs of therapies when treatment benefits are excluded is inappropriate. The clinical expert and ERG both noted that ponatinib, rather than imatinib, is more likely to be used for Philadelphia-chromosome-positive disease. The ERG's exploratory analysis matched the costs to the actual therapy taken in INO-VATE 1022 (FLAG, high-

dose cytarabine or cytarabine with mitoxantrone). The committee agreed that the additional cost of idarubicin and imatinib should not be included in the model because the benefits are not accounted for. The committee concluded that the ERG's exploratory analysis with the cost of comparators based on the actual therapy taken in INO-VATE 1022 is its preferred assumption.

Cost of subsequent therapy in the original economic model

The company's calculation of subsequent treatment costs is highly uncertain

3.12 The company's model based the cost of subsequent therapies on the INO-VATE 1022 intention-to-treat population. It was not clear why the safety population had not been used when all other clinical data were based on the safety population. The ERG mentioned the possibility of positive bias towards inotuzumab ozogamicin when the intention-to-treat population is used to calculate the cost of subsequent therapies because more expensive subsequent treatments were given to patients having standard care. Also, it was unclear whether the benefits from post-induction therapies were adequately reflected in the safety population used to inform the economic model. The committee was aware that the company's sensitivity analyses showed that the ICER was sensitive to the proportion of patients having blinatumomab or inotuzumab ozogamicin as subsequent induction treatment (see section 3.6). Given the uncertainty around which patients were included in the model and the uncertainty in the cost of the subsequent therapies, the ERG's exploratory analysis replaced the cost of blinatumomab and inotuzumab ozogamicin as second-line induction therapies with the cost of chemotherapy. The committee recalled that no other results from the intention-to-treat population were presented (see section 3.6). It concluded that because of the uncertainty in the way the company calculated subsequent treatment costs, the ERG's exploratory analysis replacing the costs of blinatumomab and inotuzumab ozogamicin with the cost of chemotherapy is its preferred analysis.

Administration costs and inpatient days in the original economic model

Administration costs based on INO-VATE 1022 and 9.5 inpatient days in both arms are preferred

3.13 The company's model assumed that administering inotuzumab ozogamicin would need 3 outpatient visits and no inpatient days per cycle, compared with

no outpatient visits and 6.2 inpatient days for standard care (based on the summary of product characteristics). The ERG stated that the company's assumptions underestimated the cost of administering inotuzumab ozogamicin because no inpatient days were included. The clinical expert agreed with the ERG and also highlighted that patients having standard care often need an extended stay in hospital. The ERG's exploratory analysis based the administration cost of inotuzumab ozogamicin on INO-VATE 1022 (including both inpatient and outpatient costs as recorded in the trial) and used a weighted average NHS reference cost for regimens used in the standard care arm, resulting in an average length of stay of 9.5 days for both inotuzumab ozogamicin and standard care. The committee concluded that it preferred the ERG's analysis with the administration cost of inotuzumab ozogamicin based on INO-VATE 1022 and an average length of stay of 9.5 days in both arms.

Costs and benefits discount rate in the original economic model

The standard 3.5% discount rate for costs and benefits is more appropriate than 1.5%

3.14 The company applied a 1.5% discount rate to costs and QALYs based on assuming that HSCT restores normal life expectancy for patients. Results with a 3.5% discount rate were presented as a sensitivity analysis. The ERG did not agree with the company's 1.5% discount rate because mortality rates remain increased after HSCT. The committee discussed the methods guide and precedents for using non-reference case discount rates. It did not consider these relevant to the data or outcomes for the proposed use of inotuzumab ozogamicin. The committee recalled the median and mean survival rates from the INO-VATE 1022 clinical trial and its conclusion that a 4-fold increase in mortality for patients 3 years after HSCT and beyond is preferred (see section 3.9). It concluded that a 3.5% discount rate for costs and QALYs was appropriate for this appraisal.

The company's original economic analysis

The probabilistic ICERs are appropriate for decision-making

3.15 The company's deterministic ICERs were £40,013 and £55,869 per QALY gained using the 1.5% and 3.5% discount rates respectively for inotuzumab ozogamicin compared with standard care. The probabilistic ICERs were

£48,459 and £67,575 per QALY gained using the 1.5% and 3.5% discount rates respectively for inotuzumab ozogamicin compared with standard care. The ERG stated that the large difference between the probabilistic and deterministic results suggested that the company's model is non-linear. The ERG highlighted that when a model is non-linear, the deterministic ICER can be biased and that the probabilistic ICER is the more appropriate estimate. The committee concluded that the probabilistic ICERs are appropriate for decision-making.

The committee's preferred economic analysis

The committee's preferred analysis results in a deterministic ICER of over £100,000 per QALY gained

3.16 The committee considered the ERG's parametric model with pooled overall survival and minimal residual disease status as a covariate fitted to the HSCT and post-HSCT state (see section 3.8) to be appropriate for decision-making, with the following assumptions (as preferred by the committee):

- a 4-fold increase in mortality compared with the general population for patients 3 years post-HSCT and beyond (see section 3.9)
- age-adjusted utilities, and pooled INO-VATE 1022 utilities (see section 3.10)
- basing the cost of comparators on the actual therapy taken in INO-VATE 1022 (see section 3.11)
- replacing the costs of the subsequent therapies, blinatumomab and inotuzumab ozogamicin, with the cost of chemotherapy (see section 3.12)
- basing the administration cost of inotuzumab ozogamicin on INO-VATE 1022 and 9.5 inpatient days for both arms (see section 3.13)
- a discount rate of 3.5% for costs and QALYs (see section 3.14).

Including all the committee's preferred assumptions, the analysis resulted in a deterministic ICER for inotuzumab ozogamicin compared with standard care of £114,078 per QALY gained.

First appraisal consultation comments

Differences between the NICE appraisals of inotuzumab ozogamicin and blinatumomab are because of differences in the available evidence

3.17 The consultees and commentators noted that NICE's technology appraisal guidance on blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia, recommending blinatumomab as an option for treating Philadelphia-chromosome-negative relapsed or refractory precursor B-cell acute lymphoblastic leukaemia, was published in June 2017. Comments received during consultation drew a comparison between the blinatumomab and inotuzumab ozogamicin appraisals and suggested inconsistencies in modelling between the 2, namely survival between transplantation and the cure point, longer-term survival post-cure point, and health-related quality of life post-cure point. The committee was aware that blinatumomab was not a comparator in this appraisal, but also noted that it was not bound by the modelling and interpretation of a separate appraisal. Furthermore, the committee noted that the marketing authorisations for the 2 drugs are different: blinatumomab has a marketing authorisation for Philadelphia-chromosome-negative acute lymphoblastic leukaemia, but inotuzumab ozogamicin has a marketing authorisation for Philadelphia-chromosome-positive and -negative acute lymphoblastic leukaemia. The ERG stated that there are differences in the mechanism of action between the 2 drugs. The ERG also highlighted that although the survival benefit with inotuzumab ozogamicin was uncertain (see section 3.4), blinatumomab showed a statistically significant benefit in survival compared with standard care in the TOWER trial. The ERG further noted that the company did not include blinatumomab in any of its analyses for inotuzumab ozogamicin. The committee understood that the populations considered in both appraisals were similar, but it concluded that because the evidence available for each appraisal is different, differences in modelling are unavoidable.

New evidence from the company before the appeal

The company submitted a new model including a patient access scheme and new assumptions

3.18 The company submitted a new analysis which included:

- a patient access scheme
- a discount rate of 3.5% for costs and QALYs
- age-adjusted utilities and pooled INO-VATE 1022 utilities
- basing the cost of comparators on the actual therapies used in INO-VATE 1022.

The company's new analysis did not include the following assumptions preferred by the committee (see section 3.16):

- modelling of overall survival in the HSCT and post-HSCT state
- 4-fold increase in mortality compared with the general population for patients 3 years post-HSCT and beyond
- replacing the costs of the subsequent therapies, blinatumomab and inotuzumab ozogamicin, with the cost of chemotherapy
- using 9.5 inpatient days for both arms.

It also used general population utilities for patients without progressed disease 3 years post-HSCT and beyond.

The company's new analysis resulted in a deterministic ICER of £37,734 per QALY gained and a probabilistic ICER of £46,152 per QALY gained. In comparison, the analysis using all committee's preferred assumptions and including the patient access scheme resulted in an ICER lower than the original committee preferred ICER of more than £100,000 per QALY gained (see section 3.16), but still substantially higher than £50,000 per QALY gained (the results were submitted as commercial in confidence and cannot be reported here).

Overall survival in the company's economic analysis before the appeal

The company's extrapolation in the HSCT and post-HSCT state is not appropriate for decision-making

3.19 The company reverted to its original method of modelling overall survival in the HSCT and post-HSCT state (fitting separate parametric curves to Kaplan–Meyer data; see section 3.7). Also, a new scenario analysis was introduced which, similar to the committee's preferred overall survival

modelling, pooled data post-HSCT with a minimal residual disease status as a covariate. However, all other covariates were removed from the company's scenario analysis and were not adjusted for. The committee recalled its earlier conclusion that the company's overall survival extrapolation in the HSCT and post-HSCT state is not appropriate for decision-making (see section 3.7). The ERG stated that all analyses based on the HSCT and post-HSCT state subpopulation are highly uncertain, but an analysis that adjusts for more observed confounders is preferable to one that adjusts only for rates of minimal residual disease negativity. The committee concluded that the ERG's modelling of overall survival with a minimal residual disease status as a covariate (including all other covariates) as accepted earlier (see section 3.7) is its preferred method of modelling overall survival.

Long-term survival in the company's new economic analysis before the appeal

A 4-fold increase in mortality and the original base-case utilities 3 years after stem cell transplant are the preferred assumptions

3.20 The company estimated mortality post-cure using cumulative survival at 2 years post-HSCT from Karanes et al. 2008 and an event-free survival hazard ratio for minimal residual disease-negative patients (compared with minimal residual disease-positive patients) after induction therapy from Berry et al. 2017. The company applied a 3-fold increase in mortality for minimal residual disease-positive patients and a 1.6-fold increase in mortality for minimal residual disease-negative patients compared with the general population. Also, the company applied a general population utility (0.88) for disease-free patients post-cure. The ERG did not agree with the company's estimation of mortality risk or with the use of general population utilities. The ERG noted that the utility values used in the company's original base case post-cure (0.74 and 0.76) were based on a relevant published study (Kurosawa et al. 2016) and are preferable to the new assumption, which is not supported by evidence. The ERG explained that cumulative survival probabilities do not suggest hazard of death compared with the general population. It further noted that in the company's model (and also in the committee's preferred way of modelling overall survival), survival for patients at 2 years post-HSCT was modelled using parametric curves from INO-VATE 1022. The ERG also stated that incorporation of an additional treatment effect on survival by differentiating the risk of mortality after the cure point according to rates of minimal residual disease negativity is not supported by any

evidence. The committee agreed with the ERG and recalled that assuming a 4-fold increase in mortality for patients from 3 years after HSCT is at the lower end of the range in Martin et al. 2010 (see section 3.9). The committee concluded that a 4-fold increase in mortality for patients from 3 years post-HSCT and utilities from Kurosawa et al. 2016 for disease-free patients are its preferred assumptions.

Subsequent therapy costs in the company's new analysis before the appeal

The committee accepted the cost of subsequent therapy based on the safety population but list prices were not appropriate

3.21 The company's original model based the cost of subsequent therapies on the INO-VATE 1022 intention-to-treat population, but its revised model used the safety population (the company deemed the safety population to be more appropriate for modelling; see section 3.6 and section 3.12). The ERG stated that, although it is questionable to include inotuzumab ozogamicin in the cost of subsequent therapies in the standard care arm, it is methodically acceptable to include the costs of subsequent therapies as seen in the trial. However, the ERG also noted that the company used list prices to calculate the cost of subsequent therapy, which would underestimate the resulting ICER. The committee's preferred base case including the company's revised cost of subsequent therapies and the patient access scheme resulted in a deterministic ICER that was more than £50,000 per QALY gained, but lower than the committee's preferred base-case ICER with the patient access scheme (the results were submitted as commercial in confidence and cannot be reported here, see section 3.18). The committee agreed with the ERG that the cost of subsequent therapy based on the safety population could be included, but it is not appropriate to use the list prices for the calculation of the cost. The committee therefore concluded that including the cost of subsequent therapy from the safety population in the company's revised model leads to the ICER being underestimated.

Inpatient days in the company's new analysis before the appeal

There is a difference in the number of inpatient days for inotuzumab ozogamicin and standard care patients

3.22 The company increased the number of inpatient days from its original base case (see section 3.13) to 1 inpatient day for inotuzumab ozogamicin and 14 days for standard care. The committee noted that the company did not base the calculation of inpatient days on INO-VATE 1022, which it would have preferred. The ERG stated that no new evidence was presented and the reason for changing the number of inpatient days was not explained. The committee's preferred base case, including the company's new number of inpatient days and the patient access scheme, resulted in a deterministic ICER that was more than £50,000 per QALY gained (the results were submitted as commercial in confidence and cannot be reported here). The committee discussed the need for hospitalisation for patients having inotuzumab ozogamicin and standard care. The committee agreed that 1 inpatient day for inotuzumab ozogamicin is too low, and that it is likely that there is a difference in the number of inpatient days for inotuzumab ozogamicin and standard care, but that the ratio is likely to be larger than the ratio used in the company's analysis (1/14). The committee therefore concluded that the number of inpatient days in the company's revised model leads to the ICER being underestimated.

The cost-effectiveness estimate before the appeal

The most plausible cost-effectiveness estimate is above what is normally considered a cost-effective use of NHS resources

3.23 The committee recalled its preferred assumptions (see section 3.16). After consultation the committee accepted that the cost of subsequent therapy should be based on the safety population (excluding the list prices; see section 3.21), and that there would be a difference in the number of inpatient days for patients having inotuzumab ozogamicin and standard care (see section 3.22). The committee further recalled its earlier conclusion that probabilistic ICERs are more appropriate for decision-making in this appraisal (see section 3.15). The committee was aware that the ERG's analysis had fewer issues with non-linearity than the company's base case and that the ERG's probabilistic ICER would be about £2,000 per QALY gained more than the deterministic ICER. Taking into consideration the deterministic and probabilistic

ICERs, the committee concluded that the most plausible ICER including the patient access scheme for inotuzumab ozogamicin compared with standard care was substantially higher than £50,000 per QALY gained.

After the appeal

3.24 At the third appraisal committee meeting, the committee considered the appeal panel decision to uphold 3 appeal points and to refer these back to the appraisal committee for further consideration. These were:

- The committee need to clearly explain its decision to reject utilities proposed by the company in response to the first appraisal consultation document (see section 3.25).
- The committee need to consider and explain the differences in assumptions post-cure point made in this appraisal explicitly compared to previously published guidance on blinatumomab (see section 3.26).
- The committee should reconsider inotuzumab ozogamicin treatment administration in the context of UK clinical practice (usually 2 cycles plus a third if needed). Also, a costing model based on appropriate stopping rules may be considered (see section 3.27).

Also, at the third appraisal committee meeting the company requested permission to submit new evidence after the appeal, which was accepted by NICE. The committee considered the company's updated model including a revised patient access scheme and new assumptions which included:

- assuming general population mortality from 3 years post-HSCT
- assuming general population utility values from 3 years post-HSCT
- capping the number of cycles of inotuzumab ozogamicin at 3, with no adjustment to the trial efficacy data
- including the cost of subsequent therapies using the price of generic imatinib and assuming a simple patient access scheme discount for blinatumomab
- assuming 3 days of administration-related inpatient days with inotuzumab ozogamicin and 14 days with FLAG.

Utility values in the post-transplant state are between Kurosawa et al. 2016 and those of the general population

3.25 The committee considered the first upheld appeal point (see section 3.24). It discussed the most appropriate utility values to use in the post-transplant state. Previously, the company and the committee had preferred the published values from Kurosawa et al. 2016 which were 0.74 for 3 to 5 years post-transplant and 0.76 for 5 years post-transplant (see section 3.10). After the first appraisal consultation document was released (see section 3.20), the company submitted an economic model using general population post-transplant utility values (0.88). The company noted that these were the same values used in the post-transplant state in NICE's technology appraisal guidance on blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia. At the third committee meeting, the clinical experts explained that although many people who have had a transplant and who did not experience complications such as graft versus host disease or relapse should be expected to return to full health, a substantial number of patients have longer-term health problems related to the transplant. They suggested that the actual utility values 5 years post-transplant are likely to be between those presented in Kurosawa et al. 2016 (0.76) and the value for the general population (0.88). The committee therefore concluded that the most appropriate post-transplant utility values are between the values from Kurosawa et al. 2016 and general population post-transplant utility (0.76 and 0.88).

A 4-fold increase in mortality from 3 years after stem cell transplant is the preferred assumption

3.26 The committee considered the second upheld appeal point (see section 3.24). It discussed the differences in post-HSCT assumptions between this appraisal and NICE's technology appraisal guidance on blinatumomab for previously treated Philadelphia-chromosome-negative acute lymphoblastic leukaemia, specifically the increase in mortality after the cure point. The committee recalled its earlier conclusions (see section 3.17) that the populations considered in both appraisals were similar, but because the evidence available for each appraisal is different, differences in modelling are inevitable. It was aware that the company had assumed general population mortality from 3 years post-HSCT in its original submission and that in NICE's guidance on blinatumomab, the mortality post-HSCT was the general population mortality risk added to the risk derived from the extrapolated parametric curve for overall survival. The committee had

previously concluded that a 4-fold increase in mortality for patients from 3 years post-HSCT based on the lowest values reported in Martin et al. 2010 was appropriate (see section 3.20). At the third committee meeting, the clinical experts noted that the Martin et al. 2010 study was well designed and included a large sample size but transplant care had improved substantially since the study was published meaning a 4-fold increase in mortality could be too high. The clinical experts suggested that any increase in mortality from 3 years post-HSCT is likely to be between the risk of the general population and the value in Martin et al. 2010. The committee accepted that transplant care had improved but it had not been presented with any new evidence to suggest that mortality from 3 years post-HSCT was lower than that presented in Martin et al. 2010. The committee noted that other smaller studies identified by the ERG had shown much larger increases in mortality (see section 3.20) and the 4-fold increase in mortality was at the bottom end of the range in Martin et al. 2010. The committee therefore concluded that a 4-fold increase in mortality from 3 years post-HSCT is preferred.

The number of treatment cycles in the economic model should reflect the number of cycles administered in INO-VATE 1022

3.27 The committee considered the third upheld appeal point (see section 3.24). It discussed the appropriate number of inotuzumab ozogamicin treatment cycles to include in the model in the context of NHS clinical practice. The summary of product characteristics for inotuzumab ozogamicin states that:

- for patients proceeding to HSCT, the recommended duration of treatment is 2 cycles. A third cycle may be considered for those patients whose leukaemia does not achieve complete remission or complete remission with incomplete haematological recovery and minimal residual disease negativity after 2 cycles.
- for patients not proceeding to HSCT, additional cycles of treatment (up to a maximum of 6 cycles), may be given. Patients whose disease does not achieve complete remission or complete remission with incomplete haematological recovery within 3 cycles should stop treatment.

The committee was aware that the company had used the number of inotuzumab ozogamicin cycles (up to 6) informed by the INO-VATE 1022 trial in its base-case analysis. It noted that the company had included a scenario analysis which capped treatment at 3 cycles. At the third committee meeting, the clinical experts explained

that patients in the UK who go on to have a HSCT would not have more than 3 cycles of treatment and would often only have 2, the intention being to move to allogeneic stem cell transplant if the disease was controlled. They explained that because inotuzumab ozogamicin is associated with high rates of hepatotoxicity and veno-occlusive liver disease, treatment would be stopped if there was no evidence of complete remission or complete remission with incomplete haematological recovery after 3 cycles, regardless of HSCT eligibility. The concern about veno-occlusive disease with longer duration of therapy had increased since the original trial leading to greater reluctance to proceed beyond 3 cycles. The committee considered the company's post-appeal scenario analyses which capped inotuzumab ozogamicin treatment at 3 cycles. The first scenario, which was the company's preferred scenario, capped the costs of treatment at 3 cycles but retained the efficacy data for inotuzumab ozogamicin from INNO-VATE 1022. The company noted that complete remission or complete remission with incomplete haematological recovery was achieved in the INO-VATE 1022 trial within the first 3 cycles. The company further explained that this is a prerequisite for HSCT and it considered it plausible to assume that the same HSCT rate would be seen when treatment is stopped at 3 cycles. The second company scenario removed data on patients in the inotuzumab ozogamicin arm of INO-VATE 1022 who did not proceed to transplant. The ERG stated that the company's second scenario would result in the breaking of trial randomisation. The committee agreed and did not consider this scenario further. The committee understood that most patients in the UK would have no more than 3 cycles of treatment. However, the INO-VATE 1022 trial (on which the clinical efficacy of inotuzumab ozogamicin is based) included up to 6 cycles of treatment. The committee agreed that the sources of efficacy and cost data in the model should be consistent and that benefit and cost should not be uncoupled. The committee concluded that the number of inotuzumab ozogamicin cycles in the economic modelling should reflect the number given in the INO-VATE 1022 trial (up to 6 cycles).

Subsequent therapy costs are appropriate

3.28 The committee had previously accepted the inclusion of subsequent therapy costs based on the safety population (see section 3.21). The committee was aware that the company had included the cost of generic imatinib in its post-appeal analyses. It was aware that company's deterministic ICERs did not include the correct price of blinatumomab because there is a confidential patient access scheme. In line with NICE processes, the ERG updated the company's post-appeal analyses with the correct price of blinatumomab

however, the results cannot be reported here since they are commercial in confidence.

There is a difference in the average number of inpatient days for treatment with inotuzumab ozogamicin compared with standard care

3.29 At the third appraisal committee meeting the committee considered the average length of inpatient days for treatment with inotuzumab ozogamicin compared with standard care. Originally, the committee's most plausible ICER (see section 3.23) had been based on the ERG's exploratory analyses. These used a weighted average from NHS reference cost for regimens used in the standard care arm. This resulted in an average of 9.5 inpatient days for both inotuzumab ozogamicin and standard care (which is often FLAG-IDA). The committee was aware that the economic model was highly sensitive to the average number of inpatient days. At the third appraisal committee meeting, after the appeal, the clinical experts noted that an average of 9.5 inpatient days for standard care is not clinically plausible and patients having FLAG-IDA are usually in hospital for longer periods. After a second appraisal consultation, the clinical experts submitted unpublished observational data on the average number of inpatient days with inotuzumab ozogamicin and FLAG-IDA from a compassionate use programme at 2 specialist centres in England (the results of which were provided as academic in confidence and therefore cannot be reported here). The committee noted the limitations with the study including its small sample size but accepted that the results were representative of clinical practice in England. The committee concluded that there is a substantial difference in the average number of inpatient days for treatment with inotuzumab ozogamicin compared with FLAG-IDA.

Company's post-appeal new evidence and updated model assumptions.

End of life

Inotuzumab ozogamicin meets NICE's end-of-life criteria

3.30 The committee discussed whether life expectancy without inotuzumab ozogamicin would be less than 24 months. It noted that median overall survival was 6.7 months with standard care in INO-VATE 1022 and concluded that the short life expectancy criterion was met. The committee discussed whether a survival benefit of over 3 months can be expected for inotuzumab ozogamicin

compared with standard care. It recalled its earlier conclusion about survival benefit with inotuzumab ozogamicin (see section 3.4) and agreed that although the survival benefits of inotuzumab ozogamicin are highly uncertain, it is likely that by increasing the rate of HSCT, inotuzumab ozogamicin would increase mean survival for people with relapsed or refractory B-cell acute lymphoblastic leukaemia by more than 3 months. The committee concluded that the extension-to-life criterion was met. The committee concluded that inotuzumab ozogamicin met the life expectancy and life extension criteria to be considered a life-extending, end-of-life treatment.

Inotuzumab ozogamicin's benefits are captured in the cost-effectiveness analysis

3.31 The patient and clinical experts explained that there is considerable unmet need for people with relapsed or refractory acute lymphoblastic leukaemia because of the ineffective and toxic chemotherapy regimens currently being used. The committee noted that the company considered inotuzumab ozogamicin to be innovative, reducing the need for hospitalisation and leading to a major change in treating a rare illness. The committee concluded that inotuzumab 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.

The cost-effectiveness estimates after the appeal

The company's updated model with the committee's preferred assumptions is suitable for decision-making

3.32 Following the appeal and a second appraisal consultation the company updated its cost model to incorporate the committee's preferred assumptions (see sections 3.25 to 3.29). The updated model comparing inotuzumab ozogamicin with standard care included:

- utility values for all patients 5 years post-HSCT between Kurasowa et al 2016 and the general population
- 4-fold increase in mortality compared with the general population for patients 3 years post-HSCT and beyond
- the same number of treatment cycles for inotuzumab ozogamicin as administered in INNO-VATE 1022 (up to 6 cycles)

- the cost of subsequent therapy from the safety population using the generic price for imatinib and the list price for blinatumomab (results using the price of blinatumomab with a commercial arrangement were updated by the ERG)
- using observational data from the inotuzumab ozogamicin compassionate use programme to inform the average number of inpatient days for inotuzumab ozogamicin and FLAG-IDA.

Inotuzumab ozogamicin is recommended for treating relapsed or refractory B-cell acute lymphoblastic leukaemia

3.33 The company's new analysis, using the committee's preferred assumptions (see sections 3.25 to 3.29) resulted in a deterministic ICER between £37,497 per QALY gained when using utility values from Kurasowa et al 2016 (0.76) and £33,749 per QALY gained when using utility values from the general population (0.88). The committee recalled that inotuzumab ozogamicin met NICE's end-of-life criteria compared with standard care (see section 3.30). The committee noted that when the confidential discount for blinatumomab was incorporated by the ERG the ICER was still within the range normally considered a cost-effective use of NHS resources (these ICERs are commercial in confidence and cannot be reported here). The committee therefore recommended inotuzumab ozogamicin for treating relapsed or refractory B-cell acute lymphoblastic leukaemia.

Other factors

3.34 No equality issues were identified.

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 document.

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 relapsed or refractory B-cell acute lymphoblastic leukaemia and the doctor responsible for their care thinks that inotuzumab ozogamicin is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

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Accreditation