NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal determination

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

1 Recommendations

1.1 Inotuzumab ozogamicin is not recommended, within its marketing authorisation, for treating relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia in adults.

1.2 This recommendation is not intended to affect treatment with inotuzumab 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.

Why the committee made this recommendation

Current treatment for relapsed or refractory B-cell acute lymphoblastic leukaemia is usually fludarabine, cytarabine and granulocyte colony-stimulating factor based chemotherapy (FLAG) with idarubicin. Clinical trial evidence did 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 were able to go on to have a stem cell transplant when compared with people having the other treatments.

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Inotuzumab ozogamicin met NICE's criteria to be considered a life-extending treatment at the end of life. The cost-effectiveness estimate for inotuzumab ozogamicin compared with current treatment (FLAG-based chemotherapy), including the patient access scheme, is higher than what NICE considers acceptable for end-of-life treatments, so it was not recommended for use in the NHS.

2 The technology

Inotuzumab ozogamicin (Besponsa, Pfizer)	
Marketing authorisation	Monotherapy for 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.
Recommended dose and schedule	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; company submission). The company has agreed a patient access scheme with the Department of Health. If inotuzumab ozogamicin had been recommended, this scheme would provide a simple discount to the list price of inotuzumab ozogamicin with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

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. In addition, patients with Philadelphia-chromosome-positive disease can have FLAG-based therapy with tyrosine kinase inhibitors or tyrosine kinase inhibitors 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 tyrosine kinase inhibitors 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 prior tyrosine kinase inhibitor. 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 (CR) or complete remission with incomplete haematological recovery (CRi) with inotuzumab ozogamicin compared 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 CR or CRi and no HSCT
- CR or CRi 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 CR or CRi 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 approximately 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 occurs 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, prior 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 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 bottom 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 CR or CRi and no HSCT state and the CR or CRi 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 impact 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 the committee's 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. 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. In addition, 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 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.

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, whereas 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. 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

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 new economic analysis

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). In addition, 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 a greater number of 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

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. In addition, 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 indicate 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

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, whereas its revised model used the safety population (the company deemed the safety population to be more appropriate for modelling; see section 3.6 and 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 observed 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 greater 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

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 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 greater 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

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 approximately £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.

End of life

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

3.24 Because the committee's preferred ICERs were not within the range normally considered to be a cost-effective use of NHS resources, the committee considered whether the end-of-life criteria would apply. It 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.

- 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

3.25 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.

Conclusion

Inotuzumab ozogamicin is not recommended

3.26 The committee concluded that the most plausible ICER for inotuzumab ozogamicin compared with standard care (FLAG-based chemotherapy) is substantially higher than what is acceptable for end-of-life treatments. The committee therefore could not recommend inotuzumab ozogamicin as a cost-effective use of NHS resource for treating relapsed or refractory B-cell acute lymphoblastic leukaemia.

3.27 The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England, noting the addendum to the NICE process and methods guides. The committee understood that the company had not made a case for inotuzumab ozogamicin to be considered for funding through the Cancer Drugs Fund. It also considered that the most plausible ICER was substantially higher than the range normally considered to be a cost-effective use of NHS resources. The committee therefore concluded that inotuzumab ozogamicin did not have plausible potential to satisfy the criteria for routine use, and that there were no clinical uncertainties that could be resolved through data collection within the Cancer Drugs Fund.

4 Review of guidance

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

Andrew Stevens
Chair, Appraisal committee C
August 2017

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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Technical Lead

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Technical Adviser

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